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Maria Cristina Galli
Mercedes Serabian *Editors*

Regulatory Aspects of Gene Therapy and Cell Therapy Products

A Global Perspective

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Preface

Discoveries in the fields of gene therapy and cell therapy continue to be reported at a rapid pace around the world, resulting in potential therapies that may help treat many unmet medical diseases and conditions. We were invited by the American Society of Gene and Cell Therapy (ASGCT) to participate in a unique opportunity to serve as editors of a book that would be an international "guideline" for those investigators (industry, academia, government agencies, and other groups) seeking to understand how to develop their gene therapy or cell therapy product from the discovery stage to clinical research, and hopefully to licensure. As regulators involved in the oversight of these promising products, we recognized the value of such a book, and we enthusiastically accepted this task.

To the inquiring investigator who is developing a gene therapy or cell therapy product, navigating the requirements of a single regulatory body can be quite daunting; thus, negotiating a pathway from bench to bedside with multiple regulatory agencies in different parts of the world can seem like an overwhelming obstacle. In an attempt to encourage such important nonclinical and clinical research, we invited prominent experts from various regulatory bodies that span the globe to contribute a chapter to this book. The result of this outreach is illustrated in the contents of this book. Each chapter contains detailed information on the regulatory procedures and requirements of a specific regulatory body to enable clinical development of gene therapy and cell therapy products in a particular region of the world. The similarities, as well as the differences, among the regions are reflected in these chapters. In addition, some countries have considerable regulatory experience with these product classes, while other countries are still building or refining their process of regulatory oversight of clinical trials that test these product types. The regulatory bodies have common goals: to assure the safety and rights of patients and ensure that the quality of the nonclinical and clinical evidence is sufficient to allow appropriate evaluation of the safety and effectiveness of the gene therapy or cell therapy product.

Our hope is that this book will assist those who are developing gene therapy and cell therapy products under the umbrella of one or several regulatory authorities across the world. We trust that our efforts, and the exceptional efforts of the contributing authors, will facilitate the global development of safe and efficacious gene therapy and cell therapy products.

Roma, Italy — Maria Cristina Galli
Silver Spring, MD, USA — Mercedes Serabian

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United States Food and Drug Administration Regulation of Gene and Cell Therapies

Alexander M. Bailey, Judith Arcidiacono, Kimberly A. Benton, Zenobia Taraporewala, and Steve Winitsky

Abstract The United States (US) Food and Drug Administration (FDA) is a regulatory agency that has oversight for a wide range of products entering the US market, including gene and cell therapies. The regulatory approach for these products is similar to other medical products within the United States and consists of a multitiered framework of statutes, regulations, and guidance documents. Within this framework, there is considerable flexibility which is necessary due to the biological and technical complexity of these products in general. This chapter provides an overview of the US FDA regulatory oversight of gene and cell therapy products.

Keywords US Food and Drug Administration (US FDA) • Cell therapy • Gene therapy • Public health • Clinical trial • Marketing application • Product licensure • Clinical development

Abbreviations

AE	Adverse event
APEC	Asia-Pacific Economic Cooperation
ASTMi	American Society for Testing and Materials International
ATMP	Advanced Therapy Medicinal Products
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CC	Confidentiality Commitment
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls

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CT	Cell therapy
EMA	European Medicines Agency
FD&C Act	Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good clinical practice
GCT	Gene and cell therapy
GT	Gene therapy
HCT/P	Human cell tissue and cellular and tissue-based product
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
MOA	Mechanism of action
MOU	Memorandums of Understanding
NDA	New Drug Approval
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
OCP	Office of Combination Products
OCTGT	Office of Cellular, Tissue, and Gene Therapies
PAHO	Pan American Health Organization
PDUFA	Prescription Drug User Fee Act
PHS Act	Public Health Service Act
PMC	Post-marketing commitments
PMR	Post-marketing requirement
POC	Proof of concept
PSA	Parallel scientific advice
RAC	Recombinant DNA Advisory Committee
RFD	Request for Designation
RMM	Rapid microbial method
SPA	Special Protocol Assessment
TPP	Target Product Profile
US	United States

1 General Regulatory Framework

The United States (US) Food and Drug Administration (FDA) is a regulatory agency within the US Department of Health and Human Services and has oversight for a wide range of products entering the US market, including food, cosmetics, dietary supplements, medical products, products for veterinary use, and tobacco products. Through this oversight, FDA strives to (1) promote and protect public health; (2) ensure that foods are safe, wholesome, sanitary, and properly labeled; (3) ensure that

human and veterinary drugs, vaccines, and other biological products and medical devices intended for human use are safe and effective; and (4) advance public health by helping to speed innovations. Within FDA's organization, the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) are primarily responsible for the regulatory oversight of medical devices and radiation-emitting products, over-the-counter and prescription drugs including biological therapeutics and generic drugs, and biologics, respectively. Gene therapies (GT) and cell therapies (CT) are considered biologics, and their oversight falls under the Office of Cellular, Tissue, and Gene Therapies (OCTGT) located within CBER. This chapter provides an overview of the US FDA regulatory oversight of GT and CT products, which will be referred to collectively as GCT products.

1.1 Statutes, Regulations, and Guidance Documents

The US FDA regulatory approach is based on a multitiered framework that consists of (1) statutes, (2) regulations, and (3) guidance documents.

Statutes (laws) passed by the US Congress and signed by the President of the United States form the basis of legal authority within which the FDA operates. The statutes that are particularly applicable to FDA's responsibilities and provide FDA with the legal authority to regulate human medical products as drugs, biologics, or devices are the Public Health Service Act (PHS Act) and the Food, Drug, and Cosmetic Act (FD&C Act) and their amendments. The "Regulatory Information" page on the FDA website provides a comprehensive discussion of the more than 200 statutes within which the FDA operates [1], many of which are discussed and referred to in this chapter.

Regulations are the written rules that help to implement and enforce the statutes. Title 21 of the Code of Federal Regulations (CFR) provides legally binding details on how FDA will carry out regulatory responsibilities set forth in the FD&C Act, PHS Act, and other statutes. The complete text of Title 21 of the CFR is available through the FDA website in a searchable format [2], and key regulatory provisions for gene and cell therapy (GCT) products, many of which are discussed and referred to in this chapter, are provided in Table 1.

Guidance documents are FDA's interpretation of regulations and are issued to communicate current thinking on regulatory policies and provide recommendations on ways to comply with regulatory requirements. In this way, these documents assist FDA staff and industry in the appropriate interpretation and application of FDA regulations. However, unlike statutes and regulations, guidance documents are not legally binding, and alternate approaches to satisfy FDA regulations may be used. Some guidance documents are broadly applicable to many human medical products (e.g., *Guidance for Industry*: *CGMP for Phase 1 Investigational Drugs* (*July 2008*) [3]), while others cover specific topics relevant primarily to GCT products (e.g., *Guidance for Industry*: *Preclinical Assessment of Investigational Cellular*

Table 1 Key regulatory provisions for GCT products [2]

Regulation of Combination Products: 21 CFR 4
Good Guidance Practices (GCP): 21 CFR 10
Protection of Human Subjects: 21 CFR 50
Institutional Review Boards (IRBs): 21 CFR 56
Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies: 21 CFR Part 58
Drugs: 21 CFR Parts 200–299, 300–369
• *Labeling*: 21 CFR 201
• *Advertising*: 21 CFR 202
• *Current Good Manufacturing Practices*: 21 CFR 210–211
• *IND Requirements*: 21 CFR 312
• *Clinical Trial Standards*: 21 CFR 314
Biologics: 21 CFR Parts 600–680
• *BLA Requirements*: 21 CFR 600–690
Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps): 21 CFR 1271
Devices: 21 CFR Parts 800–898
• *21 CFR 807 Subpart E*: Premarket Notification 510(k)
• *21 CFR 812*: IDE Requirements
• *21 CFR 814*: PMA Regulations
• *21 CFR 820*: Quality Systems Regulations/ Good Manufacturing Practices (GMPs)

and Gene Therapy Products (*November 2013*) [4]). All FDA guidance documents can be accessed through the FDA website, including those developed specifically for GCT products [5].

1.2 Medical Product Definitions

The determination of whether a specific GCT product will be regulated as a biologic, device, "human cell, tissue, and cellular and tissue-based product" (HCT/P), and/or combination product can be challenging. Because the regulations applicable to biologics, drugs, and medical devices are different, it is important to understand how a product may be categorized in accordance with their regulatory definitions. The regulatory definitions of biologic, drug, medical device, and HCT/P are provided in Table 2.

These definitions are sufficiently broad to cover a wide range of medical products, including GCT products. For example, gene therapy (GT) includes products that incorporate ex vivo genetically modified cells, nonviral vectors (e.g., plasmids), viral vectors (e.g., adenovirus, adeno-associated virus, retrovirus, lentivirus, poxvirus, herpes simplex virus), microbial vectors (e.g., *Listeria*, *Salmonella*, *E. coli*), and

Table 2 Product definitions

Biologic (42 USC 262(i))	A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except chemically synthesized polypeptide), or analogous product or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings
Drug (21 USC 321(g)(1)	(A) Articles recognized in the official US Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C)
Human cell, tissue, and cellular and tissue-based product (HCT/P) (21 CFR 1271.3(d)	Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue
Device (21 USC 321(h))	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the official National Formulary, or the US Pharmacopeia, or any supplement to them; (2) intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes
Combination Product (21 CFR 3.2(e))	(1) A product composed of two or more regulated components, that is, drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) two or more separate products packaged together in a single package or as a unit and composed of drug and device products, device and biological products, or biological and drug products; (3) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, for example, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (4) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect

oncolytic viruses (e.g., herpes, measles, reovirus, adenovirus, vesicular stomatitis virus, vaccinia). Cell therapy (CT) includes products that are stem/progenitor cell derived, mature/functionally differentiated cell derived, or tissue engineering based.

The majority of GCT products are considered biologics, although under certain circumstances, a GCT product may also be considered a medical device and/or combination product (see Table 2). GCT products often contain human cells or tissues and thus fall under the definition of HCT/Ps. As HCT/Ps, this subset of GCT products is also subject to 21 CFR 1271 Parts A–D (general provisions, registration and listing, donor eligibility requirements, and current good tissue practice) and in certain circumstances may not be required to comply with the licensure and other provisions applicable to drugs and biologics. This regulatory pathway is applicable only if the HCT/P meets all of the following criteria, as defined in 21 CFR 1271.10(a):

1. The HCT/P is minimally manipulated.
2. The HCT/P is intended for homologous use, as reflected by the labeling, advertising, or other indication of the manufacturer's objective intent.
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P.
4. The HCT/P does not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function, or is for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use.

HCT/Ps that meet all of the criteria outlined above are thus regulated solely under Section 361 of the PHS Act and 21 CFR Part 1271 (i.e., no premarket approval is required). HCT/Ps that do not meet all of the criteria outlined above would also be regulated as a drug, device, and/or biologic under the FD&C Act and/or Section 351 of the PHS Act and thus require premarket approval.

1.3 Regulatory Pathway

An important first step in the development of a GCT product is to determine the appropriate regulatory pathway to bring it to market. Jurisdiction officers within CBER, CDRH, and CDER can serve as first points of contact and assist with the determination process. For combination products, a formal determination of product jurisdiction can be made through the Request for Designation (RFD) process administered by the Office of Combination Products (OCP), which uses an assignment algorithm that considers the medical product's primary mode of action. Examples of combination products that contain GCT components may include cells or vectors that are administered using a specific delivery device (e.g., catheter for intra-arterial delivery of a GT or CT product), encapsulation/containment devices used with

cellular products, and cell-seeded scaffolds. A more comprehensive discussion of combination products, including a list of recent approvals of combination products and applicable guidance documents, can be found on the FDA/OCP website [6]. The regulatory pathway that is applicable for a specific GCT product may have important implications to its product development and approval processes, for example, reporting requirements, sponsor responsibilities, type of marketing application, and other regulatory requirements may be dependent on the applicable regulatory pathway.

2 Product Life Cycle

2.1 Investigational Use

The FDA regulates clinical research in the United States that involves investigational drugs, biologics, and medical devices. Under Section 505 of the FD&C Act and Section 351 of the PHS Act, it is illegal to sell or distribute into interstate commerce any biologic unless it is licensed or exempted, for example, through submission of an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application. INDs and IDEs are formal documents with defined structure and content that are submitted to the FDA to request exemption from premarketing requirements and to allow lawful shipment of a drug or device for use in a clinical study (typically to gather data in support of an eventual marketing application). In general, an IND is needed for the investigational use of a biologic (including the majority of GCT products), while an IDE is needed for the investigational use of a device.

IND regulations can be found in 21 CFR 312 [2], which include the requirements for use, as well as the application and FDA review processes. The sponsor of an IND is the person, company, or institution that submits the IND application, and a sponsor-investigator is an individual who both submits the IND application and initiates and conducts the clinical trial. The sponsor of an IND assumes many responsibilities, including selection of qualified investigators, conduct the clinical study in accordance with a prospectively written protocol, supervise all investigators, obtain informed consent of all study participants, report adverse events and new risks, communicate with Institutional Review Boards (IRBs), maintain adequate records, and other tasks.

The elements that should be included in an IND application include (1) Form FDA 1571; (2) table of contents; (3) introduction and description of the general investigational plan; (4) Investigator Brochure; (5) detailed clinical protocol(s); (6) chemistry, manufacturing, and control (CMC) data; (7) pharmacology/toxicology data; and (8) previous human experience. IND expectations for CMC data, pharmacology/toxicology data, clinical protocols, and other supporting clinical information are addressed in Sect. 3 of this chapter.

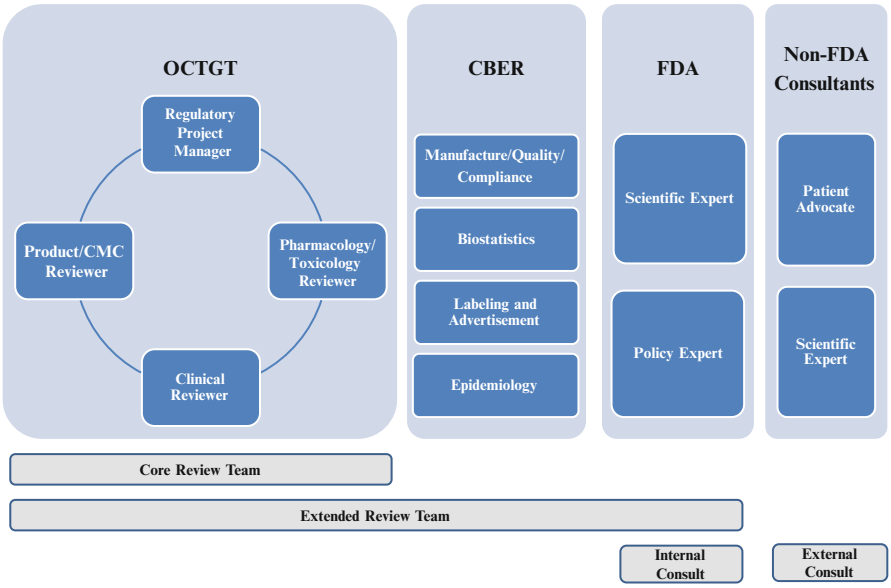

Fig. 1 Review teams for IND regulatory submissions. Schematic illustration of review teams for regulatory submissions. Following receipt of an IND, a core review team of reviewers from all disciplines is assigned. As needed, the review team may be extended to include internal experts from other FDA centers such as CDER. In special circumstances, such as when an investigational agent or proposed clinical trial raises particularly challenging scientific and/or regulatory issues, experts from outside of the FDA may be consulted

The FDA's "primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation is adequate to permit an evaluation of the drug's effectiveness and safety…" (21 CFR 312.22(a)). Thus, FDA's review of an IND primarily focuses on evaluation of product safety in the context of adequate product characterization, manufacturing, and quality control; preclinical data supportive of the safety and scientific rationale of the proposed clinical trial; and incorporation of sound scientific principles in the design and conduct of preclinical and clinical testing. The core FDA/CBER review team for an IND generally consists of reviewers from three disciplines (product/CMC, pharmacology/toxicology, and clinical) and a regulatory project manager. As needed, additional experts from other offices within CBER (e.g., statisticians) or other FDA Centers (e.g., scientific or policy experts) are consulted. In special circumstances, such as when an investigational agent or proposed clinical trial raises particularly challenging scientific and/or regulatory issues, experts from outside of the FDA may be consulted (Fig. 1).

Upon FDA receipt of an IND, the sponsor will be issued an acknowledgement letter containing the date of receipt and an IND number. For GT products, the letter will also include a reminder of the sponsor's responsibility for submission to the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA)

according to Appendix M of the NIH Guidelines [7]. The IND receipt date begins the official 30-day review clock, which requires the FDA to complete its review within the next 30 calendar days. INDs automatically become effective 30 days after receipt unless the FDA notifies the sponsor that the IND is subject to clinical hold, which is an order issued by the FDA to delay the starting of a proposed clinical study or to suspend an ongoing clinical investigation per 21 CFR 312.42. If an IND is placed on clinical hold (e.g., if subjects are or would be exposed to significant and unreasonable risk), the proposed trial may not proceed until the sponsor resolves the clinical hold issues. In certain circumstances, a partial hold may be placed on an IND, for example, one part of a clinical protocol may be delayed or suspended, while another part of the clinical protocol may be allowed to proceed.

2.2 Licensure/Marketing of Biologics

The PHS Act requires individuals or companies who manufacture a biologic to hold an approved Biologics License Application (BLA) for the product prior to introduction into interstate commerce within the United States. The BLA pathway is very similar to the New Drug Approval (NDA) process for human drugs (i.e., NDA pathway). In general, following initial laboratory and animal testing to justify the safety and scientific rationale of additional testing in humans, a biological product is evaluated in exploratory and confirmatory clinical trials in humans under an IND. If data generated by the human clinical studies demonstrate that the product is safe and effective for its intended use, the data are submitted to FDA/CBER as part of a BLA for review and approval for marketing. As part of FDA review of marketing applications, an Advisory Committee meeting may be publically held to obtain independent expert advice on scientific, technical, and policy matters related to the safety and efficacy of a product that is under consideration for licensure [8].

2.3 Post-marketing/Post-licensure

Following marketing approval, FDA continues to monitor the safety and stability of all biological products, including GCT products. For example, manufacturers must report and resolve certain manufacturing problems to FDA's Biological Product Deviation Reporting System within established timeframes. FDA also actively monitors reports of adverse events that are submitted to the agency by healthcare professionals and other individuals through the FDA's adverse event reporting program, MedWatch, which is a gateway for reporting problems with drugs and devices and for learning about new safety information. If a significant adverse event is detected either by the FDA or a sponsor, a product may need to be recalled or additional investigations may be warranted. During this phase, additional clinical studies are also sometimes required as part of commitments made during FDA review of the marketing application, as described in detail in Sect. 3.3.5.

Table 3 Types of meetings between FDA and sponsors

	Type A	Type B	Type C
Meeting description	Meetings that are immediately necessary to help an otherwise stalled product development program proceed	Meetings to obtain nonbinding feedback on specific questions. Generally no more than one of each of the Type B meetings will be granted per each GCT application	Meetings not fitting the criteria of Type A or B regarding the development and review of a GCT product
Examples	Discussion of clinical holds, dispute resolution, Special Protocol Assessment (SPA)	Pre-IND, end-of-Phase 1, end-of-Phase 2, pre-Phase 3, pre-BLA meetings	Discussion of issues that arise during ongoing development (e.g., change in manufacturing)
Scheduling timeline for meeting	Within 30 days from written request	Within 60 days from written request	Within 75 days from written request

2.4 Meetings

The FDA participates in formal meetings with sponsors who seek guidance relating to the development and marketing of medical products, including GCT products. These meetings often occur at critical points in the regulatory process where feedback is essential to the success of a product development and/or clinical testing program. Table 3 describes the types of meetings that may take place, and Fig. 2 illustrates typical points in GCT product development during which different types of meetings typically occur. Pre-IND meetings (considered Type B meetings) provide sponsors the opportunity to obtain nonbinding feedback from FDA on specific questions prior to submission of an IND application. Other meetings may be more appropriately held during clinical development (e.g., end-of-Phase 2 or pre-BLA meetings) or when specific issues arise (e.g., to discuss a clinical hold placed on an IND). Additional information on how to request meetings and how meetings should be conducted can be found in the documents titled *Guidance for Industry*: *Formal Meetings with Sponsors and Applicants* (*May 2009*) [9] and *SOPP 8101.1*: *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* [10].

The successful development of a GCT product will likely require additional interactions with other US oversight bodies. For example, one regulatory body particularly relevant to GCT products are IRBs. An IRB is an FDA-registered group formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications (to secure approval), or disapprove research. The purpose of an IRB is to assure, both in advance and by periodic review, that appropriate steps

are taken to protect the rights and welfare of humans participating as subjects in investigational research. However, only FDA may authorize the conduct of clinical trials using unapproved/unlicensed products in the United States.

3 Considerations for the Development of GCT Products

Due to their potential to address unmet medical needs, there is increasing interest and activity in the development of a diverse array of GCT products for a variety of indications. However, the biological and technological complexity of GCT products may pose challenges to the translation of these products to the clinic. For example, this complexity often presents unique safety concerns, such as the potential for prolonged biological activity after a single administration, immunogenicity, and tumor and/or ectopic tissue formation. Many GCT products are also being developed for rare/orphan diseases where the natural history of the disease may not be well understood (or otherwise pose logistical challenges for clinical testing). Thus, many GCT products are not amenable to standardized product and preclinical and clinical testing programs and instead may require comprehensive and product-specific testing programs prior to licensure. This section highlights specific CMC, pharmacology/toxicology, and clinical issues that should be considered during development of a GCT product.

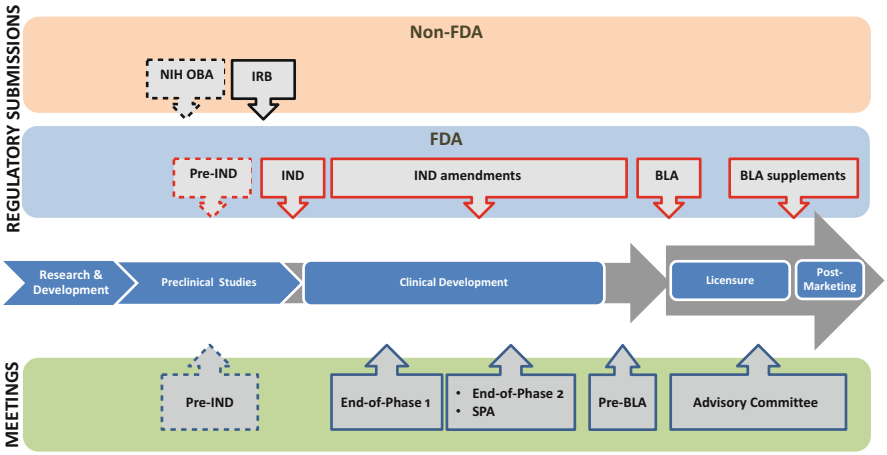

Fig. 2 GCT product lifecycle. This figure illustrates the channels through which a sponsor may interact with FDA to seek advice for product development, in the format of meetings or regulatory submissions. *Arrows* indicate the approximate timing of interactions generally applicable to investigational products, including GCT products. The *boxes with dotted lines* are interactions that are strongly recommended by FDA for the development of many GCT products due to the complexity of this product class

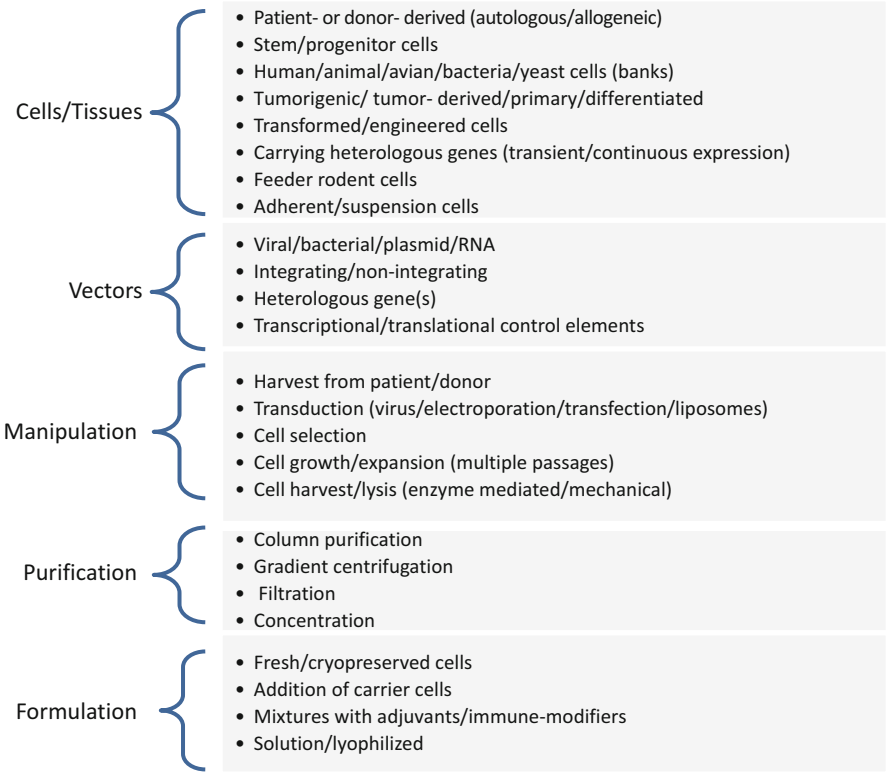

Fig. 3 Diversity of GCT product manufacturing methods.There is great diversity among GCT products in derivation, composition, and manufacturing approaches

3.1 Chemistry, Manufacturing and Controls

3.1.1 GCT Product Manufacturing and Testing

GCT products are diverse and often biologically and technologically complex, particularly with respect to how they are derived and manufactured (Fig. 3). For example, various cells, tissues, or vectors may be used as starting material to derive the GCT product. Manufacturing may involve multiple steps to select, modify and/or expand cells, or grow vectors, a process that generally takes several days of cell cultivation or ex vivo cell manipulation. Variable product-specific techniques are applied to harvest, purify, or formulate the final GCT product to meet standards of product purity, potency, and safety. The diversity and complexity of GCT products also pose challenges to the product characterization and testing programs. For example, (1) there are few/no industry standards and reference materials for the manufacturing of GCT products, (2) manufacturing is often done on a small scale or in patient-specific lots where there may be considerable lot-to-lot heterogeneity, and

(3) GCT products often have a limited shelf life and stability, which makes strategies for product testing, storage, and shipping highly product specific.

FDA's regulatory approach takes into account these aforementioned factors of GCT products and the flexibility afforded by the CMC regulations. Thus, FDA assesses GCT product testing on a case-by-case basis, depending on the current scientific knowledge, regulatory precedents and experience with similar products and/or indications, the phase of product development (e.g., preclinical, Phase 1, end-of-Phase 2), and the benefit–risk profile in the target patient population. While there is considerable flexibility in CMC regulatory requirements for GCT products, these regulatory requirements also increase in a stepwise fashion and become progressively more stringent as a product development program advances toward marketing. In the early phases of development (i.e., prior to initiation of a proposed human clinical trial), the sponsor is expected to demonstrate that the proposed GCT product is comparable in its composition and biological activity to the product evaluated in IND-enabling preclinical studies and also has a reasonable assurance of safety when administered to humans as part of the proposed clinical trial. In later phases of development, with knowledge gained over the life cycle of a product, FDA's expectation is that requirements for product manufacturing, release, stability, and shipping and the implementation of Current Good Manufacturing Practices (CGMPs) have progressively increased to the point that the product meets CMC standards for licensure through the BLA pathway.

Prior to release of a product lot for administration to patients, a GCT product is tested for safety, quality, and consistency (characterization) through a combination of testing plans for the (1) raw material, (2) starting material (cells/vector), (3) in-process material, (4) drug substance, and (5) drug product.

- *Safety testing* typically includes (1) testing for sterility (bacterial and fungal), mycoplasma, and adventitious viruses (in vitro and in vivo) when cell and/or viral banks are used and (2) testing for the presence of replication-competent viruses for viral vector-based GCT products.
- *Quality testing* typically includes (1) an evaluation of the purity of the product, such as through testing for the presence of endotoxin, process residuals (e.g., host/plasmid DNA, cytokines/growth factors/peptides, extractables and leachables, and other factor(s) selected based on product-specific properties); (2) an evaluation of potency or biological activity such as through measurement of viral titer, gene expression or gene activity, surface marker expression, cytotoxic activity, or other measurement relevant to a GCT product's purported mechanism of action; and (3) an evaluation of product identity, such as through amplification of a transgene, vector capsid analysis, cell phenotype or HLA typing, or other appropriate assay based on product-specific properties.
- *Characterization testing* typically includes an evaluation of biochemical, biophysical, and/or genetic characteristics, such as transduction efficacy or vector particle aggregation for vector-based products, analysis of cell plasticity, morphology or growth kinetics for cell-based products, or other testing relevant to product-specific properties.

The FDA has provided two guidance documents that address the general CMC requirements for GCT products studied under an IND, and these should be referenced for additional information [11, 12].

3.1.2 Examples of Challenges in the Safety, Quality, and Characterization of GCT Products

3.1.2.1 Selection and Development of a Potency Assay for Product Release

To assess potency, an understanding of the mechanism of action (MOA) is fundamental. However, for many GCT products, the MOA may be multifactorial and/or poorly defined. Consequently, there may not be a single measure that can adequately evaluate a product's potency or biological activity. For early-phase clinical studies, the primary objective is safety; thus, the assessment of efficacy is not critical. Considering that, the requirement for a potency assay may be satisfied by a single measure of product activity/identity. However, for licensure, the regulations [21CFR 600.3(s)] require product potency to be measured with an assay(s) that measures the ability of a product to effect a given result, which would be an assay(s) that can measure the composite biological activity of the product. The potency assay must also be validated before licensure and should be suitable for transfer to quality control for release testing. Meeting these stringent requirements is often challenging for sponsors of GCT products. Thus, early in development, FDA encourages sponsors to (1) adopt a matrix approach using multiple assays to understand multiple product characteristics, (2) explore surrogate measures of potency based on analytical methods and establish strong correlations between the analytical and biological method(s), and (3) work toward establishing a potency assay for product release before initiating clinical studies that are intended to support product licensure. A comprehensive discussion of the potency assay and current FDA recommendations for GCT products is available in the document titled *Guidance for Industry*: *Potency Tests for Cellular and Gene Therapy Products* (*January 2011*) [13].

3.1.2.2 Safety Assessment of Patient/Donor-Derived Feeder Cells

When developing allogeneic CT products or using allogeneic donor-derived cells for generating cell banks used in manufacturing CT products, sponsors must complete a donor eligibility determination as described under 21 CFR 1271 subpart C and in the document titled *Guidance for Industry*: *Eligibility Determination for Donors of Human Cells*, *Tissues*, *and Cellular and Tissue-Based Products* (*August 2007*) [14]. A detailed description and documentation of the screening and testing should be provided in the IND to ensure the safety of the starting material. When feeder cells of an animal origin are used to manufacture the CT product, the CT product is also considered a xenotransplantation product; thus, additional testing may be needed (*Guidance for Industry*: *Source Animal*, *Product*, *Preclinical*, *and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans* (*April 2003*)) [15].

3.1.2.3 Animal-Derived Raw Materials Used in Manufacturing

A large number of GCT products are derived or manufactured using material of animal origin. For example, CT products expanded in culture often require high concentrations of animal-derived raw materials, such as serum and growth factors, to support cell proliferation and/or plasticity. Other animal-derived raw materials, such as antibodies and enzymes, may also be used for purification/product harvest and processing. In the IND, the sponsor must submit information (e.g., certificate of analysis) to provide adequate assurance that any animal-derived material is free of adventitious agents and is of a consistent quality. This includes documentation/certificate of analysis for source and testing (per 9 CFR 113.53). For example, if a reagent is derived from bovine material, it should be sourced from countries free of bovine spongiform encephalopathy (BSE). If human serum is used in manufacturing or formulation, it should be obtained from an approved blood bank and meet all blood donor eligibility criteria.

3.1.2.4 Sterility Testing Requirements for the Final Drug Product

For GCT products, low production volumes may result in an insufficient amount of product to provide the required dose(s) and material for sterility testing. In other cases, a short product shelf life may preclude sterility testing before the GCT product needs to be administered to the patient. Revisions made recently to the sterility requirements specified under 21 CFR 610.12 provide increased flexibility to accommodate these intrinsic product-specific limitations [16]. Specifically, GCT products may be tested for sterility at an in-process stage or other stage of manufacturing process as appropriate if adequate justification is provided, instead of performing sterility testing on the bulk or final container material.

Several approaches may be taken for a GCT product with a relatively short product shelf life that must be administered before traditional compendial sterility testing on the final product is complete. An alternative growth-based rapid microbial method (RMM) may be used, provided the alternative method is validated to demonstrate that it is capable of reliably and consistently detecting the presence of viable contaminants. For additional information, please reference the document titled *Draft Guidance for Industry*: *Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products* (*February 2008*) [17]. Often a GCT product with a limited shelf-life is released for administration to patients based on a negative result for Gram staining and a "no-growth" result from an in-process sterility test, as well as the initiation of a culture on the final product sample. In such cases, when the growth-based sterility testing results are available post-release, FDA requires sponsors to propose in their IND a thorough action plan for post-release sterility failures. This plan should include follow-up measures to identify the cause of the sterility failure and corrective actions to prevent future sterility lapses. Clinical monitoring should also be proposed to ensure that appropriate medical care (i.e., diagnosis, prevention, or treatment of complications) is provided to subjects who received a product that failed sterility testing.

3.1.2.5 Safety Testing for Replication Competent Forms of GT Vectors

Replication-deficient GT vectors such as retrovirus, lentivirus, adenovirus, or adeno-associated virus are commonly manufactured using packaging cell lines or multiple helper plasmids. Due to homologous recombination, this approach carries the risk, albeit low, of generating replication-competent forms of the virus, capable of infection and potentially causing disease. To assess this risk, testing of viral banks and each product lot for replication-competent virus is part of the safety testing plan for virus-vectored products. FDA has provided specific guidance for replication-competent retrovirus (and lentivirus) testing in the document titled *Guidance for Industry*: *Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors* (*November 2006*) [18].

3.1.2.6 Long-Term Follow-up for GT Products

Some viral vectors used in GT products are capable of integrating into the genome and may result in long-term persistence. Thus, there is a risk of unanticipated adverse events that manifest long after administration of the GT product and after the observation period for acute toxicity has ended. Hence, FDA requires long-term monitoring of all subjects receiving GT products and has issued guidance on the issue *Guidance for Industry*: *Gene Therapy Clinical Trials—Observing Subjects for Delayed Adverse Events* (*November 2006*) [19].

3.1.2.7 Product Comparability

When manufacturing changes are proposed in early phases of a development program, FDA recommends that sponsors submit an amendment to the IND that fully describes the proposed change(s) and provides the results of testing on the product made after the change(s). If no safety concerns are raised, the expectations for data demonstrating comparability at this stage may be limited. However, for a product in late-phase clinical testing or a product with safety concerns identified in preclinical or clinical development, FDA requires the demonstration of product comparability. This can be shown through an evaluation of the similarities and differences in critical quality attributes of multiple lots of the product, pre- and post-change, following the international guideline *ICH Q5E*: *Comparability of Biotechnology/Biological Products Subject to Changes in Their Manufacturing Process* [20]. Through a combination of analytical testing, biological assays, and/or nonclinical and clinical data, the demonstration of comparability should ensure that differences in quality attributes of the product post-change have no adverse impact on its safety and efficacy. A sponsor can engage FDA in formal discussions (Table 3) before initiating a manufacturing change or comparability study to obtain CMC, pharmacology/toxicology, and clinical advice on the acceptability of their proposal.

3.1.2.8 Scale-Up for Late-Phase Clinical Studies

Scale-up of product manufacturing for GCT products brings forth issues not usually encountered in small-molecule drug development. For example, scale-up of autologous ex vivo-manipulated CT products generally involves increasing the manufacturing capacity to a level that allows for processing multiple patient lots simultaneously in the same facility. This type of scale-up may lead to potential challenges related to product tracking, identity, processing time, automation, and other logistical issues with storage and shipping. For scale-up of a GT product such as a viral vector, increasing the yield for commercial manufacturing may involve changes in cell culture procedures, such as a switch to animal component-free growth medium or the use of suspension cells. Any of these changes can affect product attributes that contribute to its safety and efficacy. Thus, scale-up of product manufacturing may result in the need for additional CMC and/or animal testing to establish comparability. Considering the complexity in the composition and MOA of GCT products, the development of appropriate assays to detect changes in product attributes may be challenging. Hence, FDA recommends that manufacturing changes be minimized once Phase 3 clinical trials are initiated.

3.1.3 CGMPs for Phase 1 Clinical Trials

Most investigational products used in Phase 1 clinical trials are exempt from complying with the CGMP regulations in 21 CFR parts 210 and 211 that are applicable to commercial manufacture of products. Instead, the requirements for CGMPs in the FD&C Act apply, and FDA has provided guidance on how manufacturers of early-phase products can comply with these requirements (*Guidance for Industry*: *CGMP for Phase 1 Investigational Drugs* (*July 2008*)) [3]. This document describes the importance of (1) adequate equipment and manufacturing environment, (2) trained personnel, (3) adherence to procedures and practices that are well defined and documented for environmental monitoring, (4) raw material qualification and manufacturing, (5) establishment of a quality control unit that is independent from manufacturing to review procedures for production and lot release testing, and (6) investigation of deviations and initiation of corrective actions.

3.2 Pharmacology/Toxicology

Prior to the administration of an investigational GCT product in a clinical trial, the sponsor must provide "[a]dequate information [in the IND] about the pharmacological and toxicological studies…on the basis of which [they have] concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required vary with the duration and nature of the proposed clinical investigations" (21 CFR 312.23(a)(8)). An adequate preclinical

testing program for a GCT product provides adequate scientific rationale of the proposed clinical trial, identification of biologically active dose levels and dosing regimens, optimization of the clinical route of administration of the GCT product, characterization of potential local and systemic toxicities, selection of patient eligibility criteria, and identification of physiologic parameters to help guide appropriate clinical monitoring.

However, there is flexibility in how these preclinical testing objectives are met, which is important because the biological complexity and heterogeneity of these products preclude standardized approaches to preclinical testing. As a consequence, the regulatory review process for GCT products necessitates a careful science-based, benefit–risk analysis performed in the context of the specific product properties, method(s) of delivery and route of administration, and target patient population. Although flexible, this approach is based on a general framework that incorporates many of the basic toxicological principles that underlie more traditional, standardized preclinical testing strategies. A few specific preclinical study design considerations are highlighted below and in the document titled *Guidance for Industry*: *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (*November 2013*) [4].

Proof of concept (POC) and discovery-phase preclinical studies are important to establish the feasibility and rationale for the use of an investigational GCT product in the target patient population. POC studies should investigate the following: (1) effective dose range and dosing regimen, (2) optimal route of administration, (3) timing of product administration relative to disease/injury onset and/or progression, and (4) putative MOA(s) or hypothesized biological activities. Due to the product-specific properties of many GCT products (e.g., complex nature and multiple MOAs that require interaction between the GCT product and the disease microenvironment), POC studies conducted in animal models of disease/injury (if available), as opposed to healthy animals, may be more informative and are strongly recommended. In general, POC studies should be designed to characterize the benefit–risk ratio of an investigational GCT product; thus, it is important to not only evaluate biological activity (ideally in the context of the abnormal phenotype), but also incorporate safety evaluations, as feasible, which can then be investigated further in future preclinical safety/toxicology studies.

Safety/toxicology studies should be sufficiently comprehensive to permit identification, characterization, and quantification of potential local and systemic toxicities, their onset (i.e., acute or delayed), the possibility for resolution of any toxicities, and any dose-response relationship(s). In general, the study design should mimic the proposed clinical trial design as closely as possible and include the following, as applicable: (1) blinding and randomization methods in an attempt to reduce study bias, (2) appropriate control groups (e.g., untreated, sham surgery, formulation vehicle alone, adjuvant alone, null vector, and/or scaffold alone), (3) multiple dose levels that bracket the intended clinical dose level range, (4) a route of administration that mimics the intended clinical route of administration as closely as possible, and (5) comprehensive evaluation of safety endpoints (e.g., mortality, clinical observations, body weights, physical examinations, food consumption/appetite, clinical pathology, gross pathology, histopathology, etc.).

In addition to incorporating the basic design principles outlined above, the specific testing strategy should be based on product-specific properties. For GT products, an appropriate preclinical testing program may require evaluation of the (1) potential for adverse immune responses to the ex vivo modified cells, vector, and/or expressed transgene; (2) level of viral replication in nontarget cells/tissues; (3) insertional mutagenesis or oncogenicity; and/or (4) vector biodistribution and transgene expression levels post-administration. For CT products, there may be a heightened concern of (1) tumor or ectopic tissue formation, (2) toxicity or mechanical failure associated with the resorption/degradation of a scaffold component, and/or (3) unknown donor cell fate (i.e., survival/persistence, phenotype, distribution, and proliferation) following administration, which may need to be evaluated as part of the preclinical testing program. Collectively, this information obtained from preclinical studies will help guide the design of the initial clinical trial, such as with the identification of a no-observed-adverse-effect level. In some circumstances, additional animal studies may be necessary during late-phase development after clinical trials have initiated. For GCT products, this may include the need for developmental and reproductive toxicity, dependent on product-specific properties, which can usually be conducted concurrently with Phase 3 trials.

When possible, the GCT product that will be administered to the target patient population should be evaluated in all definitive (i.e., IND-enabling) preclinical studies. However, this may not always be appropriate and there are potential exceptions. For pilot preclinical studies, it may be appropriate to evaluate related GCT products rather than the intended clinical product. For example, this may be advantageous if manufacturing methods have not yet been finalized during discovery phase or POC testing. Similarly, if the species-specific nature of the GCT product (e.g., some GT products that incorporate vector-expressed human transgenes) is expected to limit the relevance of evaluating the intended clinical product in either POC studies and/or definitive studies, it may be acceptable to evaluate an analogous animal-derived or other similar product.

3.3 Clinical Development

Clinical development programs for GCT products will not necessarily follow a linear, predetermined pathway, since the development plan should be sufficiently fluid to allow for modifications as new data emerge. However, it is important early on in development to tentatively design clinical studies that can provide a framework for the overall development program for a particular GCT product for a specific disease or set of diseases. A helpful approach for planning the clinical development program is for the sponsor to submit a Target Product Profile (TPP) to the FDA as described in the document titled *Guidance for Industry and Review Staff*: *Target Product Profile—A Strategic Development Process Tool* (*March 2007*) [21]. A TPP is a dynamic summary that outlines the overall intent of the clinical program, including a statement of concepts that the sponsor would like to appear in labeling.

A TPP can facilitate discussions between a sponsor and the FDA during the entire development process, beginning at the pre-IND stage. The concept behind the TPP is that "beginning with the goal in mind," formulating this plan allows the sponsor to use the available information to guide the design, conduct, and analysis of clinical trials, with the goal of enhancing efficiency of a clinical program that is adequately designed to support the sponsor's intended labeling claims.

The clinical development program can be divided into three phases. Some of the considerations for Phase 1, 2, and 3 studies for GCT products are described in the sections below. It is important to note that these phases have blurred borders and may overlap. The FDA draft guidance titled *Guidance for Industry*: *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products* (*July 2013*) [22] is a good resource that discusses various issues to consider when designing early-phase studies, including first-in-human (FIH) Phase 1 studies.

3.3.1 Phase 1 Clinical Studies

Most Phase 1 GCT studies enroll subjects who have the disease or medical condition for which the investigational product is being studied, in contrast with early-phase studies of small-molecule drugs, which frequently involve healthy volunteers. The reason for this practice is that there is an unfavorable benefit/risk for administering GCT products that carry the risk of long-term adverse events (AEs) to healthy volunteers. Therefore, in addition to evaluation of safety (the primary objective of a Phase 1 study), sponsors can assess for preliminary evidence of bioactivity on characteristics of the disease or condition. The preliminary evidence can help guide the subsequent clinical development program. When selecting the Phase 1 study population, considerations include, but are not limited to, the target indication, study procedure risk, and interpretability of outcome results.

A single administration dosing regimen is used in most FIH studies, since risk due to repeated dosing of the GCT product might not be acceptable until there is a preliminary understanding of toxicity and duration of activity of the product. Additionally, in the absence of preliminary safety data, FIH studies should not administer the GCT product simultaneously to multiple subjects within a given dose cohort. In order to prevent multiple subjects from being placed at risk of acute or subacute AEs related to the product, FIH studies often stagger the administration of the product to sequential subjects, which allows for an intersubject (and intercohort) monitoring interval that may detect such acute and subacute AEs.

The safety monitoring plan should have the ability to capture early, intermediate, and delayed AEs that are expected, based on theoretical concerns or based on preclinical and/or clinical data. Study stopping rules are criteria, based on the observed incidence of AEs that, if triggered, will temporarily halt enrollment and treatment of subjects, pending a safety review. For studies of CGT products, it is often challenging to adjudicate causality for adverse events, due to overlap in complications that can be related to various aspects of the study procedures (e.g., the delivery device, concomitant medications or surgical procedures, study product) or the underlying medical condition. Therefore, in order to be sufficiently conservative to

protect subject safety, stopping rules for CGT studies should in general be based on the occurrence of certain types and severities of AEs, regardless of whether a definitive causal link with the study procedures has been established. All early-phase studies should incorporate stopping rules. Choosing the sample size for the Phase 1 study could be based on the power of the sample size to rule out a certain incidence of AEs. However, there are other considerations that may play a role in sample size determination, such as availability of the GCT product or testing of the product in subjects with a rare disease.

3.3.2 Phase 2 and 3 Clinical Studies

Phase 2 studies should be designed to provide safety, efficacy, and feasibility data that can further investigate hypotheses that are generated from the data collected in Phase 1 studies. Phase 2 data are critical for informing the design of the Phase 3 trials, which are intended to provide substantial evidence of effectiveness and safety. Some of the important knowledge that can be obtained from Phase 2 studies include: (1) information that can guide the selection of a study population that would be appropriate for enrollment in Phase 3, (2) dose and dosing regimen exploration, (3) optimization of study procedures, (4) refinement of the concomitant medication regimen, (5) the treatment effect size for the Phase 3 primary endpoint, and (6) the time course and duration of product bioactivity, which can inform the choice of the primary outcome measure and statistical analysis methodology.

Optimization of the study procedures in Phase 2 studies is particularly important for CGT product development, since study product administration often involves many factors that can influence bioactivity and safety. For example, administration of a CT product to the heart can be performed using multiple routes of administration, there are often a number of available delivery devices for any given route of administration, and there can be multiple variables in the delivery methodology (e.g., the number, location, and pattern of individual injections). FDA recommends that sponsors consider including a request for a Special Protocol Assessment (SPA) (Fig. 2) when the protocol for the Phase 3 study is submitted, as described in the document titled *Guidance for Industry*: *Special Protocol Assessment* (*May 2002*) [23]. FDA concurrence on a Phase 3 study that is being conducted under the SPA program constitutes an agreement between the Agency and the sponsor that the particular Phase 3 study is adequately designed to contribute evidence of effectiveness, but is not an agreement that the overall development program will provide sufficient evidence of effectiveness or an adequate safety database to support a BLA.

3.3.3 Pediatric Study Considerations

For studies that enroll children, additional safeguards are required to protect the safety of this vulnerable population (21 CFR 50, subpart D). The considerations for allowing such studies are based on the level of risk to pediatric subjects due to the investigational product and/or study procedures and whether a prospect of direct

clinical benefit exists for any individual subject. An IRB can approve a pediatric study only after determining that the study complies with subpart D. The FDA is also responsible for determining whether the study poses an unreasonable risk (21 CFR 312.42(b)(1)(i) and (b)(2)(i)) or whether the protocol contains sufficient information to assess risk for pediatric subjects, similar to studies in adults.

3.3.4 Studies Conducted Outside of the United States

A sponsor may choose to conduct all or parts of a study at foreign clinical sites. If a foreign clinical study is conducted under an IND, the study must either meet all FDA requirements for INDs or have been granted a waiver from specific IND requirements. If the foreign study is not conducted under an IND, FDA may accept efficacy data collected from a well-designed, well-conducted foreign study in support of an IND or marketing application, provided that the study was conducted in compliance with good clinical practice (GCP; 21 CFR 312.120). A major consideration in the FDA's determination of the acceptability of data from a foreign study to support a marketing application is the degree to which the foreign data are applicable to the US population, with regard to similarity of demographics, natural history of the disease, and treatment options and clinical outcomes. An additional criterion for FDA acceptance of non-IND foreign study data is that the FDA is able to perform onsite inspections of study sites if the Agency deems it necessary to validate the study data.

3.3.5 Post-marketing Studies

Clinical studies may be conducted after approval of the product, in order to provide additional information about the safety, efficacy, or optimal use of a product in the proposed indication and/or other settings or conditions as described in the document titled *Guidance for Industry*: *Postmarketing Studies and Clinical Trials—Implementation of Section 505*(*o*)(*3*) *of the Federal Food*, *Drug*, *and Cosmetic Act* (*July 2009*) [24]. There are two categories of post-marketing studies: (1) post-marketing requirements (PMRs), which are studies that sponsors must agree to conduct as a prerequisite for approval and (2) post-marketing commitments (PMCs), which are studies that a sponsor has agreed to conduct but are not legally required. The FDA may require post-marketing studies to further assess the risks related to the administration of the product, either when product use is associated with known serious risk, when signals of serious risk have been observed, or when existing data are indicative of a potential serious risk. Post-marketing studies are also required for the following situations: (1) to demonstrate clinical benefit for products that have received Accelerated Approval (i.e., approval based on effects of a surrogate marker) as set forth in 21 CFR 314.510 and 21 CFR 601.41; (2) when the conduct of pediatric studies has been deferred, as per the Pediatric Research Equity Act (PREA) as set forth in 21 CFR 314.55(b) and 21 CFR 601.27(b); and (3) to confirm

safety and efficacy in humans for products that have been approved under the Animal Efficacy Rule, when such studies may be feasibly and ethically conducted as set forth in 21 CFR 314.610(b)(1) and 21 CFR 601.91(b)(1). Depending on the results of any post-marketing studies, FDA may approve labeling changes, including additional clinical indications; require changes in the manufacturing process; or (in rare instances) seek withdrawal of a drug from the market.

4 Additional Regulatory Mechanisms and Programs

There are a number of FDA programs that are intended to facilitate and expedite development and review of new therapeutics, including as GCT products, that are intended to treat a serious or life-threatening condition or to treat a rare disease or condition. FDA also facilitates access to investigational agents for use as treatment for patients who lack therapeutic options for a life-threatening disease or condition.

4.1 Expedited Clinical Programs for Serious or Life-Threatening Conditions

In addition to the FDA's primary role in protecting subject safety, the Agency is also committed to enhancing the efficiency of product development, with the goal of timely availability of safe and effective therapeutics. There are four pathways available to sponsors for expediting availability of CGT products that are intended to treat serious medical conditions: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review, as described in the document titled *Guidance for Industry*: *Expedited Programs for Serious Conditions—Drugs and Biologics* (*May 2014*) [25]. FDA applies these programs in a manner that is not expected to compromise the quality of the clinical evidence that serves as the basis for product approval.

4.1.1 Fast Track Designation

Requirements for Fast Track designation are as follows: (1) The product is intended to treat a serious condition, (2) has demonstrable effects, and (3) would address an unmet medical need. The type of information needed to demonstrate the potential for addressing an unmet medical need is dependent on the stage of GCT product development when the Fast Track request is submitted. For example, early in development, evidence of activity in a nonclinical model may be sufficient; however, in later phases, existing clinical data would be required. If a product is granted Fast Track designation, advantages include (1) more frequent meetings and written correspondence with the FDA to ensure that the overall development plan and individual studies are designed to generate data that appropriately support product approval;

(2) the possibility of Accelerated Approval and Priority Review of the BLA, provided that certain criteria are met; and (3) FDA review of sections of the BLA as they are completed and submitted (so-called Rolling Review).

4.1.2 Breakthrough Therapy Designation

A Breakthrough Therapy designation is a program that has a goal of expediting the development and review of products that are intended to treat a serious condition and for which there is clinical evidence of a substantial improvement over existing therapy on a clinically meaningful endpoint(s). A request for Breakthrough Therapy designation should in general be made no later than the end-of-Phase 2 meeting. The benefits of Breakthrough Therapy designation are intensive guidance from FDA on designing an efficient development program for a product and clinical indication and organizational commitment that senior FDA staff will be involved in such guidance.

4.1.3 Accelerated Approval

For GCT products that are intended to fill an unmet medical need for treating serious conditions, Accelerated Approval is a program through which products may be approved on the basis of adequate and well-controlled clinical studies that demonstrate efficacy based on a surrogate that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity or mortality (IMM) or other clinical benefit. A surrogate is a biomarker intended to substitute for a clinical endpoint. A surrogate is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. An intermediate clinical endpoint is a clinical outcome measured at an earlier time point than what would generally be considered meaningful. Accelerated Approval may expedite the approval process, since the use of surrogate or intermediate clinical endpoints may result in faster collection of efficacy data than if the study(ies) had used a direct measure of clinical benefit as the primary endpoint. Under the Accelerated Approval program, post-marketing studies are required in order to confirm clinical benefit. In the event that the post-marketing studies fail to verify clinical benefit or do not demonstrate clinical benefit that is sufficient in magnitude to justify the risks associated with the product, the FDA may either withdraw product approval or modify the labeled indication.

4.1.4 Priority Review

When a BLA is submitted, the FDA has 60 days to determine the review designation for the application. If a BLA is submitted for a product that, if approved, would demonstrate significant improvements in safety or effectiveness compared to available

treatment, diagnosis, or prevention of serious conditions, the FDA may grant Priority Review. If Priority Review is granted, FDA will direct overall attention and resources to complete the BLA review within 6 months, instead of the 10-month review time for a standard BLA submission. However, Priority Review does not alter the standards for approval of the product.

4.2 Expanded Access

Expanded access refers to administration of investigational products, including GCT products, outside of a clinical trial. The intent of expanded access pathways is to make promising therapeutics available as early as possible during their development program to patients with serious or life-threatening disease who do not have therapeutic options (e.g., because they have not responded or are intolerant to approved therapies). The objective of delivering the product under the expanded access pathway is to provide a potential treatment to the patient, rather than for research purposes. There are three categories of expanded access: (1) expanded access for individual patients, including for emergency use (21 CFR 312.310); (2) expanded access for intermediate-size patient populations (21 CFR 312.315); and (3) expanded access for large patient populations under a treatment IND or treatment protocol (21 CFR 312.320). The criteria that must be met to authorize the use of expanded access are discussed in the document titled *Guidance for Industry*: *Expanded Access to Investigational Drugs for Treatment Use—Qs & As* (*2013*) [26].

4.3 Incentives for Development of Therapeutics Intended to Treat Rare Diseases

4.3.1 Orphan Drug Designation

In order to foster research for products, including GCT products, intended to treat rare diseases, the Orphan Drug Act provides certain financial benefits and incentives for sponsors of products that have been granted an Orphan Drug designation as set forth in 21 CFR 316. A sponsor may apply for Orphan Drug designation if the GCT product being developed is intended for the diagnosis or prevention of a disease that either affects fewer than 200,000 people in the United States or affects more than 200,000 people, but for which the sponsor would not be expected to recover costs associated with its development and marketing. If an Orphan Drug designation is granted, a sponsor is entitled to receive financial benefits and incentives that include (1) eligibility to apply for annual grant funding to reduce the costs of clinical development, (2) tax credits for clinical research costs, (3) assistance in designing the clinical studies, (4) 7-year exclusivity for marketing an approved orphan product, and (5) waiver of the PDUFA fees required upon submission of a BLA.

4.3.2 Rare Pediatric Disease Priority Review Vouchers

Section 908 of The Food and Drug Administration Safety and Innovation Act (FDASIA) added Section 529 to the FD&C Act. Under Section 529, the FDA will award priority review vouchers to sponsors of rare pediatric disease products that meet certain criteria. Under this program, a sponsor who receives an approval for a biologic for a "rare pediatric disease" may qualify for a voucher which can be redeemed to receive a priority review of a subsequent marketing application for a different product. More detailed information about this program is contained in the document titled *Rare Pediatric Disease Priority Review Vouchers Draft Guidance for Industry* (*November 2014*) [27].

5 Considerations for the Global Development of GCT Products

The development of GCT products is increasingly global in nature, and FDA/CBER works closely with international partners in various ways to support the globalization of medical product development and thereby facilitate the availability of safe and effective products. In general, FDA international activities can be grouped into the following categories: information sharing, convergence of regulatory approaches, capacity building, and international standards development.

Sharing and dissemination of information by the FDA may include information that is publicly available or confidential in nature. Confidentiality Commitments (CCs) and Memorandums of Understanding (MOUs) are mechanisms by which the FDA can share confidential information with other international regulatory authorities. CCs and MOUs are typically specific in subject and scope and may be in place for specific time periods. Parallel Scientific Advice (PSA) is an example of an activity that takes place under a CC/MOU. The PSA process is one in which the sponsor of a regulatory application seeks joint advice with the European Medicines Agency (EMA) and the FDA on a specific product and indication. This process allows for an increased dialogue between the two agencies and sponsors at various points of the life cycle of a new product. This interaction may also provide a deeper understanding of the basis of scientific advice and an opportunity to optimize product development and avoid unnecessary replication of testing or divergence in testing methodologies. "Clusters" are another example of an activity that takes place under CCs and MOUs. "Clusters" are fora in which FDA and other regulatory authorities discuss specific areas of mutual interest. The Advanced Therapy Medicinal Products (ATMP) Cluster is specific for GCT products. This cluster exists as a trilateral interaction between FDA, EMA, and Health Canada. Regular teleconferences are held approximately six times per year to share thinking on regulatory approaches, both general and on specific issues; to share information on draft documents; and to engage reciprocally in workshops, advisory committees, and working parties.

International activities regarding regulatory convergence and regulatory capacity building specific for GCT products include FDA participation in the International

Pharmaceutical Regulators Forum (IPRF) Cell Therapy Working Group and the IPRF Gene Therapy Working Group. These fora are open to all regulatory authorities and regional initiatives such as the Pan American Health Organization (PAHO) and the Asia-Pacific Economic Cooperation (APEC) Harmonization Center that are interested in the convergence of regulatory approaches for GCT products. The IPRF provides participants an opportunity to share scientific knowledge and regulatory experiences.

Other efforts that support the global development of GCT products include FDA participation in standards development activities with international and domestic standards development organizations. FDA standards development activities include participation in initiatives that develop international standards with the goal of harmonizing regulatory expectations internationally (e.g., International Conference on Harmonisation (ICH)), as well as organizations seeking standardization of technical/scientific approaches for specific topics (e.g., International Organization for Standardization (ISO) and American Society for Testing and Materials International (ASTMi)). The development and use of national and international standards for GCT products may facilitate product design and reduce time to market. For example, the development of standard reference materials can provide a mechanism by which GTT products utilizing the same vector can be compared. Standards in the form of guidelines can be used to provide methodology and metrics for the characterization of GCT products.

6 Conclusion

The regulatory approach for GCT products is similar to other medical products and consists of a multitiered framework of statutes, regulations, and guidance documents. Within this framework, there is considerable flexibility, which is necessary due to the biological and technical complexity of GCT products in general. OCTGT, located within FDA/CBER, is primarily responsible for the oversight and regulation of GCT products, and product developers/sponsors should consider referencing the numerous resources available online through the FDA website, as well as communicating with OCTGT early in product development, to help guide product, preclinical, and clinical testing strategies. To support regulatory innovation and access to promising GCTs, there are also a variety of mechanisms available to product developers, and the US FDA is increasingly involved in global development initiatives.

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The National Institutes of Health Oversight of Human Gene Transfer Research: Enhancing Science and Safety

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Abstract The National Institutes of Health (NIH) oversight of human gene transfer research, which is defined as the deliberate transfer of recombinant and/or synthetic nucleic acid molecules to humans, originates with the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*). The *NIH Guidelines*, which were first published in the Federal Register almost 40 years ago, have been amended numerous times to remain responsive to scientific progress and to clearly define the responsibilities of NIH, the Recombinant DNA Advisory Committee (RAC), investigators, and institutions. Human gene transfer trials conducted at clinical sites in the United States (USA) are subject to the *NIH Guidelines* if they are conducted at, or sponsored by, an institution that receives any support for recombinant or synthetic nucleic acid research from the NIH. Human gene transfer trials conducted either in the USA or abroad are also subject to the *NIH Guidelines* if the investigational agent was developed with NIH funds and the institution that developed the investigational materials sponsors or participates in these projects. Trials are registered with the NIH Office Biotechnology Activities (OBA) and there are ongoing reporting requirements. Each new trial is reviewed by the RAC, and those that are novel or raise unique ethical or social issues are selected for review at quarterly public RAC meetings. The RAC also advises the NIH on policy and other matters relating to clinical gene transfer research and biosafety.

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Abbreviations

AAV	Adeno-associated virus
ASGCT	American Society of Gene and Cell Therapy
FDA	Food and Drug Administration
GeMCRIS	Genetic Modification Clinical Research Information System
GTSAB	Gene Transfer Safety Assessment Board
HSV	Herpes simplex virus
IBC	Institutional Biosafety Committee
IND	Investigational New Drug
IOM	Institute of Medicine
IRB	Institutional Review Board
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
OHRP	Office of Human Research Protection
PI	Principal Investigator
RAC	Recombinant DNA Advisory Committee
SAE	Serious adverse event
SB	Sleeping Beauty
VSV	Vesicular stomatitis virus
X-SCID	X-linked severe combined immunodeficiency

1 Introduction

The National Institutes of Health (NIH) seeks to foster safe, scientifically sound, and ethical clinical gene transfer research through public discussion of novel human gene transfer research protocols and emerging scientific data. Responsibility for this NIH oversight activity lies with the Office of Biotechnology Activities (NIH OBA) in the Office of Science Policy, Office of the Director, NIH. The NIH OBA carries out this function in consultation with the NIH Recombinant DNA Advisory Committee (RAC). The definition of a human gene transfer trial is one in which there is deliberate transfer of recombinant or certain synthetic nucleic acid molecules, or nucleic acid molecules derived therefrom, to one or more research participants. Clinical gene transfer research is subject to NIH oversight both in the USA and internationally if it is funded by NIH. In addition, clinical gene transfer trials that are conducted at a US

institution that receives NIH funding, such as an academic medical center, are also subject to this oversight even if the clinical trial is not funded by NIH. Since most gene transfer clinical trials include academic medical centers as trial sites, the majority of clinical trials conducted in the USA are registered with NIH OBA.

The NIH review process allows for an in-depth examination of the issues associated with this technology in a setting where public input and comment are encouraged. This open discussion has two important benefits. First, it disseminates this information to scientists, who can then incorporate new scientific findings and ethical considerations into the design of trials they are conducting and/or planning. As a result, the efficiency of the research system is improved by allowing scientists to build on a common foundation of new knowledge emanating from this ongoing process of analysis and assessment. Second, it enhances public awareness of the field and allows for a public forum for the review of the safety and ethics of gene transfer research.

The public discussions of the RAC about human gene transfer research help assure the public that scientists are attending to these important matters and sustain confidence in the research. Finally, as a major funder of human gene transfer research and the basic science that underpins it, NIH has an important responsibility to maintain appropriate stewardship of this area of scientific activity.

The framework for NIH OBA's responsibilities in this area is contained in the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*) [1]. Compliance with the *NIH Guidelines* is a term and condition of NIH funding for research in this area; failure to comply with the *NIH Guidelines* can result in termination of funding. Despite the fact that NIH grantees are required to comply with the *NIH Guidelines*, the guidelines are not considered regulations. This legal distinction between regulations and guidelines allows greater flexibility in their evolution. In the 40 years since the *NIH Guidelines* were written, they have been amended many times in order to remain responsive to the scientific progress in the field. The role of NIH in oversight of human gene transfer has also evolved.

2 Origins and History of the NIH Oversight System

The current NIH system of oversight of recombinant or synthetic nucleic acid research, including human gene transfer research, has its origins in the mid-1970s with the advent of recombinant DNA technology and concerns about the safety of this research and the potential impact on public health [2]. In 1974, in response to the growing scientific and public concerns over recombinant DNA technology, the Department of Health Education and Welfare (now the Department of Health and Human Services (HHS)) established the NIH RAC, a federal advisory committee, to provide advice on matters related to the conduct and oversight of research involving recombinant DNA.

The RAC's first task was the development of the *NIH Guidelines*, which were first published in the Federal Register on July 7, 1976 [3], and contained the principles of risk assessment, safety practices, and containment procedures for research

involving recombinant DNA. The *NIH Guidelines* also define the responsibilities of NIH, the RAC, investigators, and institutions. Under the *NIH Guidelines*, the RAC is responsible for providing recommendations to the NIH Director regarding the content and implementation of the *NIH Guidelines*. Prior to the creation of the *NIH Guidelines*, Congress and local governments were considering the development of regulations or local ordinances to restrict recombinant DNA research.

During the early 1980s, in anticipation of the scientific, safety, and ethical issues that would arise when genetic engineering extended into humans, a presidential commission established to examine these issues published the report, *Splicing Life* [4]. In response to recommendations from that Commission and from subsequent congressional hearings [5], in 1983, the RAC's responsibilities were broadened to include oversight of clinical gene transfer research, including consideration of ethical issues. Under the *NIH Guidelines*, human gene transfer research is defined as the deliberate transfer of recombinant and/or certain synthetic nucleic acid molecules to humans. The Human Gene Therapy Subcommittee of the RAC was established and developed a document outlining the process for review of human gene transfer protocols. This document, entitled "Points to Consider in the Design and Submission of Somatic Cell Human Gene Therapy Protocols," would become part of the *NIH Guidelines* with the introduction of Appendix M in 1986. Under this process, the first human gene transfer protocol began its review in 1988, and the first clinical trial of human gene transfer for adenosine deaminase deficiency was initiated in 1990.

Through the mid-1990s, the NIH Director approved each gene transfer trial after receiving a recommendation from the RAC. Therefore, protocols subject to the *NIH Guidelines* could not proceed without obtaining NIH Director approval in addition to other regulatory approvals that were, and are, still required today. NIH review of new gene transfer protocols (from initial submission to NIH Director approval) often took up to 9 months or more.

In 1995, NIH commissioned two studies by outside experts to examine the field of gene transfer and the role of the RAC. Two reports were produced: one assessed NIH's investment in the field of human gene transfer (Orkin–Motulsky Report) [6] and the other assessed the role of the RAC in the NIH review process (Verma Report) [7]. The report assessing NIH investment concluded that the NIH investment in gene transfer research should continue, the promise of gene transfer should not be oversold, and that a sound and solid scientific foundation was needed in order for the field to advance. The second report recommended that the RAC no longer carry out case-by-case review of all human gene transfer trials; rather, it should focus on those trials that contain novel applications and unresolved issues.

As a result of these reports, the RAC's role evolved. The RAC today consists of up to 21 voting members, the majority of which are knowledgeable in relevant scientific fields (e.g., molecular biology, microbiology, recombinant DNA research, including clinical gene transfer research). In addition, at least four members of the Committee are knowledgeable in fields such as public health, laboratory safety, and occupational health, protection of human research participants, the environment, ethics, law, public attitudes, or related fields. The meetings of the RAC provide a public forum for discussion and analysis of scientific, clinical, biosafety, and ethical

policy issues that arise in the field; however, the NIH Director no longer seeks a recommendation from the RAC to approve or disapprove a protocol.

Individual RAC members review all new gene transfer protocols that are registered with NIH OBA and make a recommendation to NIH regarding the necessity for in-depth review of individual protocols at quarterly public meetings. When a protocol is subject to an in-depth review at a public meeting, the Committee often develops one or more recommendations on how to improve the design of the protocol. These recommendations are communicated by NIH OBA to the Principal Investigator(s) (PI(s)) and/or sponsor and are also shared with the Food and Drug Administration (FDA) and the institutional bodies responsible for approving the protocol—the Institutional Review Board (IRB) and the Institutional Biosafety Committee (IBC). These institutional bodies may require the clinical protocol to be changed in response to the RAC recommendations, but the RAC recommendations are not binding. At the federal level, the regulatory authority to allow a gene transfer clinical trial to proceed resides with the FDA; the RAC neither approves nor disapproves a protocol.

3 Elements of the NIH System of Oversight Today

As stated above, the *NIH Guidelines* are not regulations, but compliance is a term and condition for NIH funding of certain recombinant or synthetic nucleic acid research. The *NIH Guidelines* apply to all such research conducted at, or sponsored by, an institution that receives any support for recombinant or synthetic nucleic acid research from NIH. Therefore, even if an individual gene transfer trial is not funded by NIH, if it is conducted at a US institution or is sponsored by an entity that receives such funding, it must be registered with NIH OBA and comply with the other requirements of the *NIH Guidelines*.[1] In addition, an investigator or sponsor can voluntarily submit the protocol for review or another federal agency may require that studies supported by that agency follow the *NIH Guidelines*, including registration of the clinical trial with NIH OBA.

In addition to NIH's role, at the federal level, there is regulatory oversight by the FDA and the Office for Human Research Protections (OHRP).[2] At the local level, there will be reviews by an IRB. In addition, a unique oversight body for gene transfer clinical trials is the IBC. Once an institution receives NIH funding for recombinant or synthetic nucleic acid research that is subject to the *NIH Guidelines*, it must

[1] Trials conducted abroad are subject to the *NIH Guidelines* if the investigational agent was developed with NIH funds and the institution that developed the investigational materials sponsors or participates in these projects.

[2] OHRP is a part of the US Department of Health and Human Services (HHS) and provides leadership in the protection of the rights, welfare, and well-being of subjects involved in research conducted or supported by HHS. Additional information regarding OHRP may be found at this URL: http://www.hhs.gov/ohrp/index.html

establish an IBC.[3] The *NIH Guidelines* set the requirements for the establishment of an IBC, which must be comprised of no fewer than five members with appropriate expertise to review the research being conducted and to identify any potential risk to public health (including both researchers and clinical trial participants) or the environment. At least two members of the IBC shall not be affiliated with the institution (apart from their membership on the IBC) and are selected to represent the interest of the surrounding community with respect to health and protection of the environment (e.g., officials of state or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community). The IBC must review and approve all human gene transfer protocols before they commence. While the main focus of this review is the biosafety aspects of these protocols, the IBC is also responsible for ensuring that any recommendations made by NIH regarding the individual protocol (i.e., recommendations that arise from the RAC review of a protocol) are addressed.

Final IBC approval of a human gene transfer protocol may not be given until the protocol has completed the RAC review process. For protocols that do not undergo public review, the RAC review process is complete upon receipt of the letter from NIH OBA, informing the investigator that the protocol does not require in-depth public review at a quarterly RAC meeting. For those protocols that undergo RAC review, the process is complete when the final letter from NIH OBA outlining any recommendations made during that meeting is received by the IBC. This happens within 10 working days after a meeting of the RAC. Therefore, a gene transfer protocol that is subject to the *NIH Guidelines* will require RAC review, FDA approval, IRB review, and IBC review. In terms of the timing of those reviews, the only requirement under the *NIH Guidelines* is that the IBC must wait until the RAC review process is complete before allowing a protocol to move forward. The FDA and IRB can approve a protocol at any time and do not need to wait for the RAC review process to be completed. In practice, most investigators will submit their protocol to NIH OBA and complete the RAC review process before they have final FDA or IRB review.

The NIH OBA coordinates the RAC review of human gene transfer protocols. As summarized in more detail below, new protocols are registered with NIH OBA, which coordinates the initial review of these protocols by each individual RAC member, providing not only the protocol documents but relevant information on previous related clinical protocols and any relevant data from adverse event reports submitted on related trials. The NIH OBA organizes the quarterly meetings at which novel human gene transfer protocols are reviewed, and any recommendations made by the RAC regarding individual protocols are considered by NIH OBA. If accepted, the RAC recommendations are then transmitted to the PI(s), as well as the relevant

[3] Although establishment of an IBC for review of gene transfer and other research is a requirement of NIH funding, other US government agencies that do not receive NIH funding, such as the Department of Veterans Affairs and Department of Defense, certain private institutions, and companies (which also do not receive NIH funding) require that their research be conducted in accordance with the *NIH Guidelines*, including the establishment of an IBC for review and approval of human gene transfer trials.

regulatory and oversight bodies (IBC, IRB, and FDA), that will review and approve the protocol. The NIH OBA is also responsible for reviewing safety (both clinical and relevant preclinical, as well as biosafety) data and other types of data, such as changes to trial design and annual reports submitted on ongoing protocols. The NIH OBA works with the RAC in developing timely conferences, symposia, workshops, and other materials that facilitate the growth of the field and public access to data and information that can further enhance the development of new avenues of research.

4 Overview of RAC Review and Reporting Process

4.1 RAC Review Process

To date, over 1400 protocols have been submitted to and registered with OBA. As a result of the NIH OBA registration and RAC review process, the gene transfer field and the public have benefited from access to data across active trials and the analysis of this data provided by the RAC and NIH OBA. The human gene transfer field is diverse with the use of multiple gene delivery systems, clinical applications, and phases of trials (Fig. 1a–d).

Appendix M-1-A of the *NIH Guidelines* specifies the requirements for clinical protocol submission and review and reporting of data on ongoing gene transfer clinical trials that are subject to the *NIH Guidelines*. Investigators must submit to NIH OBA the required documents, including the clinical protocol, the informed consent document, and responses to questions in Appendices M-II through M-V of the *NIH Guidelines*. Based on this information, the RAC members conduct an initial review to determine whether a protocol presents characteristics that warrant public RAC review and discussion. The subset of protocols selected for in-depth review and public discussion may involve the use of a new vector system, transgene, clinical application, or novel, ethical, legal, or social issues. From 2012 to 2014, on average, 20 % of protocols submitted to NIH OBA were publicly reviewed by the RAC.

The initial RAC review process must be completed within 15 days following the submission of a protocol to NIH OBA. Public RAC review and discussion of a human gene transfer study may be initiated by the NIH Director; the NIH OBA Director, following a recommendation to NIH OBA by at least three RAC members; or a federal agency other than NIH. Although the *NIH Guidelines* require that at least three members recommend review, in the past few years, it has been NIH OBA's policy to require that at least five RAC members recommend review prior to taking a protocol to public review and discussion. Investigators, oversight bodies, and members of the public may request specific information on each individual member's recommendation. At the end of the 15-day period, NIH OBA informs the PI(s) whether public review is required; if not, the RAC review process is deemed complete.

Protocols selected for in-depth review will be publicly discussed at a RAC meeting, which is held quarterly. These meetings provide a forum for the discussion of the novel scientific, clinical, or ethical issues associated with the protocol under review. The meetings are open to the public, and NIH OBA provides a simultaneous

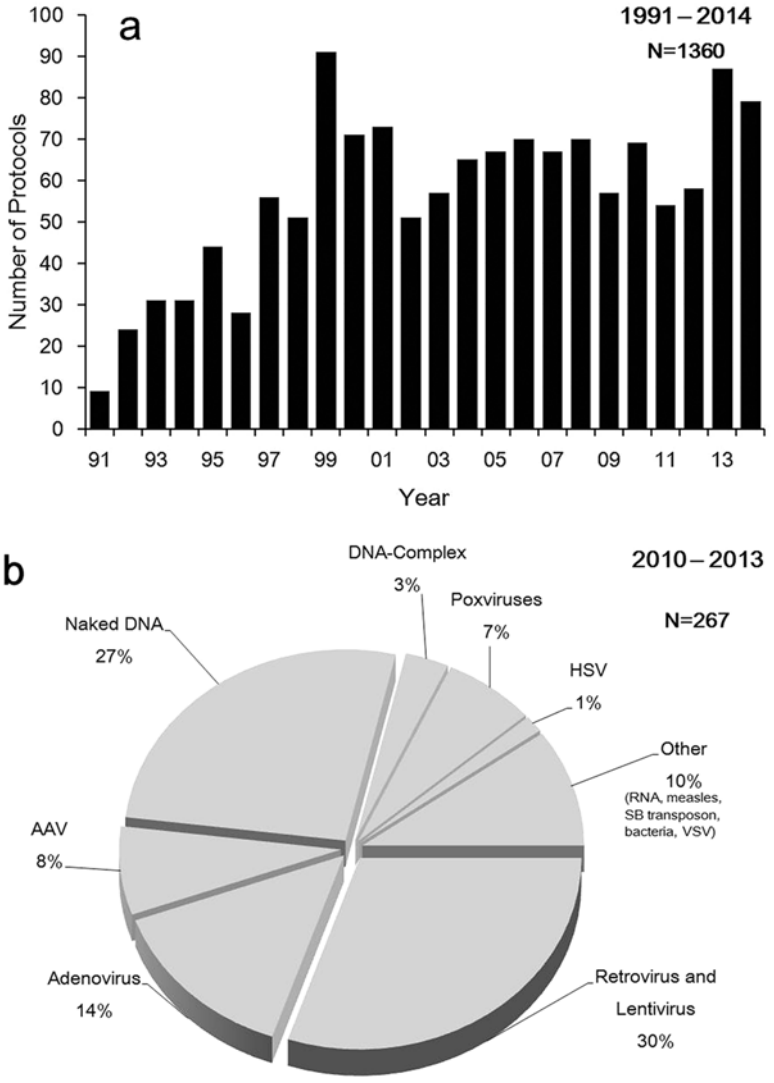

Fig. 1 Human gene transfer clinical trial trends. Panel **a**: Number of human gene transfer protocols registered with NIH OBA per year from 1991 to 2014. The total number of protocols registered in the 24-year period shown was 1360. In the last 10 years, NIH has registered on average 68 human gene transfer clinical trials per year. Panel **b**: Recent vector usage trends in human gene transfer clinical trials. The percentages reported refer to the fraction of protocols using one or more of the indicated vectors. Vectors may be administered either directly (in vivo) or indirectly (ex vivo). The category "DNA-Complex" includes liposomes and other complexes (e.g., DNA-Lysine). The category "Other" refers to less commonly used vector systems, examples of which are provided. Panel **c**: Major disease indications targeted in human gene transfer trials in recent years. Panel **d**: Snapshot of human gene transfer trials categorized by the phase of development. Phase designation as shown in this figure is that designated by the investigator or sponsor of a clinical trial. This does not necessarily correspond to a specific stage of pre-marketing development accepted by the FDA. Trials designated as "I–II" by the investigator or sponsor are listed as Phase I and those listed as "II–III" are categorized as Phase II in this figure

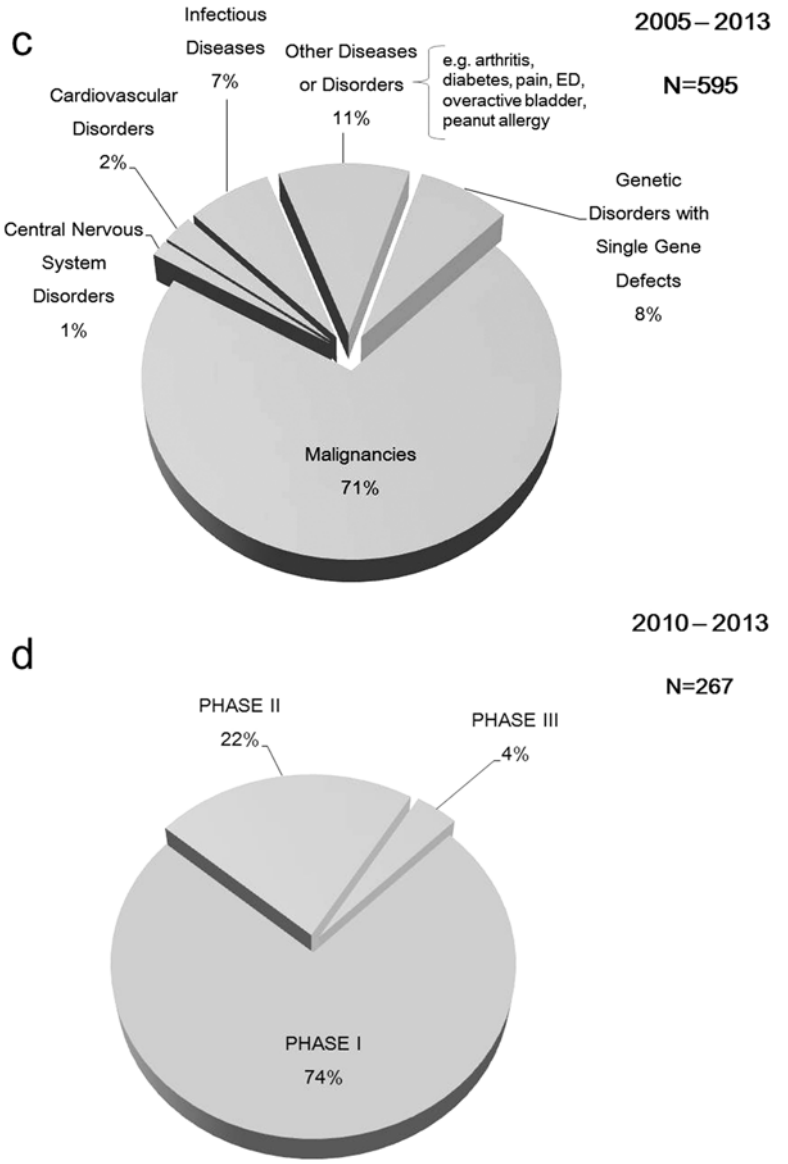

Fig. 1 (continued)

webcast, which is archived and available on the NIH OBA website [8]. At the meeting, the investigator presents the details of the clinical protocol, and the RAC members ask questions and may recommend certain changes to the protocol design or that the investigator obtain further data to support the protocol.

Protocols that are submitted to NIH OBA at least 8 weeks prior to a RAC meeting and are selected for public review are reviewed at the next quarterly RAC meeting. This time interval allows sufficient time for the primary RAC reviewers to conduct

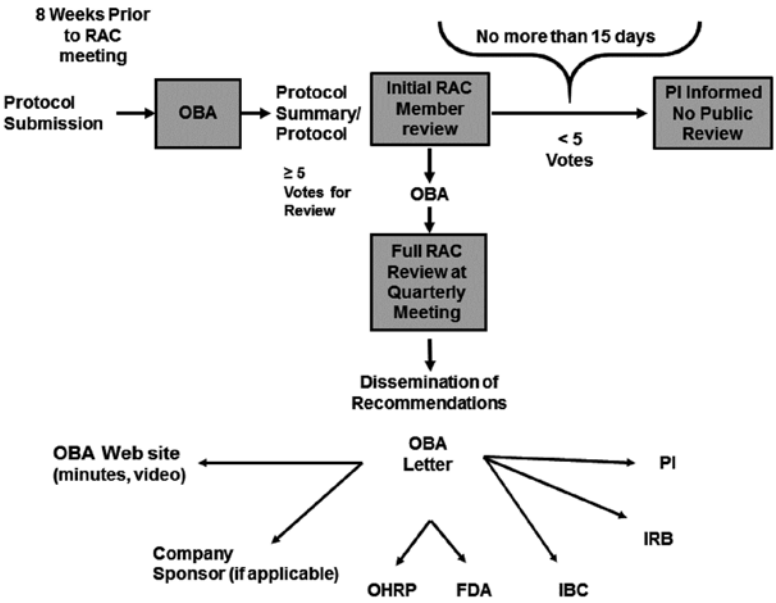

Fig. 2 Schematic overview of the current NIH Recombinant DNA Advisory Committee (RAC) review process. Clinical gene transfer protocols that are submitted to the Office of Biotechnology Activities (NIH OBA) at least 8 weeks prior to a scheduled quarterly meeting of the Committee will be eligible for review (if selected) at that upcoming meeting. The protocol is summarized by NIH OBA staff, and both the protocol and summary are made available to all RAC members to obtain a recommendation as to whether further review of a particular protocol is warranted. This recommendation must be made within 15 days. If five or more members of the RAC recommend that additional discussion is required, the RAC reviews the selected protocol at the next upcoming meeting. Upon completion of the in-depth review (discussed publicly), written RAC recommendations are made available to federal oversight agencies (Office of Human Research Protection [OHRP] and Food and Drug Administration [FDA]), to local oversight committees (Institutional Review Board [IRB] and Institutional Biosafety Committee [IBC]), and to the sponsor and/or the Principal Investigator (PI). Proceedings of the RAC meeting are webcast and archived on the NIH OBA website, as are the meeting minutes and briefing materials. If less than five RAC members recommend an in-depth review and discussion, the initial review process is complete, no public discussion is warranted, and the sponsor and/or PI (if applicable) is informed of this outcome, as are the IBC and IRB

their review and for the investigators to submit a written response to the reviews prior to the public meeting. These written reviews and responses are summarized in the meeting minutes and are publicly available with the meeting materials. Within 10 working days after the RAC meeting, NIH OBA will send a letter summarizing the recommendations of the RAC to the PI(s), the relevant IBC and IRB, the OHRP, the FDA, and, if relevant, the sponsor (Fig. 2).

The RAC recommendations inform the investigators of ways to improve their clinical trial design and assist the oversight bodies in their reviews. Therefore, although protocols may be submitted for RAC review at any time in the protocol development process, the greatest value from RAC review is obtained when the protocol is submitted relatively early in the process. Investigators are encouraged to

Table 1 NIH OBA resources

• *Genetic Modification Clinical Research Information System (GeMCRIS)* (http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/gemcris)
– Information resource and analytical tool that allows public users to access basic reports about gene transfer trials and develop specific queries (e.g., vector, transgene, medical condition)
• *Gene Transfer Safety Assessment Board (GTSAB)*
– A working group of the RAC that identifies and analyzes significant safety events or trends and reports to the RAC
• *Guidance and Frequently Asked Questions (FAQs) for Human Gene Transfer Research*
– Human gene transfer guidance for PIs and research participants (http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/guidance)
– Informed Consent (http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/guidance/web-based-informed-consent-guidance)
– Biosafety Guidance for Lentiviral Vectors (http://osp.od.nih.gov/office-biotechnology-activities/biosafety/biosafety-guidance)
• *Safety Symposia, Policy Conferences, and Workshops* (http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/policy-conferences)

submit their protocols well in advance of the submission of the required Investigational New Drug (IND) application to the FDA. Often, investigators will submit their documents to NIH OBA after they have had an informal interaction (termed a pre-IND meeting) with the FDA, at which time the clinical protocol is not final. This allows the investigator to incorporate any changes recommended by the RAC before submitting the clinical protocol in the IND submission that FDA will review.

A frequently asked question is how the role of the NIH, including the RAC, differs from that of the FDA, which has regulatory authority over human gene transfer trials. Certainly, the two agencies share common concerns when reviewing any human gene transfer trial, notably its safety. The RAC will also often take a more forward-looking approach, challenging the investigator to plan for the next stage of product development and whether the initial clinical trial, as designed, can help answer relevant questions necessary to continue clinical development of the particular agent. The RAC includes expertise from the biosafety community and addresses biosafety concerns relating to the administration of certain human gene transfer products, including the safety of the research subjects and the health-care workers involved in the trial, as well as the public. An in-depth review of the ethical issues raised by the clinical trial design and the adequacies of the informed consent are also critical parts of the RAC's review. In fact, the RAC review of many informed consent documents led to the development of the *NIH Guidance on Informed Consent for Gene Transfer Trials* that is available to all researchers (Table 1). The RAC does not focus on the manufacturing of the product, a key component of the FDA regulatory review. Finally, the RAC process is unique in the transparent nature of its review process. All proceedings are public and the webcast, minutes, and all presentations are available to investigators and the public through the NIH OBA website. Investigators are able to benefit from the reviews of other gene transfer protocols and to understand emerging trends in trial design. These discussions inform the deliberations of the FDA, the OHRP, IRBs, and IBCs.

4.2 Reporting Requirements

NIH oversight also includes an ongoing reporting component, which has resulted in the accrual of crucial data spanning the inception of the gene transfer field to the present and covering a diverse breadth of clinical trials and safety data. Appendix M-1-C of the *NIH Guidelines* specifies the reporting requirements for information to be submitted to NIH OBA at the time of trial initiation (no later than 20 working days after enrollment of the first research participant). This information should include copies of the IBC and IRB approvals and the approved versions of the protocol and informed consent document. If the protocol was publicly reviewed by the RAC, the submitted information should also include how the investigators responded to each of the RAC's recommendations. These responses are briefly reviewed at each RAC meeting, and a list of protocols initiated during the quarter is publicly available with the RAC meeting materials on the NIH OBA website.

Annual reports must be submitted to NIH OBA within 60 days of the anniversary of the date that FDA allowed the IND to proceed and on each subsequent anniversary until trial completion. An annual report should include clinical trial information in the form of a brief summary of the status of the trial. The PI(s) must also submit a progress report and data analysis of serious adverse events (SAEs) and a copy of the updated protocol.

With regard to clinical safety reporting, since 2001, the requirements for the timing of reporting of SAEs to NIH OBA have been harmonized with those of the FDA (66 Fed. Reg. 57970) [9]. Any SAE that is unexpected and possibly associated with the use of a gene transfer product must be reported to NIH OBA as soon as possible, but no later than 7 calendar days after the IND sponsor's initial receipt of the information if the SAE is fatal or life threatening and no later than 15 days if it is not. Any additional clinical or laboratory data that becomes available after the initial report must be reported within 15 days of receipt by the IND sponsor.

The SAE reports may be submitted directly using the NIH Genetic Modification Clinical Research Information System (GeMCRIS®) (Table 1). As discussed in Sect. 5 below, GeMCRIS was developed by NIH in collaboration with FDA, and certain information is available to the public. Electronic reports to GeMCRIS can be printed out and then submitted to the FDA, as the elements contained in a GeMCRIS report satisfy the FDA requirements for an SAE report. Paper reports can also be sent using the Adverse Event Reporting Template available on the NIH OBA website [10], the FDA MedWatch form [11], or other means, provided the report includes all of the elements in Appendix M-I-C-4 of the *NIH Guidelines*.

At the same time that the reporting requirements were harmonized, NIH also established a working group of the RAC, the Gene Transfer Safety Assessment Board (GTSAB). The GTSAB meets quarterly in advance of the RAC meetings to review, in closed session, SAE reports, annual reports, and other relevant safety information across gene transfer trials and to identify any significant individual events that might warrant additional discussion or trends across protocols. The GTSAB enhances the ability of NIH OBA to recognize issues that may have important implications for

human gene transfer research. The FDA staff is invited to attend these meetings. Data reviewed during these meetings may lead to discussions of individual SAEs or protocols at subsequent RAC meetings or be the impetus for development of symposia that focus on specific areas of gene transfer. In addition, public summaries of protocol amendments and annual reports are available on GeMCRIS. Public summaries of SAEs are available with the proceedings for each RAC meeting on the NIH OBA website [8]. Public summaries of safety data are being made available in GeMCRIS, making it easier for the public to review selected safety data on a particular protocol.

5 Gene Transfer Resources for Researchers and the Public

The information and analyses made possible by the RAC review, protocol submission, and SAE reporting to NIH OBA provide the public and scientific community access to many resources (Table 1) that are not readily available to other biomedical fields.

As mentioned in Sect. 4 above, GeMCRIS was developed through collaboration between NIH and FDA. GeMCRIS is a comprehensive and interactive database that functions as a public information resource, a system for reporting SAEs, and a tool for NIH and FDA to analyze trends and safety data across gene transfer trials. Investigators, research participants, oversight bodies, and the public can use GeMCRIS to access information about human gene transfer trials by searching on a particular PI or institution, disease indication, vector, transgene, route of administration, or phase of the study. Investigators and sponsors of human gene transfer trials can utilize this system to submit SAEs and annual reports. A common theme in recent discussions among participants at RAC and NIH OBA workshops has been the need for greater opportunities and means to foster sharing of data across the field. GeMCRIS can facilitate this by allowing for the identification of other trials using similar approaches, often in advance of the trial beginning enrollment. This may create opportunities for sharing of preclinical data in a precompetitive space (e.g., sharing of preclinical vector biodistribution data for a letter of cross-reference to the FDA).

To provide additional resources for researchers, the public and potential research participants, NIH OBA, and the RAC have developed many guidance documents, frequently asked questions (FAQs), and brochures, most of which are available on the NIH OBA website (Table 1). Among the available educational materials is a brochure that provides individuals interested in participating in gene transfer clinical trials with a background on gene transfer and a list of questions to ask one's health-care provider or the research team [12]. For investigators, there are FAQs regarding the protocol review process and one explaining that certain research involving vaccines to microbial immunogens are exempt from the requirements of Appendix M of the *NIH Guidelines* [13]. Biosafety guidance documents relevant to gene transfer vectors are also available, such as the guidance on the biosafety considerations of research with lentiviral vectors (Table 1).

As part of its charge to consider the ethical issues related to gene transfer, the RAC, along with NIH OBA, has focused on providing assistance to investigators in the development of informed consent documents and processes. Appendix M-III of the *NIH Guidelines* includes points to consider related to informed consent, including those unique to gene transfer (e.g., novelty of procedures, potentially irreversible consequences of gene transfer, undefined risks, etc.), as well as issues common to all clinical studies. The requirements of Appendix M-III are intended to be consistent with other federal regulations for the protection of human subjects and complementary to other guidance from OHRP and FDA.

In 2002, as a supplement to Appendix M-III, a working group of the RAC, composed of RAC members, representatives from FDA and OHRP, and outside experts, developed an informed consent guidance (Table 1). This guidance is intended to provide information useful to investigators and sponsors preparing informed consent documents, IBCs and IRBs reviewing protocols and consent forms, and potential research participants deciding whether to enroll in gene transfer trials. The guidance document aligns with the sections of Appendix M-III and discusses the main points of each section; provides sample language that could be used as a model for inclusion in consent forms, while also pointing out language that should not be included; and provides tools and background materials.

In order to inform the scientific community and public on issues arising in the gene transfer field, NIH OBA, often in conjunction with the RAC or collaboration with other federal agencies such as the FDA, Centers for Disease Control and Prevention, or United States Department of Agriculture, convenes scientific symposia and policy conferences to discuss responses to SAEs, emerging technologies, trial design, or ethical issues. The safety symposia are forums for expert review and public discussion of emerging scientific, medical, ethical, and safety issues in gene transfer clinical research. The exchange of information and in-depth discussions are intended to increase understanding of the specific approaches or vectors used in gene transfer clinical trials, maximize the safety of research participants, enhance the development of gene transfer clinical trials, and optimize informed consent processes. The NIH OBA meetings provide a public forum for these discussions, which are informed by the AE reports to NIH OBA and the cross-trial analysis facilitated by the results of GeMCRIS queries by NIH OBA.

For example, in response to reports of leukemia in research participants [14] in two clinical trials for X-linked severe combined immunodeficiency disease (X-SCID), NIH OBA and the RAC convened a series of safety symposia in 2002, 2003, 2005, 2007, and 2008, to review the clinical and molecular data, the causative mechanism of retroviral vector insertional mutagenesis, and the risk/benefit analysis of gene transfer compared to alternative treatments [15]. These discussions resulted in RAC recommendations regarding future X-SCID gene transfer trials. These recommendations were revisited and revised as new data became available. To inform all trials involving the transduction of hematopoietic stem cells by retroviral vectors, the broader topic of the clinical challenges in retroviral and lentiviral vector and trial design was explored in a subsequent symposium in 2010 [16].

A safety symposium discussing immune responses to adeno-associated virus (AAV) vectors in 2007 proved crucial later that same year in informing the RAC's

evaluation of the role of gene transfer in the death of a research participant following administration of an AAV vector in an arthritis trial (OBA Protocol 705) [15]. Two recent symposia, in 2010 and 2013, focused on optimizing trial design for T-cell immunotherapies [17, 18]. Safety symposia need not always be convened in response to events that occur in clinical or preclinical studies. Several symposia were organized to explore potential safety issues related to novel vector systems, such as lentiviral vectors in 2010 and internally deleted, helper-dependent adenoviral vectors in 2000 [15].

In addition to scientific symposia, policy conferences often provide overviews of emerging technologies, such as RNA oligonucleotides, genomic editing, and synthetic biology, and their applications to clinical approaches with the goal of defining strategies to enhance development of the field.

6 Future Directions

The field of gene transfer has continued to mature, as has our understanding of these products. In addition, FDA has acquired considerable experience in the review of new products. Upon the urging of a body of gene transfer investigators, led by the American Society of Gene and Cell Therapy, the NIH Director commissioned a study by the Institute of Medicine (IOM) to provide an independent review and assessment of select activities of the RAC. Specifically, an ad hoc Committee of the IOM was asked to "determine if gene transfer research raises issues of concern that warrant extra oversight by the RAC of individual clinical trial protocols involving gene transfer techniques" (IOM Report) [19]. If the committee determined that RAC oversight was still warranted, it was asked to recommend what criteria should guide selection of protocols for RAC review. On December 5, 2013, the IOM Committee issued its report. While affirming the value of many of the RAC's activities in developing scientific symposiums and the availability of GeMCRIS, the IOM Committee concluded that "not all gene transfer research is novel enough or controversial enough to justify all the current forms of additional oversight" (IOM Report). Therefore, it recommended that *while all individual protocols should continue to be registered with NIH*, these protocols should not be subject to public review by the RAC "*except in exceptional circumstances*, such as when novel gene therapy techniques and treatment strategies move into the realm of clinical trials" (IOM Report).

The IOM Committee recommended that protocols be selected for additional public review only if both items 1 and 2 below are satisfied:

"1. Protocol review could not be adequately performed by other regulatory and oversight processes (e.g., IRBs, IBCs, the US Food and Drug Administration).
2. One or more of the criteria below are satisfied:

   - The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.
   - The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.

- The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously.

Even if the protocol does not meet the foregoing criteria listed in items 1 and 2, the NIH Director, in consultation with appropriate regulatory and/or oversight authorities, should have the flexibility to select protocols for review that may present significant societal or ethical concerns" (IOM Report).

On May 22, 2014, Dr. Francis Collins, NIH Director, announced that he accepted the recommendations of the IOM Committee. A proposal to implement the IOM recommendations was presented to the RAC by the Director of NIH OBA on June 11, 2014. This proposal recommended working with institutional oversight committees, such as IRBs and IBCs, to determine if a protocol should be reviewed by the RAC, provided the protocol meets criterion (2) above. The RAC members would no longer make a recommendation with respect to the necessity of in-depth public review of submitted clinical protocols. To implement these changes, NIH will need to amend the *NIH Guidelines*. A notice of this change will be published in the Federal Register, and there will be opportunity for public comment prior to final implementation.

7 Conclusion

Since the early 1990s, which marked the beginning of gene transfer clinical research, the NIH RAC has provided a public forum for in-depth discussion of the science and ethics of this field. The data that are made available through this oversight process have enabled gene transfer investigators to operate in a precompetitive space and likely facilitated the translation of this field into one that is on the cusp of entering medical practice. This transparent forum has also provided the public confidence that any potential risks that might be unique to gene transfer, for example, horizontal shedding of viral or bacterial vectors, were thoughtfully addressed by the field. As the field has matured, the need for review of individual protocols has declined and the RAC will now transition to a new role where individual protocol review will be limited to the few, very novel protocols for which oversight bodies need additional assistance. The focus will be on using the data and resources available through ongoing reporting to identify and explore issues that are of interest to the field as a whole.

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Regulatory Oversight of Cell and Gene Therapy Products in Canada

Anthony Ridgway, Francisca Agbanyo, Jian Wang, and Michael Rosu-Myles

Abstract Health Canada regulates gene therapy products and many cell therapy products as biological drugs under the Canadian *Food and Drugs Act* and its attendant regulations. Cellular products that meet certain criteria, including minimal manipulation and homologous use, may be subjected to a standards-based approach under the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*. The manufacture and clinical testing of cell and gene therapy products (CGTPs) presents many challenges beyond those for protein biologics. Cells cannot be subjected to pathogen removal or inactivation procedures and must frequently be administered shortly after final formulation. Viral vector design and manufacturing control are critically important to overall product quality and linked to safety and efficacy in patients through concerns such as replication competence, vector integration, and vector shedding. In addition, for many CGTPs, the value of nonclinical studies is largely limited to providing proof of concept, and the first meaningful data relating to appropriate dosing, safety parameters, and validity of surrogate or true determinants of efficacy must come from carefully designed clinical trials in patients. Addressing these numerous challenges requires application of various risk mitigation

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strategies and meeting regulatory expectations specifically adapted to the product types. Regulatory cooperation and harmonisation at an international level are essential for progress in the development and commercialisation of these products. However, particularly in the area of cell therapy, new regulatory paradigms may be needed to harness the benefits of clinical progress in situations where the resources and motivation to pursue a typical drug product approval pathway may be lacking.

Keywords Health Canada • Regulation of cell therapy • Regulation of gene therapy • Safety of Human Cells, Tissues and Organs for Transplantation Regulations • CTO Regulations • More than minimally manipulated

1 Introduction

Cell and gene therapy products (CGTPs) offer the prospect of improved treatments, and potential cures, for currently intractable diseases and conditions and have therefore attracted much public interest and hopeful expectation. At the same time, these products and aspects of their use involve new and exploratory techniques and potential risks to patients. An appropriate regulatory framework must provide clear pathways to investigational scientists in industry and academia with informational requirements that address the risks associated with products and procedures without serving as an impediment to innovation and product development.

Canada has a dynamic medical research community and a high-quality healthcare system that is advantageous for drug development despite accounting for a relatively small proportion of world drug sales. Since the first Canadian gene therapy clinical trial in 1994, there have been close to 100 clinical protocols approved. The marketing approval granted to Glybera (alipogene tiparvovec) in the European Union (EU), for the treatment of monogenic lipoprotein lipase deficiency (LPLD), has a Canadian connection in that two of three interventional clinical trials (that provided 19 of the 27 patients) were conducted in Canada by Dr. Daniel Gaudet and collaborators drawing on a LPLD "founder population" in Eastern Québec [1–3]. The connection extends much earlier and more broadly through the work of Dr. Michael Hayden's research group at the University of British Columbia [4].

The Canadian cellular therapy research community has also been active for many years and should be significantly advantaged by the recent addition of CellCAN, a new Network of Centres of Excellence (NCE) that will bring together the efforts of many stakeholders in stem cell research and promote cooperation, partnership development and innovation in regenerative medicine and cell therapy. The NCE operates a suite of national funding programmes on behalf of the three federal granting agencies, the National Science and Engineering Research Council (NSERC), the Canadian Institutes of Health Research (CIHR) and the Social Sciences and Humanities Research Council (SSHRC), in partnership with Industry Canada and Health Canada. Seven main organisations are at the heart of the new network which will standardise practices and promote innovative treatments for various diseases such as diabetes, cardiovascular disease and cancer.

Canada became the first country to grant marketing approval to a stem cell therapy product with the issue of a Notice of Compliance with conditions (NOC/c) for Prochymal (remestemcel-L) in May, 2012. Prochymal is a population of adult mesenchymal stem cells for intravenous infusion in the management of acute graft-versus-host disease and has since been approved in other regulatory jurisdictions.

In the following sections, this chapter will address the regulatory framework and applicable pathways for CGTPs in Canada and will provide an overview of some of the regulatory expectations for these classes of products. The applicability of Canadian, international, pharmacopoeial and various non-Canadian guidance documents will be discussed.

2 Regulatory Framework

Canadian regulatory frameworks are comprised of various elements: (1) statutes, or Acts, provide scope, high-level principles and the legal authority to make regulations; (2) regulations interpret an Act and provide general details on what must be done; (3) guidelines interpret and provide details of how to meet the regulations (being faster and simpler to introduce (not legally binding), they allow flexibility and adaptation to change); and (4) policies clarify and/or modify the intent of regulations (they usually relax or simplify, providing a "quick fix" pending re-drafting). All elements play a role in the regulation of CGTPs.

At present, there is no formal Canadian regulatory definition of either gene therapy or cell therapy; and these products are not specifically listed on *Schedule D* to the *Food and Drugs Act* (*F&D Act*) [5] which identifies biological drugs (or biologics) and which brings to bear a specific set of regulations under *Part C*, *Division 4* of the *Food and Drug Regulations* (*F&D Regulations*) [6]. Nevertheless, some of these products are captured by one or more class listings on *Schedule D* and so, logically, and in step with other regulatory jurisdictions, gene therapy products (GTPs) and many cell therapy products (CTPs) are regulated as biologics. Confirming the status of these products as biologics will be addressed by changes to *Schedule D*, or by other means, as part of ongoing regulatory modernisation.

Despite the lack of a formal definition, the transfer and expression of an exogenous gene typically associated with compensating for a missing or non-functioning endogenous gene has enduringly been identified as gene therapy. In addition, various other approaches to intervention are considered to be gene therapy by Health Canada, including (1) if nucleic acid (DNA or RNA) is transduced by viral vector or other means (directly in vivo, or into cells ex vivo followed by administration) and subsequently expressed (transcribed or translated) into messenger RNA, protein or "regulatory" RNA (e.g. small interfering RNA (siRNA)); (2) if cells intended for treatment are modified using various approaches to the introduction of site-directed mutations (for gene repair or modification of gene expression without actual gene transfer); and (3) the use of oncolytic viruses to treat cancer. In contrast, direct treatment with synthetic, regulatory RNAs, or with proteins that bind DNA (in a typical

drug approach), or with cells loaded ex vivo with such RNAs or with proteins would not be considered gene therapy.

The concept of therapeutic or prophylactic effect is important to the identification as a GTP. Introducing genetic changes to cells that are not related to the mode of action, for example, to make them better vectors or carriers of loaded antigens, is not considered to be gene therapy. However, any potential misclassification is not critically important to the review process since there is no distinct pathway or set of rules for GTPs; and the same part of Health Canada would be tasked with evaluation of the product using the same regulatory framework as for other biologics.

The regulatory approach to CTPs involves two major categorisations each supported, primarily, by a different set of regulations. There is stringent regulatory oversight for CTPs considered to be drugs, governed by longstanding and widely applicable parts of the *F&D Regulations* [7]; and a standards-based regulatory approach to allogeneic transplantation governed by the more recently developed *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (*CTO Regulations*) [8].

In addition, certain provisions of the *Assisted Human Reproduction Act of Canada* (*AHR Act*) will apply to embryonic stem cells. The creation of an embryo for any purpose other than for reproduction is prohibited in Canada; however, unused embryos can be donated for research purposes with appropriate consent. The *Act* extends to gene therapy in that it prohibits "knowingly altering the genome of a cell of a human being or in vitro embryo such that the alteration is capable of being transmitted to descendants" [9].

CGTPs and medical devices whose components are integrated into a singular product are regulated as combination products. Where the principal mechanism of action for the claimed effect or purpose is achieved by pharmacological, immunological or metabolic means, the *F&D Regulations* apply; in certain other circumstances, the Medical Device Regulations may apply [10]. The Health Products and Foods Branch (HPFB) Therapeutic Products Classification Committee may be engaged to reach a final decision regarding classification; however, regardless of the outcome, appropriate expertise from across the Branch is used to assess combination products.

Under the *Canadian Environmental Protection Act, 1999* (*CEPA, 1999*), and attendant *New Substances Notification Regulations* (*Organisms*), an environmental assessment is required for new substances and microorganisms not already on the "Domestic Substances List" [11]. The relevant definition of a microorganism includes viruses (but not plasmids) and so is applicable to many GTPs. Individuals, organisations or companies that file submissions are identified as sponsors. Sponsors planning to file a New Drug Submission (NDS) or Clinical Trial Application (CTA) for a viral or bacterial vector should notify Environment Canada. The assessment is actually completed within Health Canada by staff in the Healthy Environments and Consumer Safety Directorate (HECS). This process is largely about maintaining awareness and looking for any significant lack of consideration of potential problems by the sponsor. Thus far, there has been no prevention of clinical trial activities. Information can be obtained by sending an enquiry to substances@ec.gc.ca.

Prior to the conduct of a clinical trial, the Research Ethics Board (REB) and Biosafety Committee at each institution will examine the clinical protocol to ensure it meets the institutional requirements.[1] The Biosafety Committee will also be aware of municipal requirements regarding waste management and spills.

3 Regulatory Pathways

As outlined in Sect. 2, GTPs, CTPs (unless certain specific criteria apply—discussed below) and cellular products whose regulatory status is unclear but whose development requires the conduct of clinical trials are regulated as biologics. Responsibility rests with the Biologics and Genetic Therapies Directorate (BGTD) which forms part of the HPFB.

The clinical development and marketing application process is generally similar to that in the United States (USA) and other major, ICH[2]-observant, regulatory jurisdictions. As for all investigational studies in humans, Health Canada requires that clinical trial protocols for CGTPs obtain Research Ethics Board approval at each clinical site. However, there is no involvement of a standing, dedicated, government-associated committee like the US National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC).

For biologics, the regulatory requirements are defined within Divisions 1A (Establishment Licensing), 2 (Good Manufacturing Practices [GMP]), 4 (Biologics), 5 (Clinical Trial Applications) and 8 (New Drugs) of the Canadian *F&D Regulations* [7]. Through the application of Division 4, these products are subject to On-Site Evaluation (OSE) of manufacturing sites and the testing of consistency lots as part of the premarketing evaluation process and to the Lot-by-Lot Release Programme, the extents of which are discretionary by Health Canada following a risk-based assessment [12]. The Lot-by-Lot Release Programme can incorporate suitably modified approaches to reflect the small, or even single-treatment, lot sizes and the reality of some retrospective testing for products requiring use immediately after manufacture. Guidances and policies relating to biologics also apply, as do the target time frames for drug review. A product that meets the requirements and conditions for marketing approval is issued a Notice of Compliance (NOC) with the regulations, which constitutes an authorisation for sale. Sites where biologics are manufactured also require an Establishment License, which is reviewed and approved separately by the HPFB Inspectorate.

[1] Information and guidance regarding the bio-containment of gene therapy vectors is available from the Office of Laboratory Safety (OLS), Centre for Emergency Preparedness and Response (CEPR) and Public Health Agency of Canada (PHAC). Requirements will depend on the type of virus used as a vector, any association with human or animal disease, and the amount of the virus genome that remains.

[2] International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use.

CGTPs are often evaluated in relatively small patient populations which can present challenges for the generation and analysis of statistically meaningful data. A NOC/c may be granted in certain situations where sufficient product safety has been established, where preliminary evidence is supportive of clinical efficacy, and where a particular patient population, and the process of collecting additional clinical data, would benefit from early market access. The conditions must be met within a defined period after the NOC/c is issued. An "Orphan Drug" programme, which could help address many of the regulatory issues surrounding the clinical development of products for small patient populations, has been lacking in Canada, but the introduction of new "Orphan Drug Regulations" is in progress.

Some cellular therapies that meet certain criteria or that have an established safety profile and therapeutic use (such as bone marrow transplantation) are subjected to a less stringent, regulatory approach under the *CTO Regulations* [8]. These regulations came into force in December 2007 with the purpose of minimising the potential health risks to Canadian recipients of human cells, tissues and organs (CTOs), e.g. transmissible diseases. The focus is on activities performed by establishments such as cell and tissue banks, transplant establishments for living donors and organ donation organisations. The regulations are standards based and directly reference sections of standards developed by the Canadian Standards Association (CSA) [13] that are related to the safety of human CTOs. There is no premarket review and a NOC is not issued; however, establishment registration with Health Canada is required, along with suitable attestations. The regulations also empower the inspection of registered establishments. Comprehensive information is published elsewhere on the evolution of these regulations [14] and with specific respect to blood stem cell products [15].

The *CTO Regulations* are applied only to CTPs that are allogeneic, minimally manipulated and intended for homologous use. Regarding cells, "minimally manipulated" means that the processing does not alter the biological characteristics that are relevant to their claimed utility; and "homologous use" means that the cell performs the same basic function after transplantation (both as defined in the *CTO Regulations*) [8]. The regulations prohibit the transplantation of CTOs unless they have been processed by a registered establishment and determined safe for transplantation (except under the provision for "exceptional distribution", which, for example, could cover a situation where both donor and recipient were positive for hepatitis B virus). In this context, "safe" means processed in accordance with the *CTO Regulations*, and "processing" means any of the following activities: donor screening, donor testing, donor suitability assessment, retrieval (except organs and islet cells), testing and measurements performed on the CTO after retrieval, preparation for use in transplantation (except organs), preservation, quarantine, banking and packaging and labelling.

In general, cells of human origin that do not have an established therapeutic use should undergo investigative studies authorised under Division 5 (Clinical Trials) of the *F&D Regulations* (if conducted in Canada).

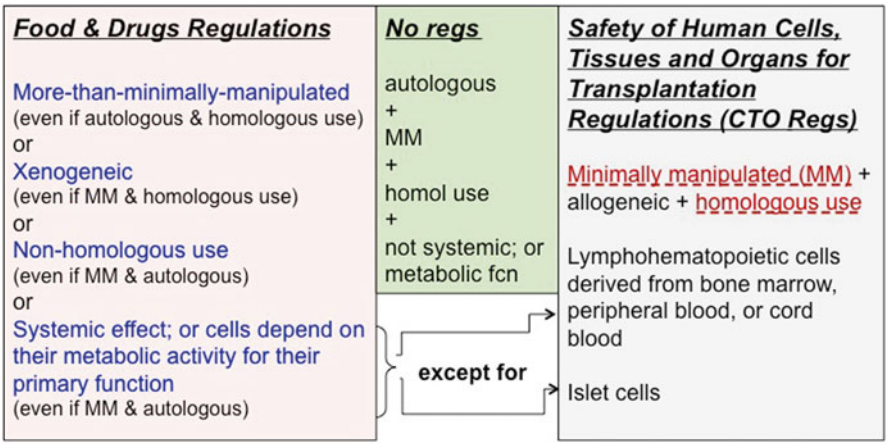

Fig. 1 Regulations governing cell therapies. Two distinct sets of regulations are available and applied based on specific criteria. Cells for human treatment meet the definition of a drug, but autologous cells that are minimally manipulated are not covered by regulations if (1) they perform the same basic function, (2) there is not a systemic effect, and (3) the primary function is not dependent on metabolic activity. "Minimally manipulated" (MM) means cell processing does not alter the biological characteristics that are relevant to their claimed utility. "Homologous use" means the cells perform the same basic function after transplantation. Two exceptions to the regulatory approach regarding CTPs with "systemic effect" or "metabolic activity" are islet cells and certain lymphohematopoietic cells. This image was originally published in [***The Regulation of Cell Therapy Products in Canada***] in [*Biologicals*, 2015, DOI: 10.1016/j.biologicals.2015.05.013]. ©[Elsevier 2015]

Essentially, there are a few "trump card" descriptors that dictate the application of the *F&D Regulations* to CTPs if any of the following apply: (1) xenogeneic, (2) more than minimally manipulated, (3) for nonhomologous use or (4) have a systemic effect or depend on their metabolic activity for their primary function (see Fig. 1). Despite this last criterion, for various practical reasons, the *CTO Regulations* are applied to lymphohematopoietic cells derived from bone marrow, peripheral blood or cord blood and to islet cells. Otherwise, with respect to cells, application of the *CTO Regulations* is restricted to cellular products that are minimally manipulated, intended for allogeneic and homologous use and not combined with non-cell or non-tissue products.

No clinical trials involving xenotransplantation have been approved by Health Canada to date, and issues unique to xenogeneic cells will not be discussed further in this chapter.

Health Canada currently has no applicable regulations for cellular products that are autologous, minimally manipulated, intended for homologous use and do not have a systemic effect or depend on their metabolic activity for their primary function.

By comparison to allogeneic cells with the same characteristics, these autologous cells are considered to represent a lower risk and are currently not a regulatory focus; however, to improve clarity, formal regulatory exemptions under the *F&D Regulations* that would cover some examples in this product class may become possible.

4 Regulatory Harmonisation and Guidance

Health Canada is a contributor to the ICH and adopts all ICH guidelines. Many of these guidelines are applicable to the therapeutic use of CGTPs, and even though some guidelines contain a product scope that excludes these products, many of the principles may still be relevant. There are also three ICH Considerations documents that address gene therapy with regard to germline integration, oncolytic viruses and vector shedding [16–18].

In addition to direct participation on ICH Expert Working Groups and Discussion Groups, Health Canada participates under the umbrella of the ICH-affiliated, International Pharmaceutical Regulators' Forum (IPRF), on the Cell Therapy Working Group and the Gene Therapy Working Group. Health Canada also participates in the Advanced Therapy Medicinal Product (ATMP) "Cluster Meetings" held regularly between the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

In the absence of specific Canadian or ICH guidance, Health Canada encourages the use of relevant regulatory guidance developed by the FDA and EMA. Three US Pharmacopeia (USP) documents are also highly relevant to the manufacturing and processing of these products: <1043> Ancillary Materials for Cell, Gene and Tissue-Engineered Products; <1046> Cellular and Tissue-Based Products; and <1047> Gene Therapy Products [19–21].

In addition, the CIHR has developed guidance for human pluripotent stem cell research and created a National Stem Cell Oversight Committee to oversee grant applications involving these cells. Those guidelines were recently incorporated within the "Tri-Council Statement: Ethical Conduct for Research Involving Humans" [22]. The Tri-Council is the research funding arm of Health Canada and comprises the CIHR, the National Science and Engineering Research Council (NSERC) and the Social Science and Humanities Research Council (SSHRC). All clinical trials undertaken in Canada should be in accordance with the guidelines outlined in the Tri-Council Policy Statement.

Health Canada is also taking steps to try to address the need for guidance for CTPs following a Stakeholder workshop co-sponsored by Health Canada and the Canadian Stem Cell Network held in December 2010. The needs of the research community that were expressed, and the input provided at this workshop, along with other regulatory considerations, form the basis for a document titled "Guidance for Sponsors: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans" which should become final in 2015.

5 Overview of Specific Considerations and Expectations for CGTPs

5.1 Product Manufacturing

Cells used with or without gene transfer in the manufacture of CTPs and cell-based GTPs encompass a wide variety of types derived from patients undergoing treatment (autologous cells) or from donated cells or established cell lines (allogeneic cells). These include cells of somatic or embryonic origin, derived from various tissue sources, at different stages of differentiation and subjected to various degrees of manipulation. The gene therapy vectors used to transduce cells ex vivo or for direct administration are also diverse, including nucleic acid (both DNA and RNA) formulated in buffer or complexed with agents to aid transduction, and viral vectors of many origins. Like other biologics, the manufacturing of CGTPs features the inherent risks associated with biological starting materials, the potential introduction of adventitious agents during manufacturing, the inherent variability of products derived from processes that use living systems, and the difficulty in precisely controlling the manufacturing process. Viral vector design and manufacturing control are critically important to overall product quality and linked to safety and efficacy in patients through concerns such as replication competence, vector integration and vector shedding. It is often stated that for biologics, processing defines the characteristics of the product; and this is particularly valid for CGTPs.

Similar to other biological drugs, the risks associated with CGTPs can be mitigated to a large extent through tightly controlling starting materials and the manufacturing process and suitably evaluating intermediates and the final product. In the following sections, we have divided CGTPs into three categories: CTPs, cell-based GTPs and virus-based gene therapy vectors, in order to discuss the risk mitigation strategies and regulatory expectations for manufacturing these products.

5.1.1 Manufacturing Process for CTPs and Cell-Based GTPs

Often, the manufacturing process for CTPs and cell-based GTPs begins with the isolation of cells from blood or various tissues with or without dissociation with digestive enzymes. The cells can also be subject to various degrees of manipulation including, but not limited to, ex vivo expansion in culture, genetic modification or reprogramming, activation to induce expression of genes or cell surface receptors, differentiation, photochemical treatment and/or irradiation or combined with biologic or nonbiologic matrices or supporting structures. Further, the ex vivo expansion of cells may involve (1) a continuous process with no intermediates, (2) a cell banking system involving one or more cryopreserved intermediates such as master or working cell banks and/or (3) the use of culture media supplemented with reagents and growth factors from a wide variety of sources (e.g. animal serum, pooled human serum, autologous serum, human platelet lysate or recombinant growth factors).

In addition, CTP and cell-based GTP manufacturing is often critically time dependent due to cell passage number limitations, the inability for hold times and the limited shelf life of hours to days of non-cryopreserved living cells held at room or refrigerated temperatures. Cryogenic storage may be necessary to extend product shelf life but can have deleterious effects on cell viability and function.

Variability in the biologic starting materials and the manufacturing process could potentially affect the safety and identity/composition of the cellular product, as well as its biologic activity in vitro and in vivo. A well-controlled and validated manufacturing process will help minimise the potential variability attributable to the manufacturing process itself and help maintain product quality, safety, identity and potency. An important regulatory expectation is a detailed description of the process with flow charts and diagrams that identify the critical control steps.

Another aspect of CTP and cell-based GTP manufacturing, important for avoiding mix-ups, is the segregation, labelling and tracking of different batches, which may be numerous and small in size. This is especially relevant for autologous cells, directed allogeneic cells (i.e. intended for a specific patient) or small-scale allogeneic cells, situations that also require tightly controlled cleaning and changeover procedures. Closed systems and automation can help with product segregation and also provide greater manufacturing consistency.

5.1.2 Starting Materials for Human-Derived CTPs and Cell-Based GTPs

The infectious disease risks associated with starting materials containing live cells cannot be mitigated via sterilisation or other pathogen inactivation or removal processes. Consequently, a combination of donor screening and infectious disease testing serve as critical control steps in the manufacturing process. For allogeneic CTPs and cell-based GTPs regulated under the *F&D Regulations* [7], the donor suitability assessment, donor screening and infectious disease testing requirements in the CSA Standards [13] that are referenced in the *CTO Regulations* [8] are mostly considered appropriate by Health Canada. These Standards consist of the National Standard for Cells, Tissues and Organs for Transplantation: General Requirements and four subset standards with specific requirements for lymphohematopoietic cells, tissues, ocular tissues and perfusable organs [13] and are further clarified in a specific guidance document [23]. However, since the *CTO Regulations* are intended for cells and tissues that are not subject to the *F&D Regulations*, alternative practices may be considered acceptable if they are supported by adequate evidence and rationales.

A controversial issue regarding the controls for starting materials relates to the testing of autologous donors for donor-derived viral pathogens, since they do not pose a risk to themselves. However, Health Canada recommends testing autologous donors for the infectious disease agents that pose a significant risk to patients in order to address concerns regarding the cross-contamination of products manufactured in the same facility for other patients and/or potential viral propagation during culture.

Another challenge relates to the use of established cell lines derived from donors that were not screened or tested in accordance with current requirements. The appropriate risk mitigation measures in these cases must include, among others, a risk assessment, re-screening and/or retesting donors where possible and testing the cell lines with appropriately validated tests.

5.1.3 Ancillary Reagents, Excipients and Materials

CGTPs are highly complex, and it is difficult to confirm critical quality attributes via final product testing. Thus, product safety, potency, quality and consistency are assured by implementing controls for various critical components. These include the ancillary reagents, excipients and certain other materials used during manufacturing. These materials, typically purchased from commercial sources, are usually not of GMP or pharmacopoeial grade, as would be preferred for use in manufacturing CGTPs, and exhibit various risk profiles. Of particular concern are materials derived from human or animal sources, which are associated with the risk of contamination with viral and bacterial pathogens as well as transmissible spongiform encephalopathies (TSEs). Consequently, critical components must be appropriately qualified prior to use in manufacturing via vendor qualification and audits, review of Certificates of Analysis and adequate in-house quality control testing as described, for example, in the USP Guidelines on ancillary reagents [19].

5.1.4 Process Validation

Process validation is required to help reduce lot-to-lot variability associated with the factors mentioned above and minimise the potential for release of CGTPs that do not meet specifications. This is especially important where release must take place before the availability of certain test results.

Some aspects of validation and process controls should be implemented during early clinical trials, with emphasis placed on aseptic process validation and the use of safety tests for sterility, mycoplasma and endotoxin. A preliminary assessment of other parameters should also be performed at this stage. Process validation should be subject to continuous improvement at later stages of product development and should demonstrate the consistency of the manufacturing process. This should include demonstrating consistency of products derived from different donors and, where applicable, the consistency of multiple lots derived from the same donor.

There are unique challenges associated with process validation for CGTPs derived from autologous donors as it may not be appropriate to retrieve cells or tissues from patients for validation purposes. In these cases, the process validation may be carried out using allogeneic donations. Potential differences between patient- and donor-derived cells or tissues are then assessed when the former becomes available.

5.1.5 Product Characterisation and Specifications

The characterisation of CGTPs typically supports the establishment of specifications for key parameters that could be used to monitor the consistency of the manufacturing process, as it relates to product safety, quality and potency. This is particularly important in cases where extensive testing cannot be performed, or where the products are released for administration to patients prior to the availability of results of final product testing. Examples include autologous products with limited samples available for quality control testing, or products with limited shelf lives.

The characterisation of CTPs and cell-based GTPs is particularly difficult because of their cellular complexity; i.e. along with the desired cell populations, they typically contain various cellular impurities such as nonviable cells, non-functional live cells and cell types that are not at the intended maturity. Other challenges, in some cases, include (1) the presence of immunogenic and tumorigenic cells that cannot be removed; (2) further maturation, migration and/or differentiation in vivo, of the desired cell types in the final drug product; (3) the contribution of more than one cell type in a heterogeneous array of cells to the effectiveness of some CTPs; and (4) the lack of reference standards.

The establishment of specifications for autologous and directed allogeneic products also warrants special consideration as this is often the only product available to these patients. Donor-to-donor variability makes it difficult to consistently meet stringent specifications, thus resulting in fairly broad specifications that reduce the number of products rejected during clinical trials. However, an appropriate level of stringency needs to be applied to these products once adequate supporting data has been accumulated.

Given the challenges identified above, emphasis is placed on safety-related parameters when setting specifications during the early phases of clinical trials, followed by the refinement and tightening of specifications for other parameters as product development progresses. The key parameters used to establish specifications for CGTPs include, but are not limited to, viability, identity, yield, purity and potency, as well as safety tests for sterility, endotoxin, mycoplasma and other adventitious agents. In some cases, the complexity of CGTPs and/or the technical limitations of the analytical methods employed may require the use of multiple tests for a single parameter. Some of the particular challenges associated with the characterisation of CGTPs are discussed below.

5.1.5.1 Identity and Purity

Assays for cell identity and purity (absence of cellular contaminants) are usually based on the expression of cell surface markers, which can be affected by the tissue source, the culture conditions or cell cycle progression. Establishing the criteria for cell identity or purity can be challenging if not all the cell types responsible for the product's biological activity and functions are known. As well, the comparison of cells manufactured in different facilities based on cell surface marker expression could be problematic if the same manufacturing process is not employed.

5.1.5.2 Viability

The choice of analytical methods used for the determination of cell viability can be an issue. Cell death may be due to necrosis or to apoptosis. Necrotic cells lose their membrane integrity and are able to take up vital dyes that are either colorimetric (e.g. trypan blue) or fluorescent (e.g. propidium iodide). In contrast, apoptosis is triggered by biochemical events that lead to characteristic cell changes. While cells in the late stages of apoptosis exhibit loss of membrane integrity, those in the early stages do not and are unable to take up these dyes [24]. Consequently, the use of dyes that are only taken up by leaky cells could lead to an underestimation of nonviable cells.

5.1.5.3 Potency

Potency testing is especially important for complex products. Assays are ideally based on the mechanism of action and should be demonstrated to contribute to the prediction of clinical efficacy for each lot (but it is understood that other analyses contribute to a summation of evidence that product will perform appropriately). CTPs could exert their effects via different mechanisms, including cell engraftment and paracrine signalling. The latter may involve the secretion of factors with anti-apoptotic, anti-inflammatory, immunomodulatory and/or angiogenic effects. In most cases, the mechanism of action of a CTP is not well understood. Consequently, potency assays and their specifications and/or acceptance criteria are difficult to develop, and multiple assays may be required to characterise these products. It is also important to provide quantitative test results for product release (this could involve a quantitative physical assay that correlates with, and is used in conjunction with, a qualitative biological assay).

Given the challenges with product characterisation that are noted above, truly relevant potency assays are generally not established for products used in early-phase clinical trials. Nevertheless, it is valuable early in development to have the ability to reject subpotent material. Thus, the evaluation of in vitro and in vivo candidate assays should begin in early-phase clinical trials and be refined as product development progresses. A suitable potency assay should be selected and implemented prior to applying for market access, in order to generate sufficient data to include in the marketing application.

5.1.5.4 Safety

CTPs and cell-based GTPs cannot be sterilised or subjected to pathogen removal/inactivation procedures because they contain live cells. Further, some CTPs and cell-based GTPs must be released for administration to patients within hours to days of final formulation. Under these circumstances, pharmacopoeial methods (e.g. USP <71> for sterility testing) [25] cannot be used as prospective lot release tests due to the time required to obtain the test results. The use of rapid,

non-pharmacopoeial methods for sterility and mycoplasma testing that are as sensitive as the pharmacopoeial methods could serve as useful lot release tests in some cases.

CGTPs must also be tested for viral agents to rule out the introduction of viral contaminants during processing. Two ICH Quality Guidelines (Q5A R1 and Q5D) provide recommendations for adventitious agent testing for various human and animal viruses by PCR assays and other in vitro and in vivo tests [26, 27]. Although intended for cell lines and banks used for the preparation of biotechnological/biological products, the guidance could be adapted for CTPs and cell-based GTPs in some situations. A risk–benefit analysis should be employed when determining the appropriate level of testing.

5.1.6 Analytical Method Validation

Biological assays involving complex CTPs are highly variable, and there are currently no reference standards for these products. Assay variability can be controlled to a large extent by using analytical methods that have been validated to establish method sensitivity, specificity, accuracy, precision and robustness. Given the challenges with the development and validation of some of the analytical methods employed, clinical trial sponsors are not required to submit full validation data to Health Canada during early-phase clinical trials. Nonetheless, all methods must be appropriately qualified for their intended use, and the methods for safety-related parameters must be appropriately validated to ensure the safety of clinical trial subjects.

5.1.7 Release Criteria

As discussed above, some CTPs and cell-based GTPs must be released for administration to patients within hours to days of final product formulation and before some final product test results (e.g. sterility, mycoplasma) are available. In these cases, the missing tests could also be performed as in-process controls, and as close to the final product as possible, to ensure preliminary results are available prior to product release.

5.1.8 Batch Analysis

Typically, sponsors are required to submit data for at least three consecutive batches of the final drug product prior to clinical use. For CTPs and cell-based GTPs, one batch of starting material could be used to produce one to several batches of drug product. To account for the variability in the starting materials, the batch analysis should also include final product manufactured from at least three consecutive batches of starting materials.

5.1.9 Stability Studies

A major challenge with CTPs and cell-based GTPs relates to the relatively short shelf life of fresh or thawed cells and the impact of storage and transportation conditions or delivery systems on cell integrity and function. Stability studies should be designed to assess the impact of all these factors on stability-indicating parameters such as cell count, viability and potency. These studies should cover the proposed product shelf life, and testing should be performed after final product formulation and following storage and/or transportation. In-use stability studies should also be performed to assess product when it is subjected to the conditions employed to prepare the cells for administration, including any hold period prior to administration.

5.1.10 Additional Considerations/Expectations for Virus-Based Gene Therapy Vectors

Bacterial plasmids and other nucleic acid-based gene therapy vectors present fewer challenges compared to other biological therapeutics than do virus-based and cell-based vectors and are not specifically addressed in this chapter. While manufacturing challenges associated with cell-mediated gene transfer have been covered in the preceding sections, some challenges particular to viral vectors are addressed below.

5.1.10.1 Replication Competence

In most situations, virus-derived GTPs are designed to be replication incompetent. In these cases, testing to confirm this attribute is an important quality and safety consideration. Aspects of vector design and manufacturing control may virtually eliminate the possibility of recovery of replication competence during product manufacturing, but with large-scale production involving high virus titres, rare events can occur. Natural infection of patients by wild-type versions of the virus upon which the GTP is based may present the opportunity for recombination or complementation events potentially capable of restoring replication competence and should be avoided, controlled and/or risk rationalised. In these instances, replication-competent virus is a form of adventitious virus.

Replication incompetence can be important for control of targeting of the vector and reducing pathogenicity. However, conditionally replicating vectors may have distinct advantages for some indications and uses (e.g. oncolytic viruses).

5.1.10.2 Vector Integration

Minimising the potential for unintended viral integration, and associated risk of insertional mutagenesis, is an important issue. Again, this is largely controlled through choice of vector and vector design, and intentional vector-mediated

integration is generally accomplished in the more-controlled conditions of ex vivo gene transfer. Replication competence presents particular concerns for integrating vectors such as retroviruses, but again, cell transduction is conducted on cells ex vivo, with cryopreservation and storage prior to patient administration, thus allowing time and opportunity for extensive analysis.

5.1.10.3 Virus/Vector Dose and Expressed Product Dose

Measurement and control of vector dose is important since this could have an impact on several factors including expressed product dose and immunogenicity. A high titre of vector could induce a sudden immune response with adverse consequences for the patient. Immunogenicity can also cause reduced efficacy via rapid removal of vector and negatively affect the potential value of repeat administration. Regulation of expression of the transduced gene is important for targeting the effect and will depend on aspects of the gene construct (e.g. tissue-specific promoter), the cellular target and the cellular host range of the vector. While obtaining sufficient expression may be a typical concern, the consequences of overexpression may also be undesirable (such as for a highly potent cytokine).

5.1.10.4 Testing for Adventitious Viruses

Testing for adventitious virus in a virus product can present significant challenges. Special adaptations may be needed for some analytical methods. For example, a conditional replication-competent oncolytic virus can interfere with assays for detection of other viruses. One approach is to use vector-specific neutralising antibodies for in vitro, cell-based assays for adventitious viruses; however, if these are not available or suitably efficient, one must rely on in vivo assays.

5.1.10.5 Potency

Biological potency assays are especially important for complex biologics like GTPs and should be well described, justified and eventually validated. There is some flexibility regarding stage of product development: early on, ability to quantify the expression of a gene therapy vector product may suffice, but later in development, the assay should measure an appropriate biological activity.

5.2 Nonclinical Evaluation

The principles in the ICH Safety guidelines (e.g. ICH S6 (R1)) [28] and the scientific content in FDA and EMA gene and cell therapy guidelines [29, 30] are applicable to clinical trial and market authorisation applications for CGTPs in Canada.

Prior to administration of an investigational product in a clinical trial in Canada, the sponsor must provide adequate nonclinical data and information in relevant animal model(s). Relevant animal species in which the CTP or GTP is immune-tolerated and biologically active should be used in the toxicology studies, if available. Studies in healthy animals can be a useful means to collect toxicology information; however, due to their distinctive features, animal models of disease/injury may be more preferable to assess product activity and safety. Due to the species-specific nature of the GTP or CTP (e.g. some vector-expressed human transgenes; human-derived cells), testing these products often requires the use of immune-compromised animals. In some cases, however, it may be necessary to investigate the safety profile of a product in an immune competent environment. As such, testing of an analogous animal product, or testing in transgenic animals, may provide suitable alternatives [28]. In these situations, the design of the nonclinical testing programme is considered on a case-by-case basis and should incorporate the fundamental principles of pharmacological and toxicological testing that underlie traditional nonclinical studies. The type, duration and scope of animal studies required vary with both the duration and nature of the proposed clinical studies as well as the inherent risk/safety profile of the product itself.

With that said, certain aspects of pharmacology and toxicology, such as absorption, metabolism, and excretion, may not be applicable to many CGTPs. The unique aspects of product characterisation and the mechanism(s) of action of CGTPs set them apart from chemical pharmaceuticals and from other biologics (such as therapeutic proteins); the traditional, standardised battery of nonclinical toxicity studies required for drug development and testing may not be appropriate for assessing their safety.

Rodents have been invaluable for the study of GTPs. While mice may provide proof of principle and allow testing of a variety of therapeutic products, murine models do have a variety of limitations, including a genetic background and organ systems that differ greatly from humans. As a consequence, some rodent studies may not directly translate to the human setting. Large animals (e.g. cats, dogs, sheep, pigs, goats and horses) may provide an acceptable substitute when adequate justification is provided. Large animals can allow for longitudinal studies and may be more applicable to the human situation in many cases. In addition, large animal models typically have more heterogeneous genetic backgrounds compared to inbred rodent models, resulting in studies that may more closely resemble clinical outcomes. Overall, Health Canada is in agreement with FDA guidelines which propose that nonclinical testing paradigms may include the use of (1) large and small animal models, (2) multiple small animal models or (3) only large animal models, depending upon the nature of both the product and the intended indication [29].

Viruses are the most commonly used vectors for gene therapy. The risk of spreading of a viral vector via secreta and excreta from the treated patient is a safety concern for healthcare professionals, family members and others. A nonclinical shedding study may be valuable to monitor the secretion and excretion profile of the vector which can then be used to make estimates on shedding in patients, such as, the likelihood of occurrence, the extent and the kinetics. One of the challenges of

investigating viral vectors in nonclinical studies is the relevance of the animal species, as a large number of viral GTPs used in clinical studies are derived from parental strains that do not readily infect and rarely replicate in nonhuman species. Therefore, the shedding profile might not directly correlate with that in humans. Prior to use in the nonclinical studies, the susceptibility of study animals to infection from the viral vector under investigation has to be considered.

5.3 Clinical Evaluation

5.3.1 Conduct of Clinical Trials

Many CGTP proof-of-concept clinical trials are being conducted in cancer, inherited disorders, immune system disorders, infectious diseases and cardiovascular disorders. However, advancing CGTPs from the nonclinical studies and early-phase clinical trials into late-phase clinical trials and marketing authorisation has proven to be challenging.

Issues that are unique to CGTPs may make it difficult to categorise clinical trials involving these products into the traditional developmental phases used to investigate pharmaceuticals. Phase I studies in healthy individuals, for example, would not be considered ethical for the majority of CGTPs. Extrapolation of nonclinical data may not be feasible for defining the appropriate dose or dose range which must then be determined on a case-by-case basis and should incorporate current knowledge regarding the biodistribution, engraftment, tumour forming potential and immunogenicity. In such cases, conservatively designed early clinical trials may still proceed if it can be clearly argued that the potential benefits of the therapy outweigh the potential risks within a specific patient population. When possible, dose estimation should be based on previous clinical experience with similar cell types. In principle, clinical trials should be designed to detect clinically meaningful endpoints that assess the therapeutic effect and duration of a CTP or GTP as well as short- and long-term adverse events. Valid surrogate endpoints are acceptable for CGTPs, particularly for those products developed for rare diseases.

Traditional pharmacokinetic studies to assess biodistribution in humans may be challenging and may require the development of appropriate cell or vector tracking technologies. The presence of CTPs or GTPs in non-target sites should be further investigated and the risks fully evaluated whenever feasible. Health Canada may insist on pharmacokinetic assessment for products associated with higher risks of tumorigenicity or ectopic tissue formation prior to the initiation of trials in a large number of patients.

5.3.2 Specific Challenges Regarding Safety and Efficacy

There are efficacy and safety concerns clearly associated with gene therapy. Increased efficiencies of vector and transgene delivery and expression may affect dosing regimens, therapeutic indices and safety profiles. The duration of gene

expression and the impact of immunological responses directed against the delivery vector or transgene are also important considerations for gene therapeutics. The transgene introduced into target cells may show only transient expression and so may not provide long-term effectiveness, perhaps implying that patients might need multiple rounds of GTP administration. However, the loss of transgene expression may be caused by the development of immune responses against the vector or the transgene. This is known to occur frequently when using adeno-associated virus (AAV) vectors, as humans are frequently exposed to wild-type AAV in the context of pathogens during childhood. In such cases, neutralising antibodies to AAV can be generated after the first injection of vector, inducing immunogenicity that would normally reduce the usefulness of repeated vector administration [31].

The type of the induced immunogenicity depends on the route of administration of the vector, the target tissue, the vector serotype and dose, the disease targeted and the expression level of the transgene. There are a number of scientific means to try to counter this immunogenicity. Co-delivery of pharmacologic and vector-encoded immunosuppressive agents may prolong vector expression. Alternatively, vectors could be developed to produce higher transgene expression levels at much lower vector doses. There might also be some value in repeating treatment using different vector serotypes.

Viral vectors present a variety of potential problems to the patient: toxicity, inflammatory response, immunogenicity and gene control and targeting issues. In addition, there is the concern that the viral vector, once inside the patient, may recover its ability to cause disease. Viral shedding should be considered as a possible source of transmission to other individuals. For most clinical applications, a viral vector should be safe and well tolerated, should not elicit a strong immune response, and should also be replication incompetent in humans. Note, however, that for oncolytic viral vectors, conditional replication competence and an eventual immune response may be desirable.

Additional concerns related to GTPs include the risk of delayed adverse events. Factors likely to increase such risks include:

- Persistence of the viral vector
- Integration of genetic material into the host genome
- Prolonged expression of the transgene
- Altered expression of the host's genes

Persistence of the viral vector could permit continued expression of the transgene. Although it may be necessary for the product to provide a continuing clinical benefit, the persistence of the viral vector could have adverse effects upon normal cell function and place patients at risk for development of adverse events, some of which may be delayed by months or years. Integration of a viral vector into the host cell genomic DNA raises the risk of malignant transformation. Prolonged expression of the transgene may also be associated with long-term risks such as uncontrolled cell growth and malignant transformation. Altered expression of the host genes could also result in unpredictable and undesirable events, such as autoimmunogenicity or cancer.

Issues that are more specific to CTPs include graft failure, tumour formation, immune responses, ectopic tissue formation, inflammatory events, viral activation and the distribution and engraftment of the cells throughout the body. Concerns specific to product administration should also be addressed, including:

- Lung emboli formation
- Respiratory and cardiac adverse effects
- Both local and systemic toxicities

5.3.3 Monitoring and Risk Management

CGTPs require longer than normal monitoring and follow-up periods compared to other biologics. Even in early clinical trials, patient monitoring may be required for 1 year or more.

The precise length of time for monitoring is dependent on considerations such as the product characteristics, the anticipated time for the occurrence of delayed adverse reactions, the clinical indication and the expected life expectancy of the treated patients. Long-term monitoring should be focused on survival and serious adverse events (e.g. oncologic, hematologic, immunologic, etc.). Detailed plans should also be put in place proactively to maintain long-term monitoring in cases of early stoppage. EMA and FDA guidances suggest 5 years and 15 years, respectively, for the follow-up of gene therapy. With the marketing authorisation application, a Risk Management Plan (RMP) should be submitted by the sponsor and can be based on the EMA's RMP with a Canadian context [32].

Measures to identify and mitigate potential long-term risks of study subjects should be discussed and carefully planned from the outset. In the absence of any detectable serious adverse events, it may be possible to initiate later stage trials with larger patient populations prior to completion of long-term monitoring. Such trials would require specific stopping rules that are directly linked to outcomes from ongoing early investigations.

6 Future Directions and Possibilities

An appropriate level of regulatory oversight has the potential to protect patients by minimising the risk of adverse events while also enabling scientific advancement by maintaining sufficient flexibility to support innovation. Health Canada has established, and continues to adapt, a regulatory framework that strives to meet these goals and is committed to working with sponsors from academia and industry, other regulatory authorities and other interested stakeholders to facilitate entry to the market of promising CGTPs.

There is already a process for conditional approval of drug products (leading to a NOC/c), and there will soon be in place a programme for Orphan Drugs. Although

these regulatory tools may be particularly useful for products targeting small patient populations, new regulatory paradigms may be needed in some situations. The cost of bringing a new drug product through the marketing approval process typically runs into hundreds of millions of dollars; and, to protect such an investment, industry requires a strong proprietary position and a suitable, projected, financial return. In the absence of biopharmaceutical industry sponsorship, some products/therapies with significant potential may face an unsure future with investigational status at a limited number of treatment sites. Additionally, a centralised manufacturing approach presents many challenges for the distribution of CTPs and cell-based GTPs that utilise autologous cells; and some such products may require the need for additional steps at the treatment site prior to administration that would currently constitute product manufacturing. An alternative regulatory option that requires proof of safety and efficacy demonstrated through clinical trials but then allows wider use at registered/licensed establishments committed to established procedures, and meeting appropriate standards, might be useful in many situations [33].

Finally, Health Canada is a strong proponent and active participant in efforts geared towards international regulatory harmonisation and convergence. The sharing of scientific expertise and regulatory experiences is always positive and will be especially valuable in this still developing field of endeavour, encompassing such a wide variety of products.

If you want to go fast—go alone ….
If you want to go far—go together (African Proverb)

Note: Some text on regulatory information in this chapter has been adapted from a conference report by Ridgway appearing in the Journal *Biologicals*, volume 43/5, in press.

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Overview of the Regulatory Oversight Implemented by the French Regulatory Authorities for the Clinical Investigation of Gene Therapy and Cell Therapy Products

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Abstract Advanced therapy medicinal products, a new class of products with promising therapeutic effects, have been classified as medicinal products and as such should be developed according to a well-structured development plan, to establish their quality, safety and efficacy profile and conclude, at the time of the marketing authorisation evaluation, on a positive risk/benefit balance for patients. An important part of this development plan is achieved through clinical trials, which have also to be approved according to a well-established regulatory process, prior any initiation.

This chapter is dedicated to describe the regulatory pathway to be followed in France, before initiating any clinical trial with those investigational advanced therapy medicinal products.

In France, to get the final authorisation to initiate a clinical trial, the legislation imposes to run in parallel two independent but complementary authorisation procedures. The first procedure is aimed at assessing the ethical aspect of the biomedical research, while the second has to review the safety and regulatory aspects. A third procedure has to be envisaged where in case the investigational product consists or contains a genetically modified organism.

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The French system herein described is in line with the EU regulation on clinical trial and follows the respective deadlines for granting the final approval. The complexity of the procedure is in fact more due to the complexity of the products and protocols to be assessed than to the procedure itself which is now very close to the well-known procedure applied routinely for more conventional chemical or biological candidate medicinal products.

Keywords French regulation • Advance therapy medicinal product • Clinical trial • Investigational medicinal product • Application dossier

1 Introduction

Gene therapy, cell therapy and tissue-engineered products have been defined by the European Union (EU) legislation [1, 2] and classified as 'advanced therapy medicinal products' (ATMPs), a new class of medicinal products, i.e. medicines for which a marketing authorisation (MA) has to be granted prior envisaging any commercialisation.

This implies that for an ATMP, the development plan will follow the same structure and approach as for any other medicinal product, with the main objectives of documenting (1) the quality aspects (characterisation, development of the production process and quality control strategy, so as to obtain a well-defined product); (2) the non-clinical testing of the desired product to establish the safety profile, as well as identify the essential pharmacological/toxicological characteristics to support the product safety and efficacy; and (3) the clinical phase to establish the efficacy profile and particularly the indication(s), dosage(s) and target population(s) along with the tolerance profile and frequency of the expected side effects which are inherent to any therapeutic strategy. The latter aspects on clinical efficacy and safety have to be documented through a well-structured and justified clinical development plan and the conduct of relevant clinical trials (CTs).

In contrast with the regulatory process for granting an MA for an ATMP, which is a central procedure under the responsibilities of the Committee for Advanced Therapy (CAT) Medicinal Products and Committee for Human Medicinal Products (CHMP) [2] at the European Medicine Agency (EMA) level, the regulatory oversight for this primary and important step in the development of such candidate ATMPs, i.e. granting the authorisation for CTs, is in accordance with Directive 2001/20 [3], under the decisions of the National Competent Authorities (NCA). This directive on CTs, in force since 2001, has been revised and will be superseded by Regulation 536/2014 [4] which is to enter into force in 2016. This new regulation is aimed at further harmonising the rules of decisions made and streamlining the authorisation process at the national level. This future procedure will take into account experiences gained through the voluntary harmonised procedure (VHP) which was put in place in 2003, after implementation of Directive 2001/20 with the intent to facilitate initiation of European multicentre CTs (see Sect. 4.2).

This chapter will describe the following aspects of regulatory oversight for ATMPs for France, which is one of the 28 member states in Europe: (1) the organisation of the regulatory system, (2) the specific aspects to consider for initiating a CT involving an investigational ATMP and (3) the relevant procedures and timetables laid down by the national legislation in application of the relevant European regulations and directives, of which Directive 2001/20 [3], Regulation 1394/2007 [2] and Directive 2001/83 [1] are to be considered primarily.

Before describing the French system, the reader is reminded that good laboratory practice (GLP), good manufacturing practice (GMP), good clinical practice (GCP) and other 'GxP' rules that are required and applied in France for medicinal products are identical to those developed at the European level, and no further specificities apply to these terms for interested parties in CT development (e.g. sponsor, investigators, manufacturer, supply chain providers, etc.) [5, 6]. They thus will no longer be discussed as it is understood that every CT will have to be conducted in fulfilment of the GCP rules and any investigational medicinal product (IMP) will have to be manufactured, quality-controlled and released under the responsibilities of a qualified person who will certify that the IMP batches have been produced in an establishment which is GMP certified. In France it is mandatory that the qualified person is a pharmacist, registered in a specific section of the 'National College of Pharmacist' as 'pharmacien responsable'.

2 The Authorisation Pathway, Timelines and Technical Requirements

The French laws and decrees, taken in application of the above-mentioned EU regulation and directives, foresee that an authorisation should be sought, before starting any CT. This regulation applies to any IMP and as such applies to investigational ATMPs with the relevant adaptations foreseen in the EU legislation and particularly the adaptation of the GLP rules.

In the French legislation, the ethical and regulatory aspects that have to be considered in a CT authorisation (CTA) have been put under the responsibilities of two independent bodies, one in charge of the ethical aspects and protection of people enrolled in a CT (patient information, informed consent, monitoring, etc.) and the second in charge of the regulatory and scientific review of the IMP dossier (IMPD), including the quality, non-clinical and clinical data (if any) and the proposed clinical protocol. These two bodies are the local ethics committee (the so-called in French Comité de Protection des Personnes—CPP) and the National Medicines Agency (current name: Agence Nationale de Sécurité des medicaments et produits de santé—ANSM), respectively.

There are thus two independent procedures to be run in parallel. In addition, a third procedure has to be considered if the investigational ATMP consists of, or contains, a genetically modified organism (GMO), which is the case for gene therapy products and may occur for some cell therapy or tissue-engineered products.

These procedures are presented and described below in the sequence depicted in the flow diagram in Fig. 1. However, before entering into a detailed description of the three procedures to be undertaken, it is noteworthy that the sponsor (the person who takes the responsibility to set up a CT and has to organise the necessary framework with investigators and regulatory steps all along the CT) must first obtain a EudraCT number using the Eudra website [7]. This EudraCT number is the unique identifier of each CT in the EU and thus will be required at all steps of the regulatory process and has to be referred to in all submission forms. There is nothing different in France regarding this procedure for submission to the French regulatory authorities, and it is thus not further explained.

2.1 The CPP Procedure

As stated above, in France the body in charge of evaluating the ethical aspects of biomedical research, the CPP, is equivalent to the 'local ethics committee' or the 'institutional review board' usually referred to in the international literature.

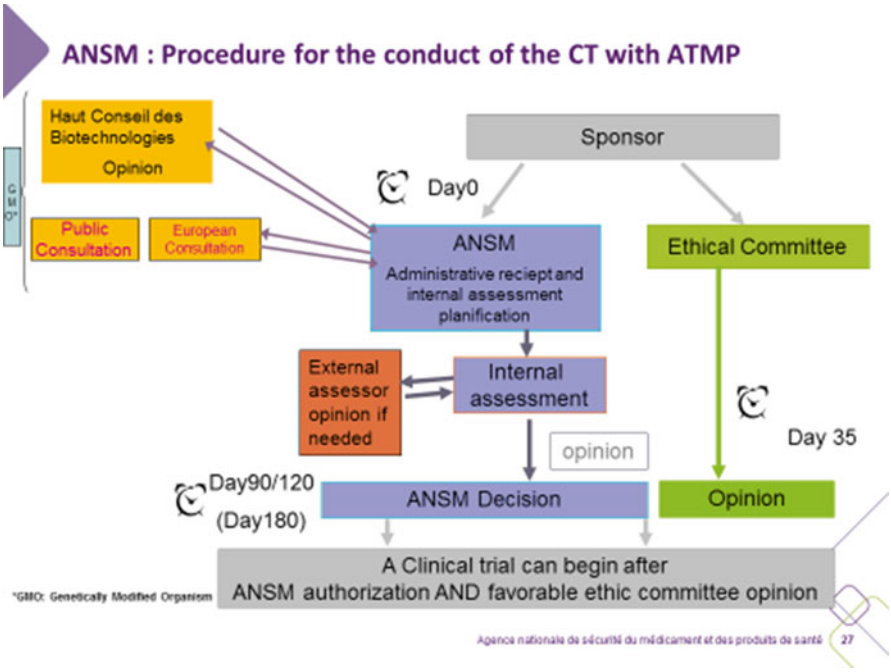

Fig. 1 Steps to be taken in the submission of a CTA dossier for an ATMP in France: the three independent and complementary bodies to be approached and the relevant timing for the procedures are shown. *GMO* genetically modified organism, *ANSM* French Regulatory Agency for medicinal product; ethical committee is represented by a local committee for protection of people involved in clinical trials (Comité de Protection des Personnes—CPP)

In France there are 40 independent committees (local CPPs) spread into seven geographical regions. For example, for Paris and its region, there are 11 CPPs. The CPPs are independent in terms of agenda, time schedule and other organisational aspects, but they all have to follow the same terms of reference and regulatory procedures to generate the opinion needed to start a CT (see Fig. 1). There is one coordination secretariat in charge of the national website and the annual meeting of the CPP's national board.

The choice of the local CPP where the CT dossier has to be submitted is left to the sponsor, who can only select one of the CPPs located within the geographical region where the sponsor and/or principal investigator (for respective definition of sponsor and [principal] investigators, readers are kindly referred to article 2 of the above-mentioned directive [3]) is registered and operates.

There is one administrative form that must accompany the dossier to be submitted to the CPP [8]. In this dossier, along with the administrative part to be completed with the same information for both the chosen local CPP and ANSM (see below), there are documents and information to be put in specified annexes in the dossier for CPP submission. For example, the informed consent form, as well as the product literature and information sheet for the trial subjects, the investigator's brochure (IB), the clinical protocol and the statistical design are all key elements to be provided. Indeed, the main criteria and questions reviewed, upon which the CPP should base their final opinion, mainly deal with the information that will be provided to the trial subjects (or their parents in the case of paediatric trials) in terms of completeness, intelligibility and procedures for obtaining consent, as well as the statistical design of the trial and other items, such as:

- The relevance of the trial, the acceptability of the anticipated benefits regarding the potential risks and the validity of conclusions which will be drawn from the results
- The relevance of the objectives of the clinical trial with regard to the resources provided
- Investigators' qualifications
- The modalities and amounts of compensation for the CT participants
- The modalities of recruitment of the CT participants

There are other questions, more administrative in nature, such as the insurance or the circuit for the documents, products and notifications of any side effects, essentially dealt with by the secretariat of the chosen CPP which are not discussed by the plenary committee, unless an important and specific issue is identified.

In France, it is noteworthy that whereas the technical and scientific parts of the dossier mentioned above can be submitted in English, the information sheet as well as the informed consent forms has to be in French so that the CPP members can assess their intelligibility by the patient.

In accordance with the EU legislation, for a CT involving an investigational ATMP, the time schedule for CPP response is 35 days after validation of the submission dossier. When the CPP needs further information, the time schedule can be increased up to 60 days.

The CPP has the ability (but is not obligated) to organise a hearing or a meeting when deemed necessary, to have the sponsor and/or principal investigator clarify some aspects of the proposed CT and/or the level of information that should be provided to the trial subjects. The CPP chairperson may also organise direct contact with the sponsor in the margin of this CPP meeting. The names of the rapporteurs (chosen among the members of the local CPP) are kept confidential throughout the procedure.

The CPP final opinion is communicated to the sponsor by an official letter. If the opinion is positive, the procedure is considered closed, and the trial can start provided that the ANSM authorisation is also available. The opinion of the committee is not open for discussion or an appeal procedure. In the case of a negative opinion, within 15 days following this opinion, the sponsor may request from the Ministry of Health a second review of the dossier by another CPP. The initial unfavourable opinion is forwarded to all 40 French CPPs.

2.2 National Agency Review and Approval

The second and independent procedure the sponsor has to initiate is the submission of a CTA dossier to the national competent authorities, the ANSM.

The format of the dossier is defined in a French ministerial order published on the 24th of May 2006 [9]. The main difference between the CPP dossier and the ANSM dossier is the IMPD part, which is evaluated by ANSM assessors. To initiate the procedure, the applicant has to submit the administrative form plus the relevant annexes.

As soon as the dossier has been validated by ANSM, the procedure starts. According to the legislation [3], ANSM has to finalise the written authorisation within 90 days for a cell therapy/tissue-engineered medicinal product. This time interval can be extended for a further 90 days if there is a need to ask for further information or to consult a relevant expert group. For a gene therapy medicinal product, the timeline for the assessment is 120 days which can be extended further by the ANSM depending on the nature of the additional information needed.

The specific technical annexes of the CTA dossier (IMPD, IB and clinical protocol) to be submitted along with the administrative form mentioned above are essentially aimed at allowing ANSM assessment in terms of quality, non-clinical and clinical aspects (clinical data, if any, and the clinical protocol). The assessors' review has to take into account the development phase of the trial (e.g. first in man or phase III pivotal trial), keeping in mind, as the main objective of the review, the safeguard of the trial subjects.

Briefly, in terms of documentation to be provided, the product quality profile should be described, including the manufacturing process and quality control strategy, as available at the time of submission. The quality data should mainly establish the level of quality achieved and justify the relevance of the storage conditions and shelf life to be applied for the CT period. More specifically, for ATMPs one of the critical issues to be considered remains the microbial safety, not only the sterility aspect but also minimisation of the viral risk, taking into account the biological

origin (human or animal) of most of the starting materials and reagents used throughout the manufacturing process and the absence of effective elimination/inactivation step(s). In addition to quality data, sponsors have to submit the available non-clinical data from which the safety profile of the product can be reasonably appreciated at that stage of development. The clinical aspects include the modalities of use of the product(s) as laid down in the CT protocol, the inclusion and exclusion criteria, the selection of the proposed dose(s) and modalities for the monitoring of the patients, as well as the criteria defining stopping the experimental treatment and the trial. The pharmacovigilance procedures are reviewed and whether or not to put in place a data and safety monitoring board (DSMB) is also assessed.

For their evaluation, ANSM assessor teams will perform a first review of the data submitted in the dossier and can raise questions for clarification or request further information as regards the quality profile and non-clinical and, where relevant, clinical data.

To complete their assessment, ANSM staff members can request contribution from external assessors where deemed necessary and can also organise an ad hoc working group of experts in order to reach a common view on the dossier and a final opinion to be proposed to the general director of ANSM, who is responsible for granting or refusing the CTA.

Although the extent of information and technical requirements to be submitted are now better harmonised among the EU member states and there are progressively less specific or additional requirements for the French regulatory review and formal authorisation for ATMPs, the final decision is essentially case by case. This is evidenced from the outcome of the most recent dossiers that have been processed using the VHP, which will be described later in this chapter.

During the ANSM procedure no hearing or direct interaction between the sponsor and ANSM is scheduled, although where clarifications are deemed necessary, in addition to the classical exchange of questions and answers by emails or postal correspondence taking place during the formal assessment, some prior discussions between the sponsor's team and ANSM staff members may take place before the official submission of the CT dossier. This procedure is handled by the Innovation Task Force set up by ANSM, with the intent of accelerating the exchange of information between both parties before the start of the procedure so as to meet the deadline in a timely and smooth fashion when the procedure starts.

2.3 Committee in Charge of GMO Risk Assessment

When the investigational ATMP consists of, or contains, a GMO (as defined in Directives 90/219 and 90/220) [10, 11], the sponsor has to undertake a third and independent procedure to complete the CTA. This step is aimed at getting the classification of the GMO contained in the ATMP which will determine the containment level to be applied for the confined use (research, development and production) as well as for deliberate release, i.e. for the CT phase and use in trial subjects.

This specific procedure and the corresponding dossier format have been organised in France in application of the above-mentioned directives. The body in charge of evaluating the GMO risk and proposing the classification and confinement measures is the 'Haut Conseil des Biotechnologies' (HCB). The necessary information on the way to handle the procedure is available on the website of HCB [12]. This committee is composed of two subcommittees, the first being in charge of the GMO assessment (classification and confinement measures), while the second is in charge of assessing the economic, ethical and social consequences of the use of the GMO in France. The final HCB opinion, both in terms of authorising the trial and the confinement measures to be fulfilled (if any), has to take into account the opinion of both subcommittees. It is well appreciated that this procedure, which is mandatory for any application of GMOs, is considered relatively complex when it applies to GMOs to be used in CTs. A ministerial decree is to be published soon that is intended to simplify the existing procedure.

The confinement measures (confined use and deliberate release) depend on the classification that will be granted to the GMO (based on the classification rules laid down in the relevant EU directives) and the potential hazards it may carry.

Currently, the interaction with the HCB consists of a two-step procedure. The first phase, which has to be initiated by the sponsor as early as possible (e.g. as soon as the GMO is identified and designed in the development plan), is aimed at getting the GMO classified for the confined used (e.g. research lab, production site, etc.). The classification granted (from level 1 to level 4) will also determine the level of confinement (if any) which will have to be applied for the trial subjects (from immediate release of the patient after administration up to a fixed period of quarantine and confinement imposed to the patient after treatment). The committee has also the ability to impose some follow-up measures and monitoring of the trial subjects regarding the risk of shedding and potential spreading of the GMO. It is noteworthy that during this procedure the Ministry for Agriculture and Environment has the responsibility of agreeing to and certifying the sites that are in charge of handling, manipulating or using the GMO. The level of agreement is also based on the GMO classification. This agreement, especially the one granted for the clinical investigational sites, is part of the administrative documents that are mandatory for the validation of the CT dossier that is submitted to ANSM.

The second phase is initiated by ANSM, as soon as it has received and validated the CTA dossier. In this second phase, the HCB will confirm to ANSM the conditions under which, for the sake of environmental risk and minimisation of the dissemination risk, the CT can be authorised. The HCB decision is essentially based on the classification level and confinement measures which have been notified to the sponsor in the first phase. In their final opinion, HCB has the possibility to impose to the sponsor to put in place additional tests in view to monitoring the trial subjects before they can be released from their confinement level.

When the HCB opinion is forwarded to ANSM, the agency will integrate this opinion in the final decision and inform the sponsor of the CTA decision. In addition, in application to article R1125-5 of the French Public Health Code, before granting the CTA, ANSM has to make a public announcement on its website that

a deliberate release of a GMO will take place in the framework of a CT. For that, an information sheet should be made publicly available for 30 days. The information sheet will be prepared by the sponsor, taking into account any remarks made by the HCB. During the 30-day period anyone has the right to make comments on the deliberate release of the GMO used in the CT. Finally, ANSM has to also inform the European Commission that a CT using a GMO will be conducted in France. This information will circulate across all member states during the period of public consultation in France.

3 Conduct of the Clinical Trial

When the various opinions and authorisations have been obtained (see Fig. 1), the CT can start. There are still some regulatory elements to be considered for seamless progression of the trial. However, those elements are common to all trials, and there are no specifics to follow for ATMP CTs. These points will therefore be only briefly described:

3.1 Who should be informed of the start of the CT

According to French regulation, when all the necessary authorisations have been obtained, the sponsor has to inform ANSM of the official start of the trial. If the CT, for whatever reason, does not start within the first year following the ANSM authorisation, the CTA is no longer valid, and a new procedure has to be initiated, unless the sponsor submits a request for a prolongation of the authorisation.

3.2 Substantial amendments

In the context of a CT, a substantial amendment is defined as a modification in the CTA dossier elements (IMPD, IB or protocol) which is deemed to impact significantly on the safety of the trial subjects, on the validity of the trial or on the quality and safety profile of the IMP(s) as well as any modifications to the modalities put in place to conduct the CT.

It is noteworthy that for investigational ATMPs, and particularly the cell-based products, the nature and quality of the various reagents used during the manufacturing process (the so-called raw materials) have a major impact both on the quality and the functionality/activity of the cells. Any modification in the selection or in the nature of these raw materials and the consequences of these changes regarding the safety and efficacy profile of the IMP need to be carefully assessed by the development team and be declared to ANSM as a substantial amendment. Such notification

has to follow the detailed guidance published by the EC [13]. In 2009 ANSM released a document to guide sponsors on such procedures [14].

3.3 Side effects, pharmacovigilance

As already stated, the pharmacovigilance procedures foreseen in the conduct of a CT are also applicable to CTs involving investigational ATMPs. As for any other medicinal product under development, safety information collected during the CTs will be used for the MA submission. There is one exception regarding the mandatory follow-up and monitoring of the subjects who have received an investigational ATMP: specific trials are initiated for long-term monitoring of the patients previously exposed to investigational ATMPs. The reader is referred to the relevant regulation and guideline regarding this exception [2, 15].

4 Additional Points to Consider for the Conduct of CT Involving ATMPs

Previous paragraphs in this chapter have described the respective procedures to be followed before starting and conducting a CT with an investigational ATMP. Those procedures have been established in accordance with the European and French regulations.

However, for the sake of completeness, some specific features in the French regulatory system regarding ATMPs should be highlighted and particularly those regarding the support for early development of candidate ATMPs.

4.1 The Pre-submission Meeting Opportunity

The ANSM has set up a dedicated team, namely, the Innovation Task Force, in charge of assisting the developers of health products (mainly medicinal products and medical devices), to solve their first questions on the regulatory status of the product they are developing, as well as on some more fundamental, technical and scientific questions concerning the candidate product. These meetings, called ‘innovation meetings’, are free of charge and are organised at the request of the developers.

The sponsor can also ask for clarification on GMP issues, notably regarding some specific steps or strategies involved in the manufacturing process of ATMPs, such as open system and sterile procedures and very specific quality control tests difficult to undertake in GMP facilities.

Also, during these meetings and exchanges with the ANSM Innovation Task Force, it is also possible for the sponsor of a CT to request that a 'pre-submission meeting' is organised, to optimise the submission of a CTA dossier. During the pre-submission meeting, the critical points and issues faced by the sponsor's team (particularly questions about completeness of the product quality profile and control strategy and the non-clinical programme) are addressed directly with the ANSM assessors who will have to review the CTA dossier when it is submitted.

This pre-submission meeting is thus a good opportunity for the sponsor to identify those issues which could lead to a major question during the CTA procedure where, as mentioned earlier in this chapter, there is no possibility to stop the review clock of the CA procedure. It is thus important to identify those major issues and consolidate them prior to completing the CTA dossier and start the two-step procedure (and particularly the ANSM phase) with as complete a dossier as possible.

This pre-submission meeting is optional; however, this pathway is highly recommended for ATMP sponsors envisaging initiation of a CT in France.

4.2 The Case of a Multicentre European Trials and the VHP

When a sponsor envisages the conduct of a European multicentre CT for an ATMP, it should be stressed that, as for any other IMP, the VHP could be considered and even highly recommended. This procedure is not under the remit of the EMA; it has instead been put in place at the initiative of the Heads of Medicine Agency board [16] and its 'clinical trial facilitation group'. It is coordinated by the member states. Detailed information on this procedure can be found on the website of the Paul Ehrlich Institute in Germany (in charge of the secretariat of this procedure) [17].

This chapter will not describe the VHP, as this procedure is well known and is described elsewhere [17].

When initiating a VHP in France for an ATMP, it should be kept in mind that the additional administrative layer consisting in the HCB evaluation for a GMO has still to be completed independently of the VHP steps. Thus, it is certainly worth considering a VHP for an ATMP in order to save time and harmonise the assessment criteria and final decision, with the only caveat being that when the VHP concerns a GMO, the HCB step has to be conducted in parallel.

4.3 The Case of the 'Hospital Exemption' and Early Phase Clinical Trials

The legal basis of 'hospital exemption', as described in article 28 of Regulation 1394/2007 [2], has been translated in the French legislation [18]. As a consequence, this specific exemption can be used in France for treating patients who will be enrolled in a formal CT [18]. The authorisation, taken in application of this

exemption, can be granted to hospitals, provided that it is for the product used (1) on a name patient basis (as stipulated in article 28 of Regulation mentioned above) and (2) under the responsibility of the prescriber (usually the principal investigator of the CT). In addition, for this specific case the manufacturing site (usually a hospital lab specialised in cell preparations) should follow specific quality standards and should be declared and authorised by the French competent authorities (namely, the ANSM), although the site is not considered a 'pharmaceutical establishment'.

This specific provision allows hospital and academic teams (which cannot be registered as pharmaceutical establishment) to initiate CTs, at an early phase of development of a candidate ATMP, when the manufacturing process is not yet transferred to licenced manufacturing sites operating under the GMP rules.

The procedures, described above, for obtaining the various authorisations needed to start a CT (CPPs, ANSM and HCB) remain the same. This is essentially the legal status of the manufacturing site which has been adapted by this regulatory provision under the clause of 'hospital exemption'.

According to the current legislation, the authorisation granted is valid for a given CT involving a well-identified ATMP, while the manufacturing site (within a hospital) will be authorised for a 3-year period and is subject to inspection in compliance with GMP rules.

5 Conclusion

Gene therapy and cell therapy products (ATMPs) are considered medicinal products, and as such the legislation on the conduct of CTs is applicable to an investigational ATMP. In France the scheme for obtaining the necessary authorisations to start and conduct a CT has been adapted to these specific products, although the main steps remain in the same framework as for any other candidate medicinal products. The timelines and procedures used by the French system have adopted the specific adaptation foreseen in the EU legislation for ATMPs.

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Regulation of Clinical Trials with Advanced Therapy Medicinal Products in Germany

Matthias Renner, Brigitte Anliker, Ralf Sanzenbacher, and Silke Schuele

Abstract In the European Union, clinical trials for Advanced Therapy Medicinal Products are regulated at the national level, in contrast to the situation for a Marketing Authorisation Application, in which a centralised procedure is foreseen for these medicinal products. Although based on a common understanding regarding the regulatory requirement to be fulfilled before conduct of a clinical trial with an Advanced Therapy Investigational Medicinal Product, the procedures and partly the scientific requirements for approval of a clinical trial application differ between the European Union Member States. This chapter will thus give an overview about the path to be followed for a clinical trial application and the subsequent approval process for an Advanced Therapy Investigational Medicinal Product in Germany and will describe the role of the stakeholders that are involved. In addition, important aspects of manufacturing, quality control and non-clinical testing of Advanced Therapy Medicinal Products in the clinical development phase are discussed. Finally, current and future approaches for harmonisation of clinical trial authorisation between European Union Member States are summarised.

Keywords ATMP • GTMP • CBMP • Clinical trials • Regulatory

1 Introduction

Advanced Therapy Medicinal Products (ATMPs) consist of Cell-Based Medicinal Products (CBMPs) and Gene Therapy Medicinal Products (GTMPs) [1] and are highly complex biomedicines which require high-level scientific evaluation of their safety and efficacy. Hence, marketing authorisation of this product class in the

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European Union (EU) is granted via a centralised procedure by the European Community [1]. At present, however, as for all other investigational medicinal products (IMPs), the approval of clinical trials for ATMPs is in the remit of the individual Member States in which the sponsor plans to conduct the clinical study [2]. Thus, the regulatory oversight for application, administrative procedures, execution and surveillance of such studies is the responsibility of the respective individual Member State. This does not imply that every Member State generates its own rules to regulate clinical investigations of novel medicines. In 2001, the so-called Clinical Trials Directive 2001/20/EC [2] was issued by the European Commission (EC). The main goal of this Directive is to implement common Good Clinical Practice (GCP) standards in all Member States by approximation of rules and requirements for the conduct of clinical trials on medicinal products for human use. Directive 2001/20/EC also addresses important aspects on the protection of clinical trial subjects as well as the formal and legal framework for the commencement, conduct, amendment and suspension of a clinical trial. The EC has also made available general guidance in the Communication from the Commission CT-1 [3], which addresses quality, non-clinical and clinical information and data requirements, information on the IMP that should be provided in the dossier and the general content of a clinical trial application.

2 Legal and Regulatory Framework for Clinical Trials in Germany

In Germany, the provisions of Directive 2001/20/EC were implemented within the 12th revision of the German Medicinal Products Act (Arzneimittelgesetz, AMG) [4]. Chapter 6 of this Act, which was newly created, contains (1) general and special conditions for clinical trials (AMG § 40, § 41); (2) procedures for ethics committee approval and authorisation by the higher federal authority (AMG § 42); (3) rules for withdrawal, revocation and suspension of the authorisation or of the so-called favourable opinion of the ethics committee (AMG § 42a); and (4) rules for publication of clinical trial data (AMG § 42b). Clause 42(3) of the AMG provided additional legislation allowing the German government to install a subordinated ‘Ordinance on the implementation of GCP in the conduct of clinical trials on medicinal products for use in humans’ for additional detailed provisions. Both the AMG revision and the Ordinance were enacted in parallel in August 2004. The latter was further detailed in 2006 by the ‘Third Notification on clinical trials of medicinal products for human use’ [5]. In addition to these documents, other EC Directives and the respective implemented German regulations concerning, for example, the procurement of ATMP starting material, manufacture of advanced therapy IMPs and the conduct of the clinical trial have to be taken into account. These areas are discussed below.

3 Clinical Trial Application and Authorisation Procedure in Germany

To receive authorisation for commencement of a clinical trial in Germany, the application has to be submitted to the responsible federal competent authority. In Germany, clinical trials are authorised by the Paul-Ehrlich-Institut (PEI) and the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). The PEI is responsible for the approval of clinical trials using vaccines and other biomedicines such as monoclonal antibodies, allergens, blood products and ATMPs, while BfArM evaluates applications for all other human medicines such as small molecules, recombinant proteins, herbals and narcotics, as well as medical devices.

Prior to clinical trial authorisation, a manufacturing license for the intended IMP that confirms compliance with European Good Manufacturing Practice (GMP) has to be obtained from the respective competent authority. The principles of GMP [6] are mandatory for the manufacture of all Advanced Therapy Investigational Medicinal Products (ATIMPs). The manufacturing license is granted in accordance with section 13 of the German Medicinal Products Act by the respective authority of the federal state in Germany (Länderbehörde), where the manufacturing site is located. That means, however, if, for example, manufacturing of an autologous cell product involves multiple sites located in different federal states in Germany, a manufacturing license for each manufacturing site has to be obtained from each state authority. If production of the ATIMP is outside Germany, but within the EU, the manufacturing license from the respective EU Member State, which confirms compliance of the manufacturing process with European GMP, is mutually recognised. If the ATIMP is not manufactured in an EU Member State, an import license into the EU as well as a GMP compliance statement from an EU-certified qualified person [7] is required. In this case, the competent authority of the import Member State could request a GMP inspection of the manufacturer.

All documentation that has to be submitted as part of a clinical trial application is listed in clause 7 of the 'Ordinance on Good Clinical Practice' [8]. This includes, among others, submission of the EudraCT[1] confirmation letter, the study protocol, the Investigator's Brochure, an Investigational Medicinal Product Dossier (IMPD), confirmation of compliance with data protection provisions and a summary risk/benefit assessment, all of them provided in German or English language. In addition, the intended labelling of the ATIMP and a summary of the main content of the clinical protocol should be provided in the German language. A more detailed description of the content of some of these documents is specified in the subchapter 4 on regulatory requirements for clinical trial approval.

[1] EudraCT (European Union Drug Regulating Authorities Clinical Trials) is the European Clinical Trials Database of all clinical trials of IMPs with at least one site in the EU commencing 1 May 2004 or later.

In addition to submitting a clinical trial application dossier to PEI, a positive opinion from the ethics committee responsible for the study site where the principle investigator is located has to be obtained for each clinical study. In Germany, there are more than 50 ethics committees, associated with the state governments, medical associations or medical faculties of universities. The procedures followed by the ethics committees are detailed in the different state laws. The ethics committee focuses its opinion on the appropriateness of the therapeutic concept of the proposed clinical trial and the clinical trial protocol, as well as patient-related documentation, such as informed consent documentation. For multicentre trials, the ethics committees responsible for the proposed clinical study sites also have to verify the qualifications of the investigators and the suitability of the study sites.

Many GTMPs consist of or contain genetically modified organisms (GMOs), which may be disseminated in the environment, such as through the patients' excreta. If such a GMO-containing medicinal product is going to be administered in a clinical trial, the potential risk of spreading the GMO to third parties and to the environment needs to be analysed. To this end, the sponsor of a clinical trial has to perform an environmental risk assessment (ERA) on the basis of the information specified in Annex III of Directive 2001/18/EC, which focuses on the deliberate release of GMOs [9], and in accordance with the principles of its Annex II and Commission Decision 2002/623/EC [10]. In Germany, the ERA for ATIMPs comprising a GMO is submitted to PEI as part of the clinical trial dossier. Evaluation of the ERA is conducted by PEI in consultation with the Federal Office for Consumer Protection and Food Safety (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL), who is the German competent authority for GMOs release approval. If the environmental risks of the GMO-containing medicinal product are acceptable, taking into account any proposed risk mitigation and minimisation strategy employed by the applicant of the clinical trial, the clinical trial approval includes the authorisation of the deliberate release of the GMO-containing medicinal product into the environment. The German federal states authorities (Länderbehörden) are then responsible for control of the ATMP deliberate release.

Assessment and approval of a clinical trial application follows a multistep process. The initial evaluation for completeness of the application currently takes at maximum 10 calendar days from receipt of the application. If needed, a letter listing any formal deficiencies is sent out, giving the sponsor 14 days to submit the lacking information or data. Then, for ATIMPs, a 90-calendar day assessment period starts, resulting in either an approval letter or a deficiency letter containing grounds for non-acceptance of the clinical trial. If the ATIMP consists of a xenogeneic CBMP, no time limit for the assessment period by the competent authority exists.

If approval of the proposed clinical trial cannot be granted immediately, the sponsor is asked to address the issues raised in the deficiency letter, which may concern quality, non-clinical, clinical and, if applicable, ERA aspects of the ATIMP and the clinical trial design, within a maximum of 90 calendar days. The sponsor's written response will then be evaluated by PEI within 30 calendar days of receipt. The PEI provides a written decision, which may be approval, approval with ancillary provision, refusal of specific aspects of the clinical trial or refusal of

the clinical trial application. For clinical trials that have received approval to proceed, subsequent substantial amendments to these ongoing trials for ATIMPs will also need approval by the PEI. This is done in a one-step procedure, with significantly shorter timelines.

Since the implementation of the Clinical Trials Directive 2001/20/EC into the German Medicinal Products Act in 2004, more than 160 clinical trial applications with ATIMPs have been submitted to the PEI. Among them, around 1/3 are GTMPs and 2/3 are CBMPs, either somatic cell therapies or tissue-engineered products. Of the GTMPs, mainly DNA plasmids, viral vectors based on vaccinia virus or adenovirus as well as genetically modified cells are in clinical development in Germany. The main clinical indication for these GTMPs is cancer. Furthermore, in Germany GTMPs based on adeno-associated virus, herpes simplex virus, retro- and lentivirus, as well as genetically modified bacteria, are investigated in clinical studies. In recent years, genetically modified oncolytic viruses have also entered clinical development. Regarding CBMPs, a great variety of products are being clinically evaluated in Germany. Among them are chondrocytes for the treatment of joint disorders, muscle-derived cells for treatment of urinary/anal incontinence, immune cells for adoptive immune therapy, various stem/stromal cells (haematopoietic stem cells, mesenchymal stromal cells) to treat graft-versus-host disease, limb ischemia, heart failure, bowel disease and visual impairment, as well as different cell types to treat burns, ulcers, sepsis, liver failure and cornea defects.

4 Regulatory Requirements for Use of ATMPs in Clinical Trials

The Committees (Committee for Advanced Therapies (CAT), Committee for Medicinal Products for Human Use (CHMP)) at the European Medicines Agency (EMA) have issued several guidelines addressing the scientific requirements for cell and GTMPs [11, 12]. However, most of these guidance documents describe the set of quality, non-clinical and clinical data needed at the level of a MAA (Marketing Authorisation Application) of an ATMP, which understandably differs from the data set available during or even at the beginning of the clinical development programme.

4.1 Procurement and Donor Testing

ATMPs are often based on a complex manufacturing process, in most cases involving eukaryotic cells either as starting material for the production of viral vectors used as a GTMP or for the production of the active substance consisting of cells which are or are not genetically modified. Hence, donor suitability and quality control of procurement for primary cells and the origin and history of any cell lines used are key aspects in the manufacturing of ATMPs.

The requirements for quality and safety standards for the donation, procurement and testing of human tissues and cells are specified in Directives 2004/23/EC [13] and 2006/17/EC [14] and Directive 2002/98/EC for human blood cells [15]. In Germany, these requirements have been implemented by a special tissue ordinance in the frame of the National Transplant Act (TPG-Gewebeverordnung (TPG-GewV)), which came into effect in July 2007 [16]. Together with the German Medicinal Products Act and the German Ordinance for the Production of Medicinal Products and Active Substances (Verordnung zur Änderung der Arzneimittel-und Wirkstoffherstellungsverordnung (AMWHVÄndVO)) [17], these laws represent the most important legal provisions governing blood components, tissues and cells.

In general, Directive 2004/23/EC [13] defines minimum standards to ensure high-quality and adequate safety for human tissues and cells used for clinical application in humans or as starting materials for the manufacture of ATMPs. The TPG-GewV [16] exceeds the minimum requirements laid down in Directive 2004/23/EC and aims at the highest level of safety for all tissues and cell-derived medicinal products distributed on the German market. This approach was generated in the context of the HIV safety issue experienced worldwide with blood products in the 1990s. Since then, the transmission of viral and nonviral infectious pathogens is considered a serious potential risk factor associated with the use of allogeneic tissue and CBMPs. Nucleic acid amplification tests (NAAT) are considered to be most sensitive at the early stages of infection and will therefore be able to narrow the diagnostic window for the detection of respective infectious agents. Thus, in Germany, NAAT on HIV-1/2, hepatitis B and hepatitis C may have to be conducted in addition to the serological donor testing regime, as specified in Annex 2 of Directive 2006/17/EC (implementing Directive 2004/23/EC) or the respective German Tissue Ordinance [14, 16]. In particular, donors of tissues and cells derived from organs with good blood supply (e.g. bone marrow, muscle tissue) have to be subjected to NAAT testing in addition to serological testing. In special cases, such as for procurement of skin or cornea for the manufacturing of tissue preparations, NAAT is not regarded as mandatory to ensure adequate safety. The establishments in Germany, where procurement of tissues and cells and the pertinent donor testing are performed, should obtain an authorisation according to clause 20 of the German Medicinal Products Act [4], which is issued by the respective authority of the federal state. The authorisation for procurement can also be covered by the manufacturing license according to clause 13 of the German Medicinal Products Act. The appropriate procedure will be selected by the federal state authorities depending on the number and the location of the procurement facilities in Germany. Import of donor tissues or cells from outside the EU requires a respective import license.

4.2 ATIMP Manufacture

ATMP development is challenging not only due to the intrinsic complexity of the products but also due to the complexity of their manufacturing processes. Thus, ATMP developers should put particular emphasis on the design of the manufacturing

process, as well as on its control. In this respect, the methodology of the risk-based approach, implemented as a tool to justify the extent of data included in the MAA, may help identify potential risks and risk factors inherent to the ATMP with respect to quality, safety and efficacy and to develop a strategy to address and minimise these risks in product manufacture, non-clinical evaluation and clinical application. Details can be found in the EMA 'Guideline on the Risk-Based Approach according to Annex I, Part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products' [18].

As with all biologicals, slight or even unrecognised variabilities in starting or raw materials or in the manufacturing process may have a major impact on the characteristics of the product. Thus, implementation of a sufficient number of meaningful and robust in-process controls and release tests is of key importance. Performing extensive characterisation studies in parallel to clinical development increases the understanding of the product. Consistent manufacturing is a key aspect already at the stage of early clinical development, in particular for those medicinal products which are individually produced for each patient (e.g. to assure consistent manufacturing from autologous starting materials) a sufficient number of batches need to be produced and analysed. In contrast, for an off-the-shelf product such as a viral vector and during early clinical phase development, it may be acceptable to rely on data from the production of just one batch, provided that the clinical trial authorisation is restricted to the use of this batch only. For the use of subsequent batches, batch-to-batch consistency within the specified acceptance limits needs to be shown.

Due to the great variety of medicinal products classified as ATMPs, the tests and analytical procedures employed and the respective product specifications are quite diverse and hence will not be discussed in detail here. In general, aspects regarding the identity, purity, safety and biological activity should be addressed in as much detail as necessary and feasible at any stage during clinical development. Detailed information can be found in the various guidelines for the different ATMP product classes published on the EMA website [11, 12]. It should be noted, however, that many of these guidance documents address the extent of requirements at the level of a MAA and may have to be adjusted to the stage of clinical development. An example where such adaption is needed is with evaluation of potency of the active substance. Potency describes the biological activity of an ATMP and is considered to be an important indicator for clinical efficacy. However, correlation between potency and clinical efficacy can only be made late in clinical development; thus, for early clinical studies potency of an ATIMP may only be addressed in a limited way. For example, when a viral vector is the active substance in a phase I clinical study, confirmed expression of the therapeutic gene is often presented and considered acceptable as evidence of potency. However, irrespective of the potency assay chosen, the resulting data should generate a conclusion on batch-to-batch consistency regarding the function of the ATIMP and help to detect potentially subpotent batches. Specifications for potency testing as well as for many other product release specifications understandably are often rather wide at the early clinical stages but should be constantly reviewed and adjusted as further manufacturing, non-clinical and clinical experiences are obtained over time in order to achieve consistent manufacture of the ATMP at MAA.

However, it is crucial to correlate the potency specifications of the ATMP produced for marketing with the lots tested clinically.

The requirements regarding validation of analytical procedures also differ during clinical development. At the early clinical stages, at least a description of the analytical procedures as well as a justification for the suitability of the methods is required, whereas for later clinical stages a validation plan and eventually full validation are mandatory. However, most critical tests for safety (e.g. evaluation of sterility or assays addressing the viral safety) should be validated early in clinical development.

Regarding stability of the medicinal product, a plan for analysis of stability of the active substance and the drug product needs to be presented to PEI prior to a phase I clinical study, proposing accompanying studies during the trial. At later stages of clinical development initial stability, data should be already available.

To a large extent, the development of ATMPs is strongly driven by new scientific knowledge which quite often results in modification of the medicinal product during the clinical development process. Predominantly this is observed with GTMPs, such as alteration of a vector sequence or when the surface protein of a viral vector particle is changed. In addition, changes in manufacturing due to upscaling or changes in up- and downstream processes (e.g. implementation of additional purification steps) are often pursued in the later stages of clinical development. It is important to consider potential consequences of such changes to the extent possible as early as the beginning of the clinical development programme and to address them accordingly during clinical development. This plan would include suitable analyses of comparability regarding the quality of the product and, if necessary, conducting non-clinical bridging studies if comparability of the products produced in the previous and current manufacturing process could not be shown. The extent of analyses needed to address changes in the design of an ATIMP strongly depends on the actual modifications to that specific product and needs to be defined on a case-by-case consideration. However, guidance providing various examples of product modifications and recommendations for addressing comparability issues from a regulatory perspective is available in an EMA reflection paper [19]. It is crucial that at the time of MAA, the relevance of the clinical data obtained during development is ensured for the ATMP finally manufactured for marketing.

In the clinical trial application, information regarding quality of the IMP is presented in the IMPD, which is structured in accordance to Module 3 of the EU common technical document (CTD) format. The detailed structure and content of the IMPD dossier should be as requested in the ‘Third Notification on the clinical trial of medicinal products for human use’ [5].

4.3 Non-clinical Regulatory Aspects for ATIMPs

Public perception regarding the safety of administered ATMPs may be higher as compared to conventional medicinal products. Such concerns may originate from existing knowledge, such as the risk of insertional oncogenesis associated with the

use of integrating vectors for transduction of haematopoietic stem cells, or from uncertainties about the mode of action and the potential toxicities of administered ATMPs. From a regulatory perspective, the safety issues relevant for ATMPs might be somewhat different from conventional drugs, and due to the nature, design and manufacture of the individual medicinal product, the non-clinical testing addressing the potential toxicities and safety concerns may not be as straightforward as for other pharmaceuticals. Nevertheless, these properties do not justify attribution of a higher risk level for ATIMPs per se; however, the safety profile of each product has to be established using a tailored approach.

The dosing regimen for a majority of ATMPs consists of a single administration. However, many are expected to remain in the human body for a prolonged period of time and thus provide a long-term therapeutic effect. This aspect requires specific considerations for non-clinical pharmacology and safety studies. For example, classical single-dose toxicity studies addressing only acute toxicity are often not adequate for such products. Instead, longer observation periods need to be included to investigate potential long-term effects that could become evident weeks or months after administration of the ATIMP. The inclusion of safety endpoints into the proof-of-concept studies could therefore be considered. Moreover, pharmacokinetic studies investigating the biodistribution, persistence and clearance of the ATIMP may be helpful to determine the appropriate study duration of the toxicity studies. In general, the design of those studies should consider the specific nature of the administered medicinal product. For example, when a replicating viral vector is intended to be administered only once, a single-dose toxicity evaluation may not be sufficient because virus vector replication and spread in the human body might result in a second or subsequent viremia. This possible scenario needs to be addressed by repeated dosing in the non-clinical study in case the viral vector is unable to replicate in the animal.

For pharmacokinetic studies with GTMPs, additional studies investigating the duration of expression of the introduced transgene may complement the quantitative PCR assays used to detect the introduced nucleic acid sequence in different organs and tissues. In case biodistribution studies reveal persistent signals of the introduced nucleic acid sequence in the gonads, studies of inadvertent germline transmission in accordance to the ‘Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors’ [20] are usually requested. Depending on the pharmacokinetic studies and the GTMP used, integration studies may also be required.

The need for genotoxicity and/or carcinogenicity studies depends on the nature and the design of the GTMP. Ex vivo transduction of stem cells using integrating vectors such as retro- or lentiviral vectors has the potential of causing insertional oncogenesis. The risk may vary depending on the design of the vector construct used, as well as on the ‘stemness’ of the cells that are genetically modified. In accordance with the potential risk of a specific genetically modified cell, the potential for insertional oncogenesis should be investigated when applying for a clinical trial in Germany. Performance of tumorigenicity studies for GTMPs will only be expected if indicated by the product construct, for example, if a GTMP is expressing a growth factor.

The biggest challenge with regard to the non-clinical development of ATIMPs is the choice of relevant animal models. When testing human cell therapeutics in animal models, the xenogeneic setting might result in clearly different outcomes compared to an allogeneic or autologous setting, such as when human cells are administered to human patients. If cells, genetically modified cells or nonhomologous therapeutic gene products are recognised as foreign and cleared prematurely by the immune system of the animal species, the informative value of the non-clinical data will be limited. Similarly, a viral vector-based GTMP might exert significant differences in the infection/transduction tropism and strength between animals and humans. This clearly impacts the translation of the non-clinical data and the selection of a safe and, if intended, efficacious starting dose in humans. Furthermore, expression of a human therapeutic gene in an animal model may affect the activity of the non-homologous protein as well as its immunogenicity; thus, additional important aspects are to be considered. Therefore, the relevance of the selected animal models has to be always scrutinised and justified. On the other hand, if no suitable animal model is available to address specific aspects regarding safety and/or efficacy of the ATIMP, the conduct of in vivo studies in nonrelevant animal models to solely fulfil requirements set in the guiding documents is not justified.

4.4 Clinical Considerations

When applying for approval of a clinical trial in Germany, the general principles which apply to all medicinal products also have to be taken into consideration for ATIMPs. Such considerations include the evaluation of pharmacodynamics, pharmacokinetics and potential toxic effects due to ATMP administration, as well as dosing. However, due to the specific nature of these products, additional concerns apply. Principal considerations to these specific clinical aspects can be found in respective EMA guidelines [11, 12] and in the chapter titled 'EU Marketing Regulatory Oversight of ATMPs—EMA/CAT' in this book. Thus, only a few particular clinical viewpoints will be highlighted here.

Cutting edge discoveries in medical science quite often result in swift development of an ATMP as therapeutic concept. This leads to an application for first-in-human clinical trials with first-in-class medicinal products. As a result, the designs of the clinical trials, such as starting dose selection or a staggered approach for patient enrolment, are important considerations. These design aspects are also important considerations if the safety profile of the active substance can be evaluated only in a limited way in non-clinical studies due to the lack of suitable animal models. This may, for example, be the situation for genetically modified cells expressing a recombinant T-cell receptor, where potential on- and off-target adverse effects often cannot be addressed in animal models due to differences in antigen presentation and HLA-restriction of the T-cell receptor.

Treatment with ATMPs often results in persistence of the active substance, cell or viral vector, within the human body resulting in a long-lasting effect. In this respect, the conduct of conventional adsorption, distribution, metabolism and excretion (ADME) studies are usually not advisable for ATIMPs. However, aspects of persistence and clearance of the ATIMP should be addressed, if possible. In addition, for GMTPs based on a viral or nonviral vector, it is important to investigate dissemination in the patient, as well as potential mobilisation and shedding. The intended long-term persistency of ATIMPs should be reflected in a long-term follow-up of the patients with regard to safety and efficacy of the ATIMP. For viral vectors, patient follow-up is recommended for at least 5 years. In the case of integrating vectors, such as those used to transduce haematopoietic stem cells, a much longer follow-up period is advised [21].

4.5 Environmental Risk Assessment

As already indicated, an ERA needs to be performed if a GMO-containing medicinal product is studied in a clinical trial in Germany. In addition to the risk to the environment per se, the ERA also considers the potential harmful effects on third parties exposed to the GMO-containing ATIMP, such as medical staff caring for the patient, or family and household members with close contact with the treated individual. Initially the characteristics of the GMO are evaluated for potential adverse effects on the biota and the health of third persons. This analysis also considers vulnerable third-party groups such as immune-compromised people, pregnant women, newborns, and children. A second step in this process evaluates the likelihood that the GMO is released into the environment or is transmitted to close contacts. Therefore, determination of the distribution of the GMO within the patient and potential shedding into excreta and other body fluids is crucial and needs to be investigated both in non-clinical and clinical studies. Depending on the nature of the ATIMP and the route of administration (e.g. when administered via intramuscular, intradermal or subcutaneous injection), dissemination of genetically modified bacteria, viral vectors or viruses may also occur. Such shedding analyses are important for determining the likelihood that a potential harmful effect on the environment or on third parties will occur. Therefore, these data are an important part of the ERA, which not only defines the risks for third parties and the environment but also determines the measures that need to be implemented to reduce any identified risk following administration of a GMO-containing ATIMP. Such measures may include application of a dressing over the injection site, specific hygienic measures, decontamination of excreta or avoiding close patient contact with vulnerable groups. Detailed guidance on how to perform an ERA is available at the EU level and should also be considered for clinical studies in Germany [22]. Please also refer to subchapter 3 of this chapter for detailed procedural information.

5 Approaches to Harmonisation of Clinical Trials in the EU

In 2004, the Voluntary Harmonisation Procedure (VHP) was established by the clinical trial facilitation group (CTFG), which is a board that coordinates implementation of the Clinical Trials Directive 2001/20/EC and harmonises assessment decisions on multinational clinical trial applications among the national competent authorities in the EU. A VHP application for a multinational clinical trial carried out in at least two Member States will be evaluated in a single procedure in a joint effort of all voluntarily participating national competent authorities of those Member States in which the trial will be conducted. This process results in a harmonised scientific assessment and a joint discussion of all issues by the involved competent authorities. Subsequent to the completion of the VHP, which takes in total 60 calendar days or 90 calendar days for ATIMPs from the confirmation of validity of the application by the CTFG-Coordinator, separate national applications have to be filed by the sponsor to the national competent authorities that are involved in regulating the clinical trial. The decision regarding the national clinical trial application will then be generally made within 10 calendar days by the competent authorities of the involved Member States.

Since its implementation, an increasing number of VHPs have been conducted, with more than 150 applications in 2013. For ATIMPs, the first application occurred in 2011; more than ten clinical trial applications for ATIMPs have now been submitted via the VHP in Germany. Among them only two were requested for GTMPs, in four and five Member States, respectively. The other applications were submitted for CBMPs involving up to 14 different national competent authorities (averaging 4–5 Member States for each). As a result, approval or conditional approval with conditions to be fulfilled in the frame of individual national applications was granted. These numbers suggest that the VHP is a suitable tool to facilitate multinational clinical trial applications, to accelerate their assessment and to result in consistent review and recommendations across the involved Member States.

6 The New Clinical Trials Regulation

Recently the European regulatory system for clinical trials was fundamentally revised. With the new EU Clinical Trials Regulation (Regulation (EU) No 536/2014) adopted in April 2014 and published in the Official Journal of the European Community in May 2014 [23], the current Directive on Clinical Trials (2001/20/EC) will be repealed. The new Regulation is implemented to further streamline the authorisation procedure of clinical trials in the EU. Although Directive 2001/20/EC is also aimed at harmonising the rules for clinical trials across the EU, its implementation into national law resulted in certain variations between the application procedures for each Member State. However, these variations may impede and prolong the application procedure, in particular for multinational clinical trials.

The new Clinical Trials Regulation is intended to apply from May 28, 2016. By then an electronic EU portal and database should be set up by the EMA, the EC and the Member States as single-entry point for clinical trial applications, irrespective of whether they are monocentric, multicentric or multinational. The EU portal and database, however, will not only be used for the initial submission of the application but also for the entire subsequent communication. Thus, the portal and database are central to the new application procedure and the Clinical Trials Regulation will come into effect no sooner than 6 months after the portal has been declared to be fully functional by the EMA and the EC, in any event no earlier than 28 May 2016 [23].

7 The Hospital Exemption: An Additional Route for Making ATMPs Clinically Available?

In addition to the obligation for a mandatory centralised marketing authorisation to place an ATMP onto the EU market, Regulation 1394/2007/EC [1] introduced an innovative regulatory concept, commonly referred to as 'hospital exemption'. This alternative regulatory route is only applicable to ATMPs which are prepared on a nonroutine basis according to specific quality standards for an individual patient and which are used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner and which are individually prescribed. The hospital exemption is an ambitious legal construct. Clause 28 of Regulation 1394/2007/EC [1] calls for the amendment of Article 3 of Directive 2001/83/EC [24]. As a consequence, the enforcement of this clause and the authorisation procedure is shifted from the EU level to the national level, thereby 'exempting' those products from the obligation to have a centralised marketing authorisation. This is also the reason why cross-border manufacturing or delivery is not possible for those products. One could reason that the hospital exemption therefore focusses on individual patient-centred care rather than on broad market distribution of an ATMP with a high commercial impact. Indeed, the wording of the article has raised intensive discussion regarding how to adequately interpret a number of legally undefined terms, such as 'nonroutine' or 'custom-made' and how and when the hospital exemption should be applicable.

In Germany, section 2 of clause 4b of the German Medicinal Products Act [4] stipulates an interpretation on what is understood by 'nonroutine'. It is the case either when (1) the ATMP is manufactured in small quantities and, if based on a routine manufacturing process, variations in the process, medically justified for an individual patient, are carried out, or (2) if the ATMP has not yet been manufactured in sufficient quantities thus, the necessary data enabling a comprehensive assessment are not yet available. For Germany, in contrast to some other Member States, a maximum number of batches allowed to be administered or the number of patients allowed to be treated with an ATMP under hospital exemption permission has not been legally set. Moreover, the type of process variation has not been further

delineated, nor is the term 'sufficient quantity' defined. However, it has to be noted that preliminary data regarding product quality, (clinical) safety and efficacy are requested in order to allow for an initial benefit risk evaluation and to support the use of the ATMP, but not to the extent required for a marketing authorisation via the centralised procedure. In conclusion, all aspects must be considered on a case-by-case basis to determine if an ATMP is eligible for authorisation according to clause 4b of the German Medicinal Products Act. As for clinical trials, the applicant has to have a procurement license for tissue or cell procurement (if necessary), a manufacturing license, and a GMP compliance statement for the manufacture of the specific ATMP.

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Marketing Regulatory Oversight of Advanced Therapy Medicinal Products (ATMPs) in Europe: The EMA/CAT Perspective

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Abstract With the release of Regulation 1394/2007, a new framework for gene and cell therapy medicinal products and tissue-engineered products was established in the European Union. For all three product classes, called advanced therapy medicinal products, a centralised marketing authorisation became mandatory. The European Medicines Agency (EMA) together with its Committee for Advanced Therapies, Committee for Human Medicinal Products and the network of national agencies is responsible for scientific evaluation of the marketing authorisation applications. For a new application, data and information relating to manufacturing processes and quality control of the active substance and the final product have to be submitted for evaluation together with data from non-clinical and clinical safety and efficacy studies. Technical requirements for ATMPs are defined in the legislation,

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and guidance for different products is available through several EMA/CAT guidelines. Due to the diversity of ATMPs, a tailored approach for regulating these products is considered necessary. Thus, a risk-based approach has been introduced for ATMPs allowing flexibility for the regulatory requirements. Since the regulatory framework for ATMPs was established, five products have been licenced in the European Union. However, the pipeline of new ATMPs is much bigger, as seen from the significant numbers of different products discussed by the CAT in scientific advice and classification procedures. In 2013, a public consultation on the ATMP Regulation was conducted by the European Commission, and the results were published in 2014. The report proposes several improvements for the current framework and established procedures for the regulation of ATMPs.

Keywords ATMP • Cell therapy • Gene therapy • Tissue engineering • Regulation • Risk-based approach

1 Introduction

Gene and cell therapy products have been regulated in the European Union (EU) as medicinal products since 2003, when they were introduced into legislation through Directive 2003/63/EC [1]. Tissue-engineered products, although already widely used in hospitals at that time, remained outside of the legal framework and were not regulated at all in most EU member states. Later, in 2007, all three product classes were brought under the same legislation as advanced therapy medicinal

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products (ATMPs) [2]. This legislation specified that marketing authorisation of ATMPs in the EU falls within the mandatory scope of the centralised procedure where pharmaceutical companies submit a single marketing authorisation application (MAA). Once granted by the European Commission (EC), a centralised marketing authorisation is valid throughout the entire EU. The European Medicines Agency (EMA) is responsible for the scientific evaluation of applications under the centralised procedure. Most of the EMA's scientific evaluation work is carried out by its scientific committees, which are made up of representatives from EU member states, as well as representatives of patient, consumer and healthcare professional organisations. These committees have various tasks related to the development, assessment and supervision of medicines in the EU. In addition, together with EMA, these scientific committees play a role in stimulating innovation and research via scientific advice, guideline development, support developers in small- and medium-sized enterprises (SMEs), orphan designation and early dialogue through the Innovation Task Force (ITF) meetings. National authorities in the EU member states will likewise support medicine development, e.g. via national scientific and regulatory advice and respective innovation offices within national Medicines Agencies.

In the ATMP Regulation 1394/2007, a possibility for national authorisation and supervision of non-industrially manufactured ATMPs used under the responsibility of treating physician was included in article 28 (the so-called hospital exemption). This allows national approval of manufacturing licences for products that fulfil the requirements defined in the regulation, pertaining mainly to quality, traceability and pharmacovigilance follow-up of the exempted products. Exemption means that such products are outside of the normal legal requirements set for medicinal products and can be produced and used only on national level.

In 2001, a Gene Therapy Working Party (GTWP) and, in 2005, a Cell-Based Product Working Party (CPWP) were established at EMA to help the Committee for Human Medicinal Products (CHMP) in scientific matters related to gene- and cell-based therapies. These two working parties, in collaboration with CHMP and its Biologics Working Party (BWP), generated the first guidelines for ATMPs in Europe. They also contributed to establishment of the technical requirements for ATMPs [3]. In 2009, with the Regulation (EC) 1394/2007, the Committee for Advanced Therapies (CAT) was established. The Committee is comprised of members and their alternates representing all member states. Five of the CAT members are also CHMP members to ensure proper collaboration and flow of information between the two Committees. Physicians and patient organisations are also represented in the CAT: these members are nominated by the EC. The CAT is responsible for evaluation and draft opinion of ATMP MAAs, which are further discussed by CHMP to generate the final opinion, followed by transmission of the opinion to the EC. Since its inception, the CAT has further discussed and revisited the regulatory requirements and guidance for ATMPs. The CAT has also other roles in regulating and supervising ATMP development in the EU, which are further described in this chapter.

Gene and cell-based therapies are manufactured from complex starting materials, they are themselves multifunctional and there are several risks and limitations related to development and approval of ATMPs that are not foreseen for other medicinal products. Thus, also the requirements and the overall regulatory framework have to be specifically tailored to fit these innovative therapies into framework of medicinal products. A risk-based approach was initially agreed as part of the new ATMP legislation [3], and guidance for the implementation of this approach was established in 2012 [4]. With the same objective, principles and requirements for long-term safety and efficacy follow-up were set in the ATMP legislation [2] and included in specific guidance [5].

In 2014, 5 years after the ATMP Regulation [2] came into force and the CAT was established, the experiences of the legislation and functionality of the overall regulatory framework were evaluated by the EC through a public consultation. A report outlining the benefits and shortcomings of the current legislation was published on April 1, 2014 [6]. Possible future directions, as described in the report, are discussed in this chapter.

2 Legal and Regulatory Framework for ATMPs

The ATMP Regulation (Regulation (EC) 1394/2007), which came into force in December 2008 [2], provides tailored regulatory principles for the evaluation, authorisation and post-authorisation follow-up of ATMPs, sets up a committee with expertise specific to ATMPs (the CAT) and provides incentives for developers of ATMPs. Some of these incentives are financial (fee reductions, e.g. for scientific advice), while other incentives are in the form of procedures intended to assist the development of ATMPs: the ATMP classification procedure and the ATMP certification procedure. The ATMP classification procedure provides ATMP developers the possibility to request the CAT to make a scientific recommendation whether their product will or will not fulfil the definition of an ATMP. The classification is especially relevant for cell-based ATMPs, which need to be segregated from traditional transplantation/transfusion products. The CAT classification will provide regulatory certainty about the legal framework that is applicable as well as the scientific guidance to be consulted during product development. The second procedure, the ATMP certification procedure, is restricted to SME developing ATMPs. During the certification procedure, CAT will perform a scientific evaluation of quality/manufacturing and, if available, non-clinical data that are generated with the product. This evaluation will give the SME a strong indication if their ATMP development programme is on track to meet the standards of a future MAA.

In general, ATMPs will have to fulfil the same scientific and regulatory requirements as other medicinal products. The manufacturing of ATMPs will have to comply with the principles of good manufacturing practice (GMP), clinical trials will have to be designed and conducted in accordance with the principles laid down in good clinical practice (GCP) and the same post-authorisation and pharmacovigilance requirements that apply to medicinal products will apply also to ATMPs.

However, the existing legislation delineates a tailored approach to take into account the specificities of ATMPs: most notably to mention is the amended Annex II to the EU guide to GMP [7] and the draft guidance on GCP for ATMPs [8].

Regarding the requirement for the MAA, ATMPs will also follow the general requirement to document the quality, non-clinical and clinical development of their product as described in the Annex I to Directive 2001/83/EC (implementing Directive 2009/120/EC [3], which lays down the technical requirements for all medicinal products). Here as well, the ATMP Regulation provided the legal basis for the revision of this Annex I: tailored requirements are set for ATMPs, not only to take into account the specificities of ATMPs but also to lay down the legal basis for ATMP development on the basis of a risk-based approach. The latter allows the ATMP developer from the beginning and throughout the product development programme to determine and justify the extent of quality, non-clinical and clinical data to be included in the future MAA, on the basis of a risk profiling strategy specifically developed for these products. The CAT has published a scientific guideline on how to apply this risk-based approach [4]. The high-level technical requirements defined in Directive 2009/120/EC are further substantiated in scientific guidelines published on the EMA website [9, 10].

ATMP developers will also have to take into account other legislation when developing or marketing their product. Most important are the following:

- For ATMPs based on human cells, Directive 2004/23/EC [11] and its implementing directives for the donation, procurement and testing of the human tissues or cells that will become the starting materials of the ATMPs [12, 13].
- Legislation concerning traceability and pharmacovigilance follow-up [14].
- For gene therapy medicinal products (GTMPs), legislation on genetically modified organisms (GMOs) [15, 16].
- For combined ATMPs, including one or more medical devices, the legislation on medical devices [17, 18]. It should be noted that the medical device legislation is currently under revision with the most recent information provided on the EC website on medical devices [19].
- For ATMPs based on human blood and blood components, Directive 2002/98/EC [20] with its implementing directives "Setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components" that will become the starting materials of the ATMPs [21, 22].

3 Special Considerations on Quality and Manufacturing Aspects for ATMPs

The manufacture of ATMPs is generally perceived as complex and needs to be tailored to the intended product. Since the ATMPs are a very varied group of medicines, it is difficult to advise on a single approach that fits all. However, general

strategies that also apply to non-ATMP products should be followed during development aside from considering product-specific requirements.

For GTMPs that are based on viral vectors or plasmids, product development is similar to that of biotechnology-based medicinal products, and guidelines related to quality and manufacturing aspects have been developed at EMA/CAT and at the international level (ICH). For ATMPs based on human cells and tissues, the manufacturing processes are different from those of other medicinal products, and quality control requires specific methodologies. While acknowledged that often manufacturing processes are considered to follow established protocols used in preparation of transplantation materials, a properly established and controlled manufacturing process is required to ensure consistency of a medicinal product. The legislation demands that data generated in clinical trials provides the basis for commercial use of a product, and it is therefore important to note that if the quality of the ATMP is not adequately defined, the validity of the entire clinical trial may be jeopardised. The knowledge gained from process development is paramount for an adequate characterisation programme and is often needed to support a more reduced release testing strategy, namely, for autologous products.

The first step in the establishment of the manufacturing process for an ATMP should be a thorough planning exercise resulting in the definition of a quality target profile. The initial question to be addressed in this context is "what is my product?" i.e. is it a pure or mixed cell population, a tissue, genetically modified cells or a viral vector, etc., followed by "what is the (hypothesised) mechanism of action?" and "what are the product-related substances and impurities that can be expected?" From the answers gathered, a manufacturing process supported by a control strategy should arise. Ultimately, characterisation should cover relevant assays for identity, purity, safety and biological activity [23, 24]. In order to ensure consistent manufacture, product stability and comparability after manufacturing changes, the potency/functional assays provide valuable information.

3.1 General Quality and Manufacturing Aspects

3.1.1 Starting and Raw Materials and Excipients for Production of ATMPs

The source of the starting materials and raw materials used during the manufacturing process needs to be chosen to avoid the risk of transmitting adventitious agents. While clear legal requirements are defined for human source materials used as starting materials for ATMPs [11–13], a developer will need to consider the reagents of biological origin used in the product-specific manufacturing process for adventitious agent testing. Avoidance of materials of human and animal origin in manufacturing reduces testing requirements, but it is usually not feasible for ATMP manufacture. A number of EMA guidance documents provide support in approaching the issue of adventitious agents including viral risk assessment [25].

Also guidance regarding raw materials used in the manufacture of ATMPs has been developed by EMA/CAT experts and the European Directorate for the Quality of Medicines (EDQM) to be included as a general text in the European Pharmacopoeia [26]. For excipients, an active substance master file cannot be submitted in the EU, and full module 3 data are required at the time of MAA. For excipients derived from human blood, the CHMP guideline on plasma-derived medicinal products provides guidance on data requirements [27].

As already mentioned, the manufacture of ATMPs frequently entails the use of biological substances, such as growth factors. Unless they are available as licenced medicinal products where composition, content and viral safety are addressed (i.e. interleukin-2, human albumin), the burden of qualification of these raw materials lies with the manufacturer. Detailed knowledge on the materials used is required not only to assure a consistent manufacturing process but also to support a change of suppliers if required. Therefore, a given growth factor used during cell culture needs to have consistent biological activity across lots, and the composition of the solution/lyophilisate that contains the protein needs to be known. For example, if the solution contained albumin, the origin of the albumin needs to be known, as well as the testing the protein has been subjected to. Again, the requirements are not only of relevance from the manufacturing consistency perspective but also from a safety point of view. Obtaining this detailed information is not necessarily easy for developers buying these raw materials and might require considerable effort. It should be noted that expensive raw materials claimed to be of "GMP-grade" do not necessarily fulfil all regulatory requirements. GMP is a pharmaceutical quality assurance system, not intended for reagents and cannot be taken as a statement of proven quality for raw materials.

As for all biological medicinal products, the issue of adventitious agents needs to be addressed comprehensively, by using raw materials with minimal risk, a well-controlled manufacturing process and a control strategy that provides further assurance of safety for the patient.

3.1.2 Manufacturing Process

A well-controlled manufacturing process is one that reproducibly yields a product of desired quality, i.e. target profile. That profile needs to be defined as clearly as possible for the given stage of product development. The process parameters and in-process controls should be derived from studies investigating the critical quality parameters of the product. Scientific knowledge from research and development can be of value to justify the expected link between the manufacturing process and the quality parameters selected to control the manufacturing process. Hence, closely linked with the definition of the target profile is the definition of critical process parameters, i.e. which process steps and operating conditions are essential to obtain the desired product quality and what are the operating conditions required to achieve that goal. A risk-based approach [4] could be considered (and brought to this deeper level) to scrutinise the critical process steps and identify the optimum conditions for those steps that will ensure generation of a consistent product for marketing authorisation.

3.1.3 Quality Control

A prerequisite for meaningful results is analytical methods that have been proven to be suitable for their intended use during early development and are fully validated at the time of submission of a marketing authorisation. Products with complex biological activities will require multiple orthogonal (i.e. independent) analytical methods for characterisation. It is highly recommended to aim at an in-depth characterisation of the product with a range of different analytical methods beyond those that will be used to measure the specifications. The more varied the analytical toolkit, the better and with more confidence can a comparability exercise be managed later on, where it might be necessary due to manufacturing changes.

The specifications should reflect the target profile and be well justified by results from characterisation studies and published knowledge. If conforming to specifications, the ATMP needs to be capable of performing its intended biological function. Regulators will ask for data to support the established specification limits. Specifications should be numerical values (i.e. quantitative) as much as possible. Surrogate markers, for example, surface molecules, measured by flow cytometry can be used, but their correlation to biological activity needs to be demonstrated, in particular their acceptable ranges in the context of biological activity.

Finally, the stability and shelf life of the ATMP need to be established to ensure that the product is still safe for use and performing its intended function at the end of the specified shelf life.

3.2 Gene Therapy Medicinal Products

A GTMP is described in the European legislation [3] as a biological substance that contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. Additionally, its therapeutic, prophylactic or diagnostic effect has to relate directly to the recombinant nucleic acid sequence it contains or to the product of genetic expression of this sequence. Vaccines against infectious diseases are excluded from this definition due to their specificities and impact on public health.

GTMPs can be based either on viral or nonviral (plasmids) vectors and contain transgene(s) responsible for the therapeutic effect. The choice of the vector depends on the condition to be treated and the persistence of the intended effect (short or long term). Especially for treatment of monogenetic, inherited diseases, integrating viral vectors (retro-, lentiviruses) are usually used in order to achieve a sustained effect. However, the use of early versions of integrating vectors led to safety problems (insertional mutagenesis [28]), which have since been minimised through modification of vector design (e.g. self-inactivating/SIN vectors) and with dedicated testing and characterisation of the insertion sites. For various cancers, on the other hand, for example, immune cells are manipulated through gene therapy, and in those cases viruses with short-term effect (adeno-, vaccinia viruses, etc.) are preferred.

Nonviral vectors are used to a lesser extent perhaps due to less effective transduction of cells. For every product, the vector chosen and design of the transgene should be well documented and justified [29]. Administration of GTMPs can take place either directly (in vivo) or through transduced patient cells (ex vivo). For genetically modified cells, specific aspects are discussed later in this chapter.

The manufacture of GTMPs resembles that of other biologicals, i.e. bigger batch sizes can be produced allowing enough products for multiple patients, and the products can be stored and release testing completed before use. The current manufacturing processes for both viruses and plasmids are well advanced and controllable. Quality requirements for GTMPs may depend on the stage of product development, but an initial risk assessment as a first step is highly recommended [4].

For GTMPs, as for CBMPs, special attention should be paid to the starting and raw materials, especially if of biological origin. The product as a whole should be characterised to an extent allowing identification of critical quality attributes that can be further used for lot release and stability testing. For release, the ratio of full/empty particles should be as high as possible, and infectivity (where needed), purity, potency and sterility testing is required. For potency testing functionality of the GTMP or expression level and functionality of the produced therapeutic protein may be required. If ex vivo application of the GTMP is anticipated, transduction efficiency of the GTMP should be followed.

Development of GTMPs may lead to significant changes in the construct, and sometimes an improved version of the original vector construct is proposed. In such cases comparability of the various constructs and the final therapeutic product should be carefully considered [29]. It is especially important to pay attention to safety aspects of various vectors and how they may be altered, if major changes to the vector and design of the construct are planned.

As GTMPs may contain GMO, in those cases an environmental risk assessment (ERA) addressing possible shedding and transmission to the environment is obligatory in the EU. The procedure is twofold: (1) an ERA assessment will be done as part of the MAA evaluation and (2) all member states will be consulted about the release of the GMO. For both procedures, the applicant should provide all necessary information about the characteristics of the GMO and data from shedding and transmission studies. Further guidance on ERA can be found from CHMP guideline on ERA [30].

3.3 Cell-Based Medicinal Products

Common scientific requirements apply to all CBMPs independent of their classification as somatic cell therapy, tissue-engineered product (TEP) or genetically modified cells (gene therapy). By nature these products are complex, sensitive to their manufacturing environment and challenging to comprehensively characterise. In the autologous setting, where every product is produced for a specific patient, it is challenging to define appropriate specifications with the inherent background of

donor variability. Due to potential limited amount of patient material, characterisation and validation might be conducted with cells from healthy donors; however, it must be established that these cells behave similarly as the patient cells during manufacture, i.e. that they can be considered representative. Usually there are also additional limitations as to the overall cell number that can be obtained for the final product which requires that the control strategy makes the most efficient use of the material available.

The manufacturing process for CBMPs needs to be clearly defined in terms of duration of the doubling times of the cells in the culture conditions, as it is known that certain characteristics, such as differentiation potential, might be lost during long-term culture.

A specific issue for CBMPs based on mixed populations is the need to demonstrate that product-defining analytical results (i.e. specifications) relate to the cell population responsible for the biological function. Further, characterisation studies should aim to demonstrate whether additional cell populations present in the product contribute positively, negatively or not at all to the activity of the target population.

3.4 Genetically Modified Cells

For products based on genetically modified cells, technical requirements as set in Directive 2009/120/EC [3] and available guidelines both for CBMPs [9] and GTMPs [10] should be considered. Where ex vivo transduced cells are used, transduction efficiency should be followed, and product-related impurities (free viral/nonviral particles and non-transduced cells) should be controlled.

3.5 Combination Products

The classification of combination products requires that a given ATMP incorporates one or more medical devices as an integral part of the active substance or of the final product [2]. It is relevant to consider this aspect as early as possible in order to set an adequate control strategy for the product. In addition, there are products that contain devices with no direct function and that are mainly used to ensure proper administration of the cells. Similar considerations also apply for these products in terms of scientific data requirements to characterise the product. Cells grown on matrices prior to human administration are examples that can be found in the EMA summaries of scientific recommendations on classification of ATMPs [31]. In short, it cannot be assumed that each part behaves the same independently and in combination. Thus, the medicinal product and medical device components for these products have to be independently characterised, followed by the characterisation of the combination. Suitability of medical devices for their intended purpose is evaluated by Notified Bodies in the EU as part of CE (Conformité Européenne) certification.

Consideration needs to be given to CE-marked medical devices that are not used in the context of their CE mark in the ATMP. The extent of characterisation is determined by the specific product. For biodegradable devices the investigation of the combination should address the impact of the degradation products on the cells that are cultured on it. In addition, the release specifications need to relate to the combined product, which poses a particular challenge for the choice and design of potency assays for combination products.

4 Non-clinical Evaluation of ATMPs

Non-clinical studies are a central element in the development of medicinal products, and in general, their objectives do not differ between the evaluation of small molecules and ATMPs. However, the realisation of such studies including challenges in their design and the significance of the resulting data to the situation in the human body may vary considerably for these product classes.

The objectives of non-clinical studies are to demonstrate proof of principle for the medicinal product and to define the pharmacological and toxicological effects that are predictive for the responses in humans. Furthermore, in such studies the establishment of safe doses for subsequent clinical studies and information to support the preferred route of administration of the medicinal product could be achieved. Non-clinical studies could also help to identify target organs for toxicity and parameters to be monitored in the patients as well as patient populations at risk for toxic events [9, 10, 32].

In general, non-clinical in vivo studies are an absolute necessity for almost all ATMPs under development. In some cases, where hazards, specific risks and risk factors have been identified based on known risks associated with the nature of the product, the findings observed in proof-of-concept studies or in in vitro tests may adequately justify the position that additional animal studies would not further substantiate the risk. In these cases a risk-based approach [4] might be used as a rational tool for justification of the omission of certain non-clinical in vivo studies, and the specific risk could be mitigated with appropriate clinical measures.

4.1 Animal Model Selection

The most challenging step in the design of non-clinical studies for ATMPs is the selection of appropriate animal models, since basic characteristics necessary to mimic the situation in humans might be absent or different in the selected animals such as tropism of the viral vector or activity of the promoter driving the therapeutic gene in GTMPs or the reactivity of the immune system against the cells in a CBMP. Ideally, the animal models should display similar characteristics to humans in terms of their physical, mechanical, chemical and biological properties. To this end, for the

different questions to be answered with respect to safety and efficacy of the ATMP, likely different animal models, perhaps even from different species, need to be established and used.

Such models may comprise genetically modified animals such as receptor knock-in animals to allow a range of infection with a viral vector comparable to the human situation, knockout animals to mimic the human disease or specifically humanised animals to establish a human immune system for the evaluation of therapeutic immune effects or immunotoxicities triggered by the cell or gene therapeutic approach. In some cases homologous models using animal cells of the respective species instead of human cells might be most indicative. For example, this approach might be considered if the therapeutic effect of a cell therapy can only be determined in the presence of the immune system and the administration of human cells in the animal would lead to immediate rejection. In this case, however, cells/tissues from the model animal need to be harvested, isolated, manipulated and applied in a manner as similar as possible to the intended clinical ATMP. While homologous models mimic the environment within the patient to a high extent, the model also comprises uncertainties. At first glance, similar manufacturing processes may lead to different impurities and characteristics of the product, which may result in a different pharmacological and toxicological profile. In addition, the respective animal-derived cells and/or their components are often less characterised than their human homologues. Therefore, these cell preparations may have different functions or may be regulated differently in the animal body when compared to the actual medicinal product.

In any case, the criteria upon which a particular animal model is chosen have to be scientifically justified, and limitations of the animal model should be identified and discussed, in particular if it has been established for a particular ATMP. In this respect, it is important to determine which of the potentially harmful effects of an ATMP—associated with either intrinsic characteristics of the ATMP or with its manufacture—are evaluable in the chosen animal models or not.

The number of animals in the individual studies may vary depending on different factors such as the disease model, the test species, the delivery system and other considerations. The total number of test animals per study group should be in a range allowing a statistically and biologically significant interpretation of the results. Where evaluation of the pharmacological or toxicological effects requires large animal disease models, e.g. for TEPs for cartilage repair, the animal number per study group is often at the lower limit.

The duration of the non-clinical studies for ATMPs may be extended, and the time points of monitoring may be more frequent and flexible than would be anticipated for classical medicinal products depending on the intended duration of the treatment and the kinetics of distribution, replication, persistence and clearance of a given product in the body. Cells may persist in the animal for longer time periods or may induce long-term effects. The same considerations apply to viral vectors or replicating gene-modified oncolytic viruses. Such products may exert different transduction efficiencies, tissue tropism and/or replication kinetics, or they may undergo latency and reactivation cycles or may stably integrate into the host cell

genome, potentially resulting in long-term therapeutic gene expression. All of these parameters have to be taken into consideration for the design of the non-clinical studies.

It is also important to use animals of both genders, where possible, and provide adequate positive and negative controls. For the latter, sham treatment or vehicle might be used. In addition, the rationale for each functional test needs to be provided.

For some ATMPs, especially those which are based on an immunological mode of action or are tackling immunological indications, relevant animal models may not be available or cannot be developed to address particular aspects of pharmacology or toxicology. In these cases in vitro studies may replace the animal studies, but the underpinning rationale to use in vitro studies needs to be justified.

4.2 Biodistribution of CBMP and GTMP

Depending on the mode of application of the CBMP, the cells may be distributed within the whole body passively by the blood or even actively, as multipotent cells may also migrate to sites of injuries. For example, mesenchymal stem/stromal cells (MSCs) encounter different microenvironments during their biodistribution, which may lead to unintended effects of these cells. In addition, adverse events may also be induced by the secretion of biologically active molecules. In order to predict unintended physiological effects for the patients, it is necessary to study the biodistribution and the fate of the CBMP in a relevant model. One possibility may be a systemic application reflecting a "worst-case scenario" by injecting the CBMP into the bloodstream of an animal to follow their distribution and the possible resulting adverse effects on unintended target organs. For example, MSCs infused into baboons distribute into the lung, thymus, bone, skin, cerebellum and gastrointestinal tract, whereas following administration in rats, they relocate primarily to the lung and secondarily to the liver after both intra-arterial and intravenous injection [33–35]. Such data from biodistribution studies may explain observed target organ toxicity.

Biodistribution studies for GTMPs should on the one hand address the distribution, persistence, clearance and mobilisation of the vector or virus used to deliver the therapeutic sequence and on the other hand address the transcription/expression profile of the delivered gene. The observation time in these studies is ideally until no signal of vector presence and therapeutic sequence expression is detected. However, for some products such as integrating vectors, the transgenic sequences might be present in the animal lifelong. In this case, the ideal observation duration is until the vector genome concentration and/or transgene expression level reaches a plateau that remains stable. Moreover, potential silencing of the therapeutic gene should be addressed. Integration studies to achieve information on the integration profile of the vector and the potential risk of insertional oncogenesis may also become necessary, particularly if used for genetic modifications of stem cells [28]. When using oncolytic viruses or when targeting a gene therapy vector, for example, by using specific envelope proteins to allow transduction of only a subset of cells or

tissues or by employing tissue- or tumour-specific enhancer/promoter elements to target expression of the therapeutic sequences to specific cell or tissue types, the specificity of the vector/virus needs to be confirmed in vivo. Finally, data from biodistribution studies are also used to determine whether the risk of germ line transmission of a given GTMP needs to be further addressed [36]. In any case, the GTMPs which may lead to the introduction of genetic modification into the human germ line cells are not allowed to be clinically evaluated in the EU [37].

4.3 Aspects of Toxicology

Toxicity of CBMPs may arise from different factors such as (1) unknown cellular alterations that take place during the manufacturing process such as modified excretion of chemokines or specific differentiation, (2) allogeneic use of the product, (3) interaction with components that were used during product manufacturing or that are part of a structural component of the medicinal product or (4) proliferation of the applied cell in an unwanted quantity and/or in an unwanted location. Therefore, the toxicology studies should be performed with the finished ATMP in order to determine any of these potential hazards. To gain a better understanding of the product, individual testing of components of the finished product such as excipients, additional substances and process-related impurities should be considered. Single- and repeated-dose toxicity studies may be necessary depending on the intended clinical use of the ATMP. In these studies the application route and the dosing regimen should reflect the intended clinical use, and the duration of observation in these studies may need to be much longer than anticipated from the standard single-dose studies in conventional toxicity studies.

To evaluate potential toxic effects associated with the application of a GTMP, many different aspects have to be taken into account. When using a viral vector, for example, the virulence of the parental virus, the capability of the vector to integrate or to undergo latency and reactivation as well as its replication capacity have to be considered in the design of the toxicological studies. Recombination with and complementation by wild-type viruses present in the patient may modulate these properties. Toxic effects, however, may not only be triggered by the vector itself but also by the delivered therapeutic sequences. Their expression products potentially include aberrant gene products and nontherapeutic vector proteins as well as process-related impurities. Hence, the toxicological study programme has to be well adjusted to the medicinal product. In general, besides the single- and/or repeated-dose toxicity studies, analysis of genotoxicity, tumorigenicity, immunotoxicity and reproductive and developmental toxicity may be warranted. Repeated-dose toxicity shall be performed when multiple dosing with the GTMP is intended.

From a current regulatory viewpoint, the risk of tumorigenicity should be carefully addressed in adequate studies. A recent report indicated [38] that occurrence of cell abnormalities in MSCs, for example, seems to be mainly related to the manufacturing process, as opposed to patient-specific factors. It is therefore important

to determine, at the quality level, whether the manufacturing process leads to chromosomal abnormalities, although no evidence of tumour formation has been reported from studies using human adipose-derived MSCs in nude mice and athymic rats with different application routes up to a 6-month follow-up period [38]. In addition, the immunological status of the animals in such studies is an important consideration. For example, if allogeneic cells are used in immunocompetent mice, their rejection may preclude tumour formation. Tumorigenicity studies should preferably be performed with cells that are at the limit or even beyond the limit of the number of cell doublings that is routinely used during manufacturing. To detect genetic instability the current standard method is karyotyping, although this technique only allows detection of large chromosomal rearrangements. Therefore, based on the state of the art, conventional karyotyping can be considered a valuable and useful technique to analyse chromosomal stability. If recurrent aberrations are identified, other complementary tools such as spectral karyotyping and comparative genomic hybridisation could be used to look for these aberrations as they have better sensitivity to detect a low proportion of abnormal cells.

To evaluate potential toxic effects associated with the application of a GTMP, diverse aspects have to be taken into account. When using a viral vector, for example, the virulence of the parental virus, the capability of the vector to integrate or to undergo latency and reactivation as well as its replication capacity have to be considered in the design of the toxicological studies. Recombination with and complementation by wild-type viruses present in the patient may modulate these properties. Toxic effects, however, may not only be triggered by the vector itself but also by the delivered therapeutic sequences and their expression products including aberrant gene products and nontherapeutic vector proteins as well as process-related impurities. Hence, the toxicological study programme has to be well adjusted to the medicinal product. In general, besides the single- and/or repeated-dose toxicity studies, analysis of genotoxicity, tumorigenicity, immunotoxicity and reproductive and developmental toxicity may be warranted.

5 Clinical Studies

5.1 General Considerations in the Clinical Development of ATMPs

As outlined in ICH E8 [39], drug development is ideally a logical, stepwise procedure in which information from small early studies is used to support and plan subsequent larger, more definitive studies. This concept also applies to ATMPs. The clinical development plan of an ATMP should include pharmacodynamic (PD) studies, pharmacokinetic (PK) studies, mechanism of action studies, dose-finding studies and randomised clinical trials in accordance with Directive 2001/20/EC [37] and the existing general guidelines [9, 10], including specific guidelines available

for the conditions to be treated [40]. However, due to the specificities of ATMPs, the development programme will need to be adapted to the individual characteristics of the product, both with regard to exploratory and confirmatory studies. Although specific regulatory pathways can be considered in specific situations, such as for rare genetic diseases for which an unmet medical need is identified, robust data are required to demonstrate safety and efficacy of the product and to allow an overall benefit/risk assessment of the product.

Therefore, it is important that all studies are adequately designed to allow assessment of the feasibility and risks of the approach, carefully balancing the need for retrieving information with respect and protection for vulnerable and rare patients. The applicants are strongly encouraged to seek advice at the national or European level prior to initiating the clinical development of a product, to address the specificities of the ATMP and to discuss possible deviations from current guidelines.

5.2 Special Clinical Aspects of Cell-Based Medicinal Products

According to the EU definition, somatic cell therapy medicinal products (sCTMPs) are intended for treating, preventing or diagnosing a disease through pharmacological, immunological or metabolic action of its cells or tissues. TEPs are products that contain or consist of engineered cells or tissues and are administered with a view to regenerate, repair or replace the patient's defective tissue [2, 3]. sCTMPs and TEPs are developed in different therapeutic areas. In Europe sCTMPs are developed, for example, for cancer immunotherapies or to treat graft-versus-host disease (GvHD). The main therapeutic areas for TEPs are cardiac and vascular diseases, musculoskeletal diseases, renal and urinary diseases, and eye and skin diseases. The existing general guidelines for the specific therapeutic areas have to be taken into account when designing the development programme for these products [40].

5.2.1 Exploratory Studies with CBMPs

The objectives of exploratory studies with CBMPs are to (1) study the pharmacodynamics and biodistribution in the target indication, (2) assess the safety, (3) provide information on the optimal effective dosage for subsequent studies and (4) provide a basis for confirmatory studies. It needs to be considered that the translation of safety data derived from non-clinical studies with ATMPs has often severe limitations in predicting safety issues and target organs of toxicity in humans. Limitations may be related to the mode of action of the ATMP and the lack of relevant animal models. In these cases it is recommended to follow the EMA guideline on strategies to identify and mitigate risks for first-in-human clinical trials [41]. Although gene therapy and cell therapy medicinal products are exempted from the scope of this guideline, its principles apply.

Patient Population

All phases of the clinical development of cell-based therapies are usually conducted in the target patient population. When a sCTMP is developed in haematological and oncological malignancies, the selection of the target population follows general requirements defined for anticancer medicinal products [42]. When developing a TEP, the patient population is selected according to relevant criteria, such as symptoms, functionality and degree of impairment, size of tissue defect and type of previous treatments [43].

Safety

As with other medicinal products, assessment of safety should be the focus of exploratory studies and included as a main objective. The number of cells to be administered is either derived from non-clinical studies with the product that suggest safe use in humans or from literature data of related products. The use of literature data is expected to be more difficult in cases where the product has been extensively manipulated or where a product contains a noncellular component which may pose additional safety concerns. In this case the safety of both components needs to be addressed prior to entering clinical development.

The safety monitoring has to take into account the route of administration, as administration of CBMPs is highly variable. For example, sCTMPs are often injected systemically by intravenous infusion, as in the case of dendritic cells intended for cancer immune therapy or in the case of MSCs used to treat GvHD. In contrast many TEPs are administered locally or during surgery. Examples are TEPs for cardiac indications, when cells are injected into the coronary artery or administered by intramyocardial injection using specific delivery systems. In these cases information regarding the safety and compatibility of the delivery system should be provided. This information is in general derived from non-clinical studies that have been designed to assess performance of the delivery system. When a surgical procedure is involved, as is the case for implantation of chondrocyte-containing products, potential problems associated with variability of the surgical implantation procedure among centres and surgeons should be taken into account. Standardisation of the administration procedure prior to entering clinical studies is recommended and is expected to facilitate the assessment of the therapeutic procedure as a whole, as stipulated in Directive 2009/120/EC [3].

Pharmacodynamics

The aim of pharmacodynamic assessments is to study the effects of the CBMP on the patient. For example, for sCTMPs developed as cancer immunotherapies, the PD read-outs include assessment of, for example, cellular and humoral immune response. In the case of TEPs, PD addresses structural and/or functional repair of

the target tissue, which can be assessed by, for example, histological evaluation of the repair tissue or by sensitive imaging techniques. Robust and safe functional integration of the product may require months or years, as is the case for chondrocyte-containing products. This should be considered in the timing of endpoint assessment.

Pharmacokinetics

PK studies examine the fate of the CBMP in the patient, including biodistribution and persistence. As imaging techniques in humans are still challenging and limited, the majority of issues regarding biodistribution are thus usually addressed in non-clinical studies.

However, information from non-clinical models may be of limited value due to the fact that the influence of the environment in an animal on human cell characteristics and functionality may not be comparable to the human situation. The need for biodistribution data depends on the risk profile of the product and is a good example for applying the risk-based approach. Relevant safety data on systemically administered CBMPs where the number of cells increases over time due to a high proliferation potential or on culture-expanded undifferentiated cells with inherent tumorigenic potential, for example, are considered indispensable prior to starting clinical development. In this case the development of safe cell tracking methods in humans is encouraged. On the other hand, for terminally differentiated products administered into a closed environment and for which no migration capacity is expected, biodistribution data may not be required.

Dose

The selection of the dose should be based on the findings obtained in the quality and the non-clinical studies, suggesting safe use in humans. Pre-existing data from relevant published literature could be supportive for dose definition, provided that the cellular and structural components and the formulation of both products are comparable.

In general, the safe and effective dosage of the cell-based product should be identified in dose-finding studies. For example, dose-finding studies in patients with acute myocardial infarction suggest that higher cell numbers are correlated with better outcome, indicating a dose-response relationship of cell-based therapies in this indication [44]. It is acknowledged, however, that dose-finding studies are not always feasible, e.g. due to limited amount of cells available for testing. Also, when the product contains a structural component with a fixed number of cells, dose-finding studies may be difficult to perform. Similarly, when there is considerable proliferation of the cells in vivo, dose-finding studies may not be meaningful. In these cases the omission of dose-finding studies should be justified.

5.2.2 Confirmatory Studies

To demonstrate efficacy of CBMPs, pivotal clinical (phase III) studies, designed to confirm the preliminary evidence generated in exploratory studies, are usually required. As with other medicinal products planned to enter confirmatory trials, the main points to address in the designs are choice of target population and of control group, blinding, choice of primary and secondary endpoints, sample size estimation and statistical design.

Clinical efficacy endpoints as defined in specific guidance for the studied indication or disease are the basis for the clinical evaluation of CBMPs. Additional cell- and tissue-specific endpoints may be required such as biochemical, morphological, structural and functional parameters, which are relevant for the targeted therapeutic claim. These endpoints can be used as co-primary or secondary variables and are expected to support the clinical primary efficacy variable. In cases where long-term efficacy is expected, the endpoints should also focus on the duration of the response. As for any conventional medicinal product, any nonvalidated endpoint or surrogate endpoint, such as novel biomarkers, would have to be validated in a prospective study before being used in confirmatory clinical trials.

Specificities in the design of confirmatory studies with certain TEPs are related to the fact that administration is often performed within surgical procedures. Examples are the administration of chondrocyte products during arthrotomy or arthroscopy. In this case blinding of the physician and/or patient may not be feasible. Furthermore, the requirement to randomise patients with advanced tissue defects to control or experimental surgical therapy may be challenging from a methodological point of view, as a standard surgical control arm may be difficult to identify.

The design of confirmatory studies is thus dependent on the product, the administration procedure and the indication explored. The design of confirmatory trials in cardiac disease, oncology and haematology or GvHD, for example, is less affected by methodological problems and thus more likely to follow the conventional design.

5.3 Special Clinical Aspects of Gene Therapy Medicinal Products

In general, for GTMPs the same principles as for any other medicinal product should apply to their clinical development, and especially current guidelines focusing on specific therapeutic areas should be followed. However, there are also issues specific for GTMPs that need to be taken into account when designing the clinical development for a given ATMP. When cancer or infectious diseases are the target diseases for gene therapy, the existence of alternative treatments as well as a high prevalence of some tumours will make GTMP development very similar to other medicinal products. In cases where a GTMP is developed for treatment of an inherited genetic disorder, new challenges may arise. Many of these diseases are orphan diseases affecting only a small number of patients throughout the world. In this case, large cohorts of patients

are not available for performing a classical development programme with exploratory and confirmatory studies. Therefore, small-sized studies involving a limited number of patients may need to address many endpoints together in order to determine the dosing and benefit/risk relationship of the GTMP. This is why in many instances, early GTMP studies are merged into a combined clinical trial for rare indications. Similarly, large confirmatory studies may not be feasible, and MAA evaluation may have to be based on a limited amount of data.

The clinical strategy for gene delivery and the manufacturing process of the GTMP also need to be taken into account. When gene transfer vectors (either viral or nonviral) are delivered in vivo to the human body, production of large batches of a clinical-grade GTMP as well as non-clinical studies is usually required before entering the clinical studies. Alternatively, when autologous ex vivo gene therapy is considered, harvesting patient's cells with further transduction and re-administration of the GTMP may be challenging and may not be completely reproducible in non-clinical animal studies. Also release testing of the product may face limitations, and production of large batches of the GTMP may not be possible. In such situations, extensive characterisation of the product and validation of the production process are required to ensure comparable results in a cohort of patients.

5.3.1 Exploratory Studies

First-in-human (FIH) studies in the field of gene therapy are usually combined phase I/II studies performed in a limited cohort of patients. Safety of the product and safety of the administration procedure are the primary endpoints.

Combined phase I/II studies are aimed at providing preliminary data supporting the proof of concept (PoC) of the therapeutic strategy. This PoC should strengthen and complete the data gained from the non-clinical phase. PoC in the field of gene therapy is not easy to define. For monogenic diseases, PoC may rely on the demonstration of short- or long-term expression of a therapeutic protein. Ideally, expression of the protein will result in a therapeutic effect. Therefore, in this situation, the follow-up of the patients who are included in early phases will bring a clear picture of the benefit and risks of the gene therapy approach. This was the case for the X-SCID patients who were treated years ago [45]. Most of the children are still alive and healthy 10 years after treatment, bringing the overwhelming demonstration of the validity of the concept. Similarly, the follow-up of haemophilia B patients treated with AAV vectors [46] can be considered a remarkable support for the use of gene therapy for coagulation factor deficiencies.

Patient Population

In most if not all clinical trials performed so far, FIH studies included selected patients and not healthy volunteers. This is mainly due to the unknown risk of such novel therapies, and the same approach is seen also for other medicinal products, such as in the field of oncology.

The invasiveness of the procedure used to deliver the vector is also a reason precluding inclusion of healthy individuals in FIH studies. As an example, AAV gene therapy protocols for neurodegenerative diseases (Parkinson's disease, X-linked adrenoleukodystrophy, etc.), which entail the surgical delivery of the vector in the brain through burr holes in the skull, are not considered appropriate in healthy individuals for ethical reasons.

Finally, when the ex vivo gene therapy approach requires harvesting specific cells from the patients to manufacture an autologous gene therapy product, the risks associated with the harvest of the cells may be considered too high to be performed in healthy individuals. This is the case for gene therapy requiring lentiviral transduction of bone marrow-derived or blood-derived haematopoietic stem cells. In addition, the potential risks related to insertional mutagenesis may be considered too high to allow FIH studies to be conducted in healthy individuals for these products.

Safety

For GTMPs, safety of the product including the administration procedure should be established during the exploratory studies. Furthermore, specific safety issues, such as insertional mutagenesis, should be addressed earlier as part of the non-clinical studies conducted before FIH studies with such products. Also the dose in relation to safety (e.g. high viral titres) should be considered and justified before human use.

Pharmacodynamics

The aim of PD studies is to explore the biochemical and physiological effects of a drug on the body and to define relationships between dose and effect. The primary effect is usually related to modification of the pattern of nucleic acid expression on target cells. These modifications may include transcription of new DNA sequences, alteration of transcription of existing sequences and/or alteration in the translation of a specific sequence. Direct measurement of such effects is usually not possible in patients, and therefore, data from PD studies in humans are usually not requested for GTMP. One exception is the measurement of circulating nucleic acids (e.g. miRNA) in body fluids. Sometimes it may be possible to monitor the levels of the expressed protein and the metabolic effect of the GTMPs. For example, the efficacy of gene therapy for haemophilia can be evaluated by measurement of the missing coagulation factor in the blood. Similarly, for patients suffering from severe combined immunodeficiency linked to adenosine deaminase (ADA) mutation, measurement of ADA activity in the blood after treatment is valuable evidence of efficacy of the GTMP.

Other direct or indirect investigations of the PD of GTMPs are also useful if they bring relevant information for safety and efficacy of the product, such as imaging studies of tumour evolution after treatment with oncolytic viruses to validate the elimination of cancer cells by the treatment.

Pharmacokinetics

Testing for traditional PK parameters, i.e. absorption, distribution, metabolism and excretion (ADME), is often not fully relevant for GTMPs. However, absence of any information regarding distribution and excretion should be justified. When a GTMP is administered, it is important to carefully analyse the biodistribution throughout the body to better predict the safety and tolerability of the product. Biodistribution studies should include investigations on persistence, clearance and mobilisation of the GTMP. This is particularly important for oncolytic and conditionally replicating viruses. Also, biodistribution may indicate for integrating vectors whether or not germ line transmission is an issue. Some PK data are normally available from non-clinical animal studies. However, in some cases such as genetically modified cells of human origin, animal studies are of limited value, and biodistribution studies in humans become compulsory.

Excretion of a novel GTMP is also an important issue together with shedding, as GMOs may cause environmental risks. Shedding studies are usually required to address the excretion of the GTMPs especially when GTMPs are capable of transferring genetic material to third parties. Investigations of shedding and risk of transmission to third parties are required as part of the ERA, which is obligatory for GMOs [15, 16].

Dose-Finding Studies

Whether or not dose-finding studies should be performed with GTMPs is a matter of debate. There is no global answer to this question, and the decision should be based on a case-by-case analysis. In the context of GTMPs administered in vivo, a complete dose-response analysis should be performed. In the case of very rare orphan diseases for which the number of patients could preclude such studies, a solid justification based on data from comprehensive dose-response analysis in a relevant animal model could be discussed. However, as a rule, a clinical trial including a dose escalation should be considered as mandatory.

The situation may be different with ex vivo gene therapy strategies in which genetically modified cells from autologous or allogeneic origin are infused into the patient. In this setting, the approach should be similar for gene therapy and cell therapy medicinal products, and a dose-finding study is normally expected. One exception could be again rare diseases which affect a limited number of patients. The situation is even more complicated when therapeutic cells are expected to proliferate in the patient's body. In these specific situations, the completion of a dose-finding analysis can be discussed by the applicant.

5.3.2 Confirmatory Studies

As discussed above, confirmatory studies should be conducted to demonstrate the efficacy and safety of the product and to validate the benefit/risk relationship of the product in the given indication to support a marketing authorisation. The development and evaluation of a GTMP should follow the same rules as for classical medicinal products as much as possible. In cases where other treatments for a disease are available, performance of a randomised clinical trial to demonstrate the superior efficacy of the GTMP as compared to available drugs is recommended.

However, with regard to very specific situations whereby rare diseases are treated with gene therapy, data gained from limited studies can be considered to support the evaluation of the benefit/risk relationship of the product. The applicants should bear in mind that in these situations in which a statistical analysis is hampered by the poor power gained from a limited cohort of patients, a strong therapeutic effect will be required to support the claims of benefit to the patients. The approval of GTMPs should be based on an undisputable and compelling therapeutic effect.

6 Challenges in Development of ATMPs

ATMPs are complex pharmaceuticals with many limitations and challenges. Not only is the development of ATMPs often hampered by lack of relevant non-clinical models and difficulties relating to manufacturing, quality controls and clinical trial designs for these products but also by special safety issues that increase the workload of the developers. The product administration systems (e.g. surgical, via catheters or specific devices for intracranial, intramyocardial or other surgical deliveries) are also very different from the route of administration of traditional drugs (oral, intravenous) and may impact the final outcome. Continuity of material supply can also be a hurdle, if proper quality reagents and materials are not available in larger quantities for confirmatory trials and to support commercial production. However, the major issue for all ATMPs thus far has been the demonstration of efficacy. Factors impacting the outcomes of efficacy studies include standardisation of the product when manufactured in multiple sites, potency tests and their capability to detect changes in the quality and activity/functionality of the product, as well as the overall design of the trials (comparators, blinding, concomitant treatments, etc.).

The number of approved ATMPs in the EU is still quite low with only five products approved thus far (one GTMP [47], four CBMPs [48–50, 57]). However, hundreds of ATMPs have been tested in clinical trials during the past decade, and also the numbers of scientific procedures for ATMPs (154 as of May 2015) [51] and CAT classification procedures are numerous (129 as of May 2015) [51] suggesting a large pipeline of products under development. The majority of the clinical trials in Europe, however, are early-phase studies and conducted by small developers (SMEs, academia, charities, etc. [52]). These small entities are often struggling with poor resources and huge workloads and may be not fully aware of all regulatory requirements. Also the

differences in regulatory requirements for clinical trials in different member states have posed problems especially for multicenter trials. This hopefully will be solved by the new regulation on clinical trials, which is intended to harmonise the requirements in the EU [53]. Additionally, different interpretations of article 28 of Regulation 1394/2007/EC [2] defining specific restrictive conditions to authorise ATMPs at the national EU level, the so-called hospital exemption (HE), have caused a lot of confusion for developers and even conflicts between industry and stakeholders working under this HE national framework [54].

Finally, from an economic point of view, the ATMPs may also be more expensive than other medicines, and the developers of the first marketed products have faced difficulties in getting reimbursed. For many ATMPs the production batches are small (one batch per patient in the worst cases), which increases costs related to development, manufacturing and testing. However, these products are intended to treat the cause of the disease, with a goal at best for permanent recovery/repair, which should be taken into account when assessing the value of ATMPs for patients.

7 Conclusion on Possible Future Directions for ATMPs

On April 1, 2014, the European Commission published a report, based on public consultation on Regulation 1394/2009/EC and its impact on ATMP development [6, 55]. The most commented part of the Regulation was article 28 and diverse implementation of the hospital exemption (HE) in EU member states. Also, the complex marketing authorisation procedure was criticised, as well as the regulatory requirements posed especially on minimally manipulated cells. On the other hand, the report concludes that patients should not be exposed to unsafe/ineffective treatments. According to the report there should be balance between access of ATMPs for patients and regulatory requirements safeguarding public health. Furthermore, clarification and harmonisation of conditions for HE are foreseen, and clarification of all derogations allowing production and use of ATMPs outside the medicine legislation (e.g. article 5, Directive 2001/83 [56]) is needed. If the ATMP Regulation is opened for revision, a proper discussion between developers and regulators should take place to address the regulatory constraints that are currently hampering the development of novel treatments for unmet medical needs.

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Requirements for Clinical Trials with Gene Therapy and Transplant Products in Switzerland

Andreas Marti

Abstract This chapter aims to describe and summarize the regulation of gene and cell therapy products in Switzerland and its legal basis. Product types are briefly described, as are Swiss-specific terminologies such as the term "transplant product," which means products manufactured from cells, tissues, or even whole organs. Although some parts of this chapter may show a guideline character, they are not legally binding, but represent the current thinking of Swissmedic, the Swiss Agency for Therapeutic Products. As so far the experience with marketing approval of gene therapy and cell therapy products in Switzerland is limited, this chapter focuses on the regulation of clinical trials conducted with these products. Quality, nonclinical, and clinical aspects are summarized separately for gene therapy products and transplant products.

Keywords **S**witzerland • Swissmedic • Regulatory authority • Gene therapy • Transplant product • GMO • Clinical trial • Quality considerations • Nonclinical considerations • Clinical considerations • Scientific advice • Marketing authorization

1 Introduction and Legal Aspects

During the last 25 years, scientific progress has resulted in improved ways of cultivating and manipulating cells for therapeutic or preventive interventions. New gene transfer technologies allow the introduction of genetic material into somatic cells with the help of specifically designed vectors, such as non-replicating viral vectors and DNA plasmids. Gene and cell therapy products are regulated similarly to medicinal products. In Switzerland, clinical trials using gene and cell therapy

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products have been performed since the early 1990s. More than 60 clinical trials have been approved so far, and the trend for new clinical trial applications is increasing. Besides local Ethics Committees (EC), the Swiss Agency for Therapeutic Products (called Swissmedic) is the principal regulatory authority for approving gene and cell therapy clinical trials in Switzerland. For gene therapy clinical trial approvals, the Swiss Expert Committee for Biosafety (SECB), the Federal Office of Public Health (FOPH), and the Federal Office for the Environment (FOEN) are also involved as regulatory authorities in the approval process as defined in the clinical trial ordinance (ClinO) [1]. All clinical trial applications are submitted in parallel to the EC and to Swissmedic. The time to the approval of a clinical trial after the submission of the complete clinical trial dossier is 30 days for investigational cell therapy products and 60 days for investigational gene therapy products.

The principal legal basis for the regulation of gene and cell therapy products at the levels of clinical trials and marketing authorization is the Swiss Therapeutic Product Act (TPA, in effect since January 2002) [2] and its linked ordinances. Several other laws need also to be considered. For cell-based products, Article 49 of the Federal Law on the Transplantation of Organs, Tissues, and Cells (Transplantation Act, in effect since July 2007) [3] refers to various articles in the TPA that regulate the cell-, tissue-, and organ-based products called transplant products (TpPs) in Switzerland. For all research involving human beings, the Human Research Act (HRA) and its ordinances (in effect since January 2014) are relevant [4]. The ClinO, which is an ordinance relevant for the TPA and the HRA, describes in detail the approval process of clinical trials involving investigational gene and cell therapy products. Specifically, for gene therapy products, the Federal Law on Gene Technology and its ordinances (in effect since January 2004) is relevant [5]. All clinical trials with human subjects have to be strictly performed according to good clinical practice (GCP), as described in the ICH E6 “Guideline for Good Clinical Practice” [6]. In addition, all investigational products for human use have to be manufactured according to good manufacturing practice (GMP) [7].

2 Gene Therapy Products

Gene therapy can be defined as a medical intervention with the aim to treat or prevent a genetic disease either by adding a curative gene sequence or by correcting the affected gene. Presently, the introduction of corrective DNA or RNA sequences into somatic cells has been established at the clinical stage. More advanced technologies whereby mutated genes in affected cells are directly corrected at the genomic DNA level by using gene-specific zinc finger nucleases [8], CRISPR/Cas [9], or other means have not yet reached the clinical stage in Switzerland. Since the 1990s, many different indications have been evaluated using a gene therapy approach at the level of clinical trials using plasmids and viral vectors as gene transfer vehicles. At the present time no gene therapy product has been approved at the marketing level in Switzerland.

The development of gene therapies involves in vivo gene therapy and ex vivo gene therapy approaches. In vivo gene therapy encompasses all approaches whereby therapeutic genes carried by gene therapy vectors are directly introduced into a patient's body (e.g., by intramuscular injection, intravenous injection). On the other hand, ex vivo gene therapy usually requires the short-term cultivation of somatic cells and the introduction of the therapeutic gene into these cells in culture with the aid of retroviral or lentiviral vectors. After successful gene transfer, the cells are administered to the patients. It is important to note that according to the Federal Constitution of the Swiss Confederation (Art. 119), it is forbidden to alter the genetic material of germ cells [10]. Therefore, all ex vivo gene therapy approaches have to be strictly limited to the use of somatic cells. In Switzerland, ex vivo gene therapy products are classified as TpPs, as they are based on the administration of cells to patients.

Non-replicating and replication-competent viral and bacterial vectors harboring foreign gene sequences introduced by means of recombinant technology are classified as genetically modified organisms (GMOs). For in vivo gene therapy and vaccination approaches, gene therapy products and GMO products are regulated based on the same legal requirements. Therefore, in Switzerland, GMO products are regulated in the same way as gene therapy products, both at the level of clinical trials and at the level of marketing authorizations. Most GMO products that had been submitted to Swissmedic as clinical trial applications represented preventive vaccines (e.g., to protect from HIV virus infection) or therapeutic vaccines (e.g., cancer vaccines to treat melanoma).

Unmodified wild-type viruses with oncolytic properties for treating cancer patients represent a special case. These viruses are neither gene therapy products nor GMOs. Presently, no such product has been submitted to Swissmedic. In the regulatory praxis, the same procedure will most likely be applied for regulating unmodified wild-type oncolytic products for use in clinical trials and for a marketing authorization as has been established for GMO and gene therapy products.

3 Transplant Products

Cell therapy products contain either genetically modified cells or genetically unaltered cells and are subcategorized as TpPs in Switzerland. Genetically modified cells are considered ex vivo gene therapy products (as described under Sect. 3). In Switzerland, numerous TpPs are under regulation at the clinical trial level. Examples of ex vivo gene therapy products are T cells expressing chimeric antigen receptors (CARs) to treat cancer indications or genetically modified $CD34^+$ cells for the treatment of immune deficiencies. Examples of genetically unmodified TpPs are keratinocytes to treat burns, mesenchymal stem cells to treat cardiovascular disease, and chondrocytes to treat cartilage defects. In addition to the use of one cell type to treat a medical condition, several cell types can be combined that may form tissue-like structures in culture, such as keratinocytes plus fibroblasts that form skin-like structures consisting of an

epidermal layer and a dermal layer. Furthermore, cells can be combined with special matrices such as collagen, to support their biological function and restrict unwanted spreading, or they can be encapsulated (especially useful for allogeneic cells) to assure local activity and to prevent unwanted spreading in the body.

According to the Transplantation Act, TpPs are defined as products manufactured from human or animal organs, tissues, or cells, and the manufacturing process has to be standardized, or the product itself is standardized. A TpP has either undergone a substantial manipulation or it is not designed to fulfill the same function in the recipient that it had in the donor (this includes the autologous setting). In this sense TpPs consist of autologous, allogeneic, or even xenogeneic vital organs, tissues, or cells that have been subject to substantial manipulation, which has changed their original biological characteristics, physiological functions, or structural properties. Further criteria currently used to circumscribe the term "substantial manipulation" are the expansion in culture during the manufacturing period. Of note is that even a whole organ can be defined as a TpP when manipulated accordingly. At the present time, there is, however, no regulatory experience with a TpP at the level of a whole organ.

The terms "standardized process" and "substantial manipulation" are difficult to define in a general manner, especially in the context of the classification of a given TpP. Therefore, Swissmedic uses a similar approach as in the EU. In Annex 1 of the EU Regulation 1394/2007 [11], the term "substantial manipulation" is not defined; however, a separate table lists the types of activities that are NOT "*SUBSTANTIAL MANIPULATIONS*." In addition, an information sheet regarding "requirements relating to the authorization documentation for transplant products" has been published on the Swissmedic website listing transplants that are not considered TpPs (refer to Table 1 of this chapter) [12].

4 Regulatory Requirements for Gene Therapy and Transplant Product Clinical Trial Applications

Because of the complex nature of gene and cell therapy products at the molecular level, specific regulatory guidelines have been developed over recent years, mainly by the US Food and Drug Administration (FDA) [13] and the European Medicines Agency (EMA) [14], to support the development of these products. Although these guidance documents are not legally binding in Switzerland, the Swiss regulatory authorities take into account the FDA and EMA guidelines for defining requirements for clinical trial applications involving gene therapy products and TpPs. Of note, these guidelines mainly outline regulatory requirements at the level of marketing authorization. For clinical trials, these requirements therefore often need to be rediscussed and adapted on a case-by-case basis. For this purpose Swissmedic offers the applicant scientific advice meetings prior to filing the clinical trial dossier to Swissmedic. Annex 4 of the ClinO lists the documents that have to be submitted

Table 1 Non-exhaustive list of transplants that are not considered to be "transplant products" (in accordance with Annex 1 of the EU Regulation 1394/2007 of 13 November 2007)

Type of transplant	Preparation, conservation (examples)
Organs	Kidneys, heart, liver, etc.
Musculoskeletal tissue	
Bones: major transplants, femoral head	Untreated deep-frozen, freeze-dried, sterilized by irradiation, aseptically washed (after bone marrow depletion)
Osteochondral transplants and menisci	Untreated deep-frozen meniscus, cryoconserved, sterilized by irradiation, freeze-dried
Fascia lata or other fascias	Untreated deep-frozen, freeze-dried, sterilized, cryoconserved, aseptically washed
Ligaments and tendons	Untreated deep-frozen, aseptically washed, cryoconserved, sterilized by irradiation, freeze-dried
Cartilage	Untreated, deep-frozen, sterilized, deep-frozen washed, cryoconserved
Skin	Untreated fresh, cryoconserved, glycerol conserved, glycerol conserved sterilized air-dried/lyophilized, air-dried/ lyophilized sterilized
Amniotic membrane	Untreated fresh, cryoconserved, glycerol conserved, glycerol conserved sterilized, air-dried/lyophilized, air-dried/ lyophilized sterilized
Cardiovascular tissue	
Heart valves, heart vessels, heart arteries, heart veins	Untreated fresh, cryoconserved
Pericardium	Untreated fresh, cryoconserved, sterilized by irradiation
Eye tissue	
Cornea	Untreated fresh, stored in culture medium, stored in Optisol
Sclera	Deep-frozen

to Swissmedic in the frame of a clinical trial application for an investigational gene therapy product. For further information the reader is referred to the ClinO and the Swissmedic "Merkblatt" [1, 15].

4.1 Specific Considerations for Gene Therapy Products

The following sections highlight some regulatory requirements for the clinical trial dossier to be submitted to Swissmedic with respect to quality, nonclinical, and clinical requirements for gene therapy products.

Quality Considerations. For clinical use in humans, the respective investigational medicinal product (IMP) has to be produced according to GMP [7]. For first-in-man (FIM) and phase I/II clinical studies, the individual production steps of the IMP are usually not fully validated. From the very beginning, the development of the

manufacturing process of the gene therapy product is a critical step, as it will determine its suitability, safety, and efficacy. As gene therapy products are based on nucleic acids, the IMP needs to be sequenced at an appropriate step during production, and the full sequence should be submitted in a readable and understandable form (annotated, graphically formatted) with a short verbal description of its main characteristics. The different sequence elements of the vector(s) and the therapeutic genes need to be explained in detail in the clinical trial dossier, including the rationale for its use. The origins and history of the sequences and all construction steps during cloning need to be described in detail. Any selection markers that could pose a risk to the human subjects (e.g., an antibiotic gene) should be removed in the final IMP. Cells used during the amplification of the IMP need to be fully characterized. For viral vectors, the origin and biological characteristics of the parental wild-type virus need to be described. The IMP needs to be stable throughout its use in the frame of the clinical trial. Therefore, the stability of the product needs to be addressed from the very beginning. An approach often used is that a "sentinel" clinical grade batch is produced several months ahead of the batch intended to be used in the clinical trial. Based on the data derived of this "sentinel" batch, the stability of the clinical trial batch can be extrapolated. Accelerated stability tests at elevated temperatures (stress test) are also recommended. Transport and storage of the IMP need to be described in detail.

The cell banks and/or viral seeds used for production and all raw materials need to be characterized during production with respect to identity and safety, using appropriate quality controls. During production, adequate in-process controls need to be established, and a flowchart needs to be provided that describes in detail all steps during production. Acceptance criteria for critical parameters should be appropriately set, and more than one batch of the bulk product should be characterized to determine identity, purity, safety, and potency. Product identity can be shown at the level of the nucleic acids, as well as at the level of the gene product (e.g., immunological characterization of the expressed protein). Regarding purity, each batch should be within specific limits that are defined, established, and justified with respect to the developmental stage of the IMP. Special attention shall be given to limits of residual RNA, DNA, proteins, and endotoxin. Safety needs to be documented based on product-specific risk assessments. For viral vectors, this also includes the evaluation of the risk of replication-competent viruses (RCVs) that could potentially be generated during production. Potency tests can be established in vitro or in vivo and are highly product specific, and the parameters to be measured may be discussed with Swissmedic in the frame of scientific advice meetings before submitting a clinical trial dossier.

Plasmids and viral vectors are the most commonly used vectors for gene transfer. Plasmids can either be used in a naked form or in a complex with polymers, liposomes, or proteins as carriers. When complexed plasmids are used, the carriers need to be specifically characterized, especially with respect to purity, dose, safety, and stability. For viral vectors there are some peculiarities that need to be specifically addressed. Similar to complexed plasmids, viral vectors consist of the therapeutic gene sequence (DNA or RNA) packed in a protein or protein/lipid coat. The dose definition and dose determination of viral vectors need to be addressed very early

during development. These parameters can be measured at three different levels: total particles, packed particles (containing the therapeutic gene), and infectious particles (based on the particles that transduce target cells plus the expression of the therapeutic gene). For non-replicating viral vectors, it is also important to determine the RCV that may be generated during the manufacturing process. The specifications with respect to acceptable RCV levels should be justified by the applicant.

Ex vivo gene therapy products consist of cells that have been genetically modified, usually by means of retro- or lentiviral vectors. In Switzerland, these products are TpPs, and most of what is described in Sect. 4.2 is also applicable to ex vivo gene therapy products. There are, however, a few specific aspects related to ex vivo gene therapy that need to be mentioned here. As retro- and lentiviral vectors have the capacity to integrate the reverse transcribed therapeutic gene into the genome of the recipient cells, the potential integration sites should be characterized. Over the years, several methods have been established for integration site analysis that are acceptable. Furthermore, it is important to determine the percentage of transduced cells, the expression of the therapeutic gene, and the stability of gene expression prior to administration of the genetically modified cells to the human trial subjects. Since viral vectors are used for transduction of the cells in culture, it is important to determine the presence of RCVs during production and in the final product. Transport and storage need to be described in detail, and stability data of the product should be available before clinical trials can be initiated.

Nonclinical Considerations. The nonclinical evaluation of investigational gene therapy products aims to collect relevant information with respect to the (1) biological activity, (2) biodistribution profile, (3) potential shedding, and (4) toxicological effects. This information should allow for an adequate assessment with respect to potential risks the human trial subjects are exposed to after treatment with the gene therapy IMP. The nonclinical evaluations should be conducted with the proposed IMP or with a product with very similar characteristics. Published data with comparable products are considered supportive data; however, they are usually not sufficient on their own to fully support the clinical use of the IMP and can therefore not replace nonclinical studies specifically designed to evaluate the IMP. The nonclinical evaluations should provide adequate information with respect to a safe starting dose, the optimal route of administration, and the dosing schedule. Regarding the starting dose, a "no observed adverse effect level" (NOAEL) and ideally a minimal biologically effective level should be determined. An adequate safety margin with respect to the planned clinical starting dose should be established in a relevant animal species. For pivotal toxicological safety studies, clinical grade material should be used, and the evaluations should follow the principles described in the ICH (M3 [16]), EMA (EMEA/CHMP/GTWP/125459/2006 [17]), or US FDA guidelines (e.g., the guidance document "Preclinical Assessment of Investigational Cellular and Gene Therapy Products" [18]). The relevance of animal models (e.g., the choice of the most relevant species or the use of a specific disease model) is a difficult issue, and the choice of the most relevant species and disease model needs careful case-by-case consideration and justification by the applicant.

The evaluation of the biological activity of the gene therapy product under investigation can be performed in vitro and in vivo. The actual proof of concept is usually performed in vivo. No extensive studies are required, and published data with similar products are also acceptable as supportive data. One good study in one good animal species/disease model is usually sufficient as long as the scientific rationale is adequate. The conduct of pharmacodynamic/proof-of-concept studies does not need to be performed according to good laboratory practice (GLP).

Extensive pharmacokinetic analyses to characterize absorption, distribution, metabolism, and excretion (the so-called ADME studies) are usually not required for gene therapy products. The focus with respect to pharmacokinetics lies on the investigation of the biodistribution profile of the gene therapy product in question. Published data with similar products are considered supportive data. However, specific nonclinical studies with the IMP in its final formulation are often required, and the dose and the route of administration that are planned in the clinical trial should be used for the determination of the biodistribution profile in animals. The biodistribution profile facilitates the definition of risks of the gene therapy product. As an example, the accumulation of the gene therapy product in the gonads might point to the risk that the product might integrate into the genome of germ cells. In this case germline transmission studies might be required. Regulatory guidance with respect to germline transmission studies can be found on the ICH website ("ICH Considerations: General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors") and the EMA website (EMEA/273974/2005) [14, 19].

The potential for shedding of a gene therapy product (the dissemination of the product through secretions or excreta of treated humans or animals) should be investigated early in nonclinical evaluations. A specific ICH Considerations paper with respect to shedding studies is available on the ICH website ("ICH Considerations: General Principles to Address Virus and Vector Shedding" [20]). In addition, there is a specific Swiss guideline published with respect to assessing the risk to humans and the environment [21]. Based on this Swiss guideline, the applicant is asked to classify the proposed clinical trial as (1) type A clinical trial (no shedding), (2) type B1 clinical trial (transient shedding but no release into the environment), or (3) type B2 (shedding with release into the environment). As with proof-of-concept studies, biodistribution and shedding studies generally do not need to be performed according to GLP.

Studies that assess toxicity should be conducted using a gene therapy product which is manufactured according to the specifications for the clinical batch. Especially for pivotal toxicity studies, it is recommended to use a clinical grade product which is manufactured according to GMP. These pivotal nonclinical safety studies need to be performed under GLP conditions [22]. The route, dose levels, and number of doses should mimic the planned clinical study, with adequate safety margins. The choice of the relevant species to be used for the toxicological evaluations needs careful case-by-case consideration and justification by the applicant.

The nonclinical safety studies that need to be conducted prior to clinical use will encompass single-dose/multiple-dose studies with an evaluation of local and systemic toxicity, with end points relevant to the respective IMP. Furthermore, the

potential for immunogenicity/immunotoxicity needs to be addressed (especially if multiple dosing with viral vectors is planned or if the therapeutic gene product may pose a risk of inducing adverse effects on the immune system). Tumorigenicity studies may become relevant if retro- and lentiviral vectors are to be used in an in vivo setting. For non-integrating vectors, tumorigenicity studies may generally not be necessary in the frame of an in vivo gene therapy approach. The potential for reproductive and developmental toxicity needs to be analyzed in case a risk assessment suggests any risks in the patient population. The extent of the nonclinical reproductive and developmental toxicity evaluations will depend on the disease to be treated, the route of IMP administration, the vector and therapeutic gene delivered, the age of female patients, and the potential effects on the reproductive organs due to the treatment.

Long-term expression of therapeutic gene products with growth factor activities or effects on the immune system may trigger long-term toxicity studies in animals. These long-term risks have to be appropriately assessed on a case-by-case basis by the applicant in order to define the full spectrum of studies for an adequate risk profile of the gene therapy IMP. Appropriate long-term toxicity studies need to be carried out if replication-competent vectors are used that have the capacity for latency and reactivation (as in the case of herpes viruses).

Ex vivo gene therapy products show specific risks that need to be addressed in in vitro or in vivo settings. Cells transduced with integrating retro- or lentiviral vectors need to be assessed for tumorigenic changes. The number and location of the integration sites need to be determined, and the activation of oncogenes close to the integration sites needs to be investigated. Other risks that should be evaluated are the pathological behavior of transduced cells in vivo. This may be especially relevant for T cells transduced with certain T-cell receptors (e.g., CARs). The migration, proliferation, distribution, and any pathological changes to specific organs need to be studied in at least one appropriate animal species. The extent of these studies may depend on the existing clinical experience with similar gene therapy IMPs.

Clinical Considerations. The clinical evaluations (FIM, phases I–III) of investigational gene therapy products aim to determine safety and efficacy. The clinical evaluations have to be performed according to the GCP principles as described in the ICH E6 "Guideline for Good Clinical Practice" [6], and the gene therapy IMP needs to be produced according to GMP [7].

Based on the indication, vector type, and clinical experience with similar investigational products and the nonclinical safety data, a clinical risk assessment needs to be submitted to Swissmedic. This assessment should list all possible risks to the study participants and the measures to be taken to minimize the identified, possible, and potential risks. In addition, the clinical study needs to be classified according to the Swiss guideline with respect to shedding [21] as explained above under "Nonclinical Considerations." If possible, the starting dose should be based on relevant nonclinical studies and clinical data with similar IMPs. For safety reasons a staggered approach is usually needed in the frame of FIM studies, where only one study participant is treated at a time and adequately observed for adverse events before a second study participant is treated. The exact manner in which this staggered

approach is performed is dependent on the type of gene therapy product and needs to be based on the expected time delay before potential occurrence of identified, possible, and potential severe or serious adverse events. During this time, the volunteer or patient may have to be kept at the hospital for observation and rapid application of predefined measures should adverse events occur.

The extent of clinical monitoring and the need for long-term follow-up (LTFU) studies should be based on the clinical experience with similar products and the nonclinical safety evaluation of the clinical gene therapy IMP. Based on the vector type, clinical experience with similar IMPs, and findings in nonclinical safety evaluations, the clinical monitoring plan should take into account potential targets of toxicity and immunotoxicity. For integrating vectors, genome integration sites and the potential for tumorigenicity need to be closely monitored. An LTFU plan is usually required, especially for gene therapy products that tend to be expressed over a long time period. The LTFU can already be part of the clinical protocol, or a separate LTFU study can be designed and submitted for approval.

Any severe adverse events that occur in the frame of a clinical trial with a gene therapy IMP should be reported to Swissmedic according to ClinO and published checklists on the Swissmedic website [1, 23].

4.2 Specific Considerations for Transplant Products (TpPs)

In this section, aspects that need to be considered when performing clinical trials with TpPs are described. As there is overlap between this section and Sect. 4.1 above, concerning gene therapy products, TpP-specific issues will be specifically addressed here, although some repetition cannot be avoided. As there is no experience in Switzerland with TpPs consisting of complex tissues, whole organs, or xenogeneic cells, these products will be excluded; thus, the considerations described below will only focus on human cells. The cells may show stem cell characteristics or be more committed cells, and they may be allogeneic or autologous in nature. Some aspects of genetically modified cells used for ex vivo gene therapy approaches are already described in Sect. 4.1; however, the TpP-specific considerations described in this section are also applicable to genetically modified cells.

Quality Considerations. The overall principles of assuring product quality during the manufacturing, transport, and storage of an IMP are similar whether it involves a gene therapy product or a TpP. The inclusion of a detailed flowchart describing all steps (from procurement of the cells to the final formulation of the TpP) is recommended. As described for gene therapy IMPs, investigational TpPs need to be manufactured according to GMP standards. For TpPs, the procurement of the cells is a critical step, especially if the final cell product is allogeneic. Testing the donor of an allogeneic product for infections (i.e., HIV, HBV, HCV) and testing of the obtained cells for the presence of viruses and bacteria are required as described in the ordinance on transplantation [24]. Master cell banks (MCBs) and working cell banks (WCBs) need to be established and characterized according to the ICH Q5D guideline [25]. Testing of the donor for the manufacture of autologous TpPs is also

needed. The autologous cells obtained from one donor can be defined as a single batch. As cell numbers are usually limited in the autologous setting, testing throughout manufacturing is challenging. Evaluation of bacterial and viral removal or inactivation is usually not possible. Therefore, all starting material needs to be obtained aseptically and characterized appropriately, and each manufacturing step needs to be established in a way that prevents contamination of the product. If bovine material is used during production, the risk with respect to spongiform encephalopathy needs to be assessed, and a special form must be filled out and submitted to Swissmedic [26]. All additional auxiliary material and structural components need to be described in detail and qualified.

There are often only small manufacturing differences between the starting material, the active substance, and the final investigational TpP; all three need to be clearly defined for each TpP. The active substance is usually the cells with or without additional components. Specific consideration should be given to define appropriate markers for monitoring cell identity (e.g., cell morphology, biochemical markers, cell surface markers). In products where matrices are used as supportive structural elements, data confirming the identity of these components need to be provided.

Appropriate assays have to be established to control cell purity and cellular impurities (e.g., quantification of contaminating cells). The control of noncellular impurities (e.g., fetal calf serum, dimethyl sulfoxide, degradation products, antibiotics, etc.) is critical because they may be introduced into the product at various manufacturing stages. It is therefore crucial to establish validated in-process controls and to define acceptance criteria for each material in the final TpP. An in vitro or in vivo potency test needs to be in place at very early stages of the TpP development program (ideally for phase I clinical trials) to demonstrate the intended biological activity. As is the case for gene therapy products, potency assays are highly product specific, and the parameters to be measured may be discussed with Swissmedic in the frame of scientific advice meetings before submitting a clinical trial dossier. Transport and storage need to be described in detail, and the stability of the product needs to be investigated before clinical trials can be initiated.

Nonclinical Considerations. The nonclinical evaluations of TpPs should aim to collect relevant information with respect to (1) proof of concept, (2) migration and proliferation potential of the cells after administration, and (3) the potential toxicological effects. Similar principles as described under Sect. 4.1 for gene therapy products also apply to TpPs. The evaluations should be performed with the intended clinical TpP. Data from publications are considered supportive, especially for the proof of concept. However, specifically designed studies with the proposed TpP manufactured in a manner identical to the planned clinical batch are usually required. This applies especially to safety studies. In the case that the human TpP cannot be adequately studied in animals, an autologous TpP may be developed for the nonclinical evaluations in one relevant animal species.

Proof of concept can be obtained using in vitro and in vivo studies. Usually, one relevant animal model is sufficient for these pharmacological evaluations. The establishment of a relevant animal model is often a challenge, especially if a homologous model needs to be used for the evaluation of an autologous TpP.

The proof-of-concept data may also enable defining a potentially efficacious dose for use in the clinical trial. Ideally, the migration and proliferation capacity of the cells constituting the TpP is analyzed in the same models. However, if large animal models are needed for proof of concept, the in vivo analysis of cellular migration and distribution is often difficult; thus, a small animal species may be used for evaluating the aspects of proliferation, migration, and distribution. The need for studying migration, distribution, and proliferation of the TpP following administration in animals and the technical details can be discussed with Swissmedic in the frame of a scientific advice meeting prior to the submission of the clinical trial dossier.

The extent of the nonclinical safety evaluation is strictly product dependent. A risk assessment facilitates an understanding of what parameters need to be evaluated for the establishment of an adequate safety profile. A safe starting dose that may be the basis of the FIM study should be established. If the TpP is intended to be applied to humans as a single administration, a single-dose toxicity evaluation in one animal species is usually sufficient. All pivotal in vivo toxicity evaluations should be performed under GLP conditions. In these nonclinical safety evaluations, the product should be administered according to the clinically relevant route. Besides potential local toxicity, the systemic effects on various organs and effects on the immune system may need to be considered. The design of the pivotal toxicity studies can be discussed with Swissmedic in the frame of a scientific advice meeting prior to the submission of the clinical trial dossier.

For most TpPs, it is necessary to evaluate the tumorigenic potential of the product. In vitro and in vivo studies may be performed to address this risk. This includes the in vitro analysis of chromosomal stability, the integration site analysis and transformation potential for ex vivo gene therapy products (as described above), and in vivo studies addressing tumor growth and unwanted tissue formation in target and nontarget tissues, such as the formation of teratomas.

Clinical Considerations. The general principles of studying TpPs at the clinical level do not differ from other IMPs. Safety and efficacy need to be addressed, and all studies have to be performed according to GCP principles. Similar to gene therapy products, where the risk is dependent on the vector type, the transferred gene, and the clinical use, the risk associated with TpPs is dependent on the characteristics of the cells, the noncellular components in the final product, and the intended clinical use. Therefore, a TpP-specific clinical risk assessment needs to be performed, and measures to be taken to minimize these risks need to be defined.

In the early safety studies (FIM, phase I), a safe dose needs to be established. Risks and toxicological effects identified in relevant nonclinical studies should be addressed in the clinical studies. Product-specific safety and efficacy end points need to be established, and, as for the gene therapy products, LTFU is usually required. Further, any adverse event that might be related to a procedure which the patient has to undergo in order to receive the TpP, but which he or she would not have undergone otherwise, has to be classified as an adverse drug reaction (ADR). Any adverse event arising due to, for example, administration of a medication (such as G-CSF) or due to performance of a biopsy in order to obtain the autologous cells needed for the

manufacture of a TpP might also qualify as an ADR. In the same line, a microbiological contamination occurring during manufacture but not detected before administration to the patient or to the volunteer should also be considered an ADR.

Further, the route of administration (e.g., cutaneous, intra-articular, or intramyocardial) of a TpP will each carry a different level of risk. The clinical significance of the chosen end point will need to be greater in the case of a TpP requiring a potentially dangerous administration procedure. Swissmedic takes this into account in its overall benefit-risk analysis.

In case of a future marketing authorization, specific consideration should be given to the above points in the pharmacovigilance and risk management plan development. Not only the pharmacovigilance system will need to be organized to include procedural adverse events related to TpPs, but the treating physicians should be informed of the need to report such events. As clinical trials with autologous TpPs will rarely reach a sample size as large as for drugs based on small molecules, rare adverse events may often not be detected until after marketing authorization. The pharmacovigilance system and the physicians will need to be sensitized to the potential risks specific to TpPs, so that they can be identified should they occur.

5 Regulatory Requirements for Gene Therapy Products and Transplant Products for Marketing Authorization

The marketing authorization for gene therapy products and TpPs requires the submission of a complete dossier that has to be structured into five modules according to the ICH Common Technical Document (CTD) M4 guideline titled "Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use" [27]. The following description is based on the more detailed information sheet "requirements relating to the authorization documentation for transplant products" published on the Swissmedic website [12].

Module 1 has to contain the actual application, GMP certificates, information regarding the state of any authorizations in other countries, information relating to experts (including curriculum vitae), a risk assessment of the environmental data, pharmacovigilance and risk management plans, labeling information, patient information, and professional information.

Module 2 should give an overview of the product. It is sub-structured into quality, nonclinical, and clinical sections, with each section summarizing key information. The nonclinical section should contain a table summarizing all nonclinical studies, with the GLP status indicated. The clinical section should also contain a product-specific benefit-risk assessment based on nonclinical and clinical data.

Module 3 should contain detailed information with respect to the quality of the clinical product. Details including the active substance, the finished product, transport, and storage conditions need to be provided.

Module 4 should contain (in the form of final study reports) the detailed nonclinical information, including all data with respect to primary and secondary pharmacodynamics, safety pharmacodynamics (where applicable), and pharmacokinetics (e.g., migration potential and biodistribution data) and toxicology data.

Module 5 should contain (in the form of final study reports) the detailed clinical information, including all data with respect to pharmacodynamics/clinical efficacy, pharmacokinetics, dose-finding studies, safety, and long-term effects. The pharmacovigilance planning should also be included.

6 Conclusions

Since the 1990s, substantial experience has been accumulating in Switzerland for the regulation of gene therapy products and transplant products. Although rather complex in nature, the experience with the current approval process for clinical trial applications is positive from both, the regulatory perspective and the perspective of sponsors and investigators. The early planning of scientific advice meetings with Swissmedic is the central gateway for a cost-effective development of gene and cell therapy investigational products and an adequate planning of clinical trials in Switzerland.

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Regulatory Frameworks for Gene and Cell Therapies in Japan

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Abstract The regulations for the human use of advanced therapy medical products such as gene and cell therapy products have evolved in accordance with advance of clinical experience, scientific knowledge, and social acceptance to these technologies. In Japan, two laws, the Pharmaceuticals and Medical Devices (PMD) Act and the Act on the Safety of Regenerative Medicine (ASRM), were enacted in November 2014. The PMD Act defines regenerative medical products for the first time and introduces a system for the conditional and time-limited marketing authorization of regenerative medical products. Under ASRM, the responsibilities of medical institutions to ensure the safety and provide transparency of such medical technologies are described. Amendments to accompanying guidelines for these two Acts are currently in preparation. It is expected that the new legislative frameworks will promote the timely development of new products and technologies, to bring safe and effective regenerative medicines to Japanese patients.

Keywords Japan • Gene therapy • Cell therapy • Pharmaceuticals and medical devices act • Act on the safety of regenerative medicine • Guidelines

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Abbreviations

ASRM	Act on the Safety of Regenerative Medicine
ATMP	Advanced therapy medical products
CT	Cell therapy
DNA	Deoxyribonucleic acid
GCP	Good clinical practice
GCT	Gene and cell therapy
GL	Guideline
GT	Gene therapy
HSC	Health Science Council
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iPS	Induced pluripotent stem
JSRM	Japanese Society for Regenerative Medicine
MA	Marketing authorization
MAA	Marketing authorization application
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
NIHS	National Institute of Health Sciences
OCTP	Office of Cellular and Tissue-based Products
PAL	Pharmaceutical Affairs Law
PASFC	Pharmaceutical Affairs and Food Sanitation Council
PMD Act	Pharmaceuticals and Medical Devices Act (revised PAL)
PMDA	Pharmaceuticals and Medical Devices Agency
RNA	Ribonucleic acid

1 Introduction

Gene therapies are expected to provide new therapeutic options for patients with inherited disorders due to genetic abnormalities or cancers for which no effective treatments currently exist. Cell therapies which involve cells that are manipulated in vitro and functionally modified to mimic normal cells enable repair and replacement of damaged/degenerative tissues, improvement of the patient's quality of life, and enhanced immunity to cancer, among others. These advanced therapies are anticipated to improve the quality of medical care, which cannot be accomplished by conventional pharmaceuticals so far.

On the other hand, technologies such as those used to introduce a transgene into targeted cells or tissues, to control expression of a transgene, to differentiate cells to the desired stage, or to eliminate abnormal cells in the manufacturing process are not yet sufficiently developed and remain challenging. Thus, the efficacy and safety

of the advanced therapies that result from such technologies for use in medical care are far from established.

In recent years, some problems relating to stem cell therapy have emerged in Japan [1]. Emblematic of the problems, it has been reported that a patient died from pulmonary embolism soon after receiving stem cell therapy which was prepared overseas and administered at a clinic in Japan. Since it was unlawful to commission cell processing to establishments outside the medical institutions except in the case of approved marketed product, medical doctors or their collaborators had to conduct cell processing within their own institutions. Therefore, it was understandable for the general public to assume that the manufacturing control and quality control might not be fully assured for the cells prepared by third parties. This situation was noticed as a barrier to the appropriate and timely development of the advanced therapies. The Japanese Society for Regenerative Medicine (JSRM) issued its "Yokohama Declaration" in March 2013, calling the Japanese government for constructing an appropriate regulatory framework for the regenerative medicine [2].

Under these circumstances, the Regenerative Medicine Promotion Law was passed on May 10, 2013 [3]. This law states that the Japanese government must make comprehensive policy to promote the developments of regenerative medicine and to inform the public and increase public acceptance and that medical professionals and investigators should cooperate with the policy. In line with this law, two related laws, the Pharmaceuticals and Medical Devices (PMD) Act (which is the revised Pharmaceutical Affairs Law (PAL)) and the Act on the Safety of Regenerative Medicine (ASRM), were passed on November 27, 2013, and enacted on November 25, 2014 [4, 5]. As a result, the measures to ensure the safety of regenerative medical products/technologies and the means to expedite the patient's access to these products have been strengthened. This is a historical event in Japanese regulation of medical products that will lead to advancement of gene and cell therapies (GCTs) [6].

In this chapter, the essence of these two important Acts will be summarized, and the related standards and guidelines for GCTs will be discussed.

2 Japanese Regulatory Frameworks of GCTs

2.1 Definitions

In Japan, gene therapy (GT) is defined as the administration of genetic materials or genetically modified cells into humans for therapeutic purposes [7]. Administration for prophylactic purposes may be permitted and included as GT if the benefit/risk balance for the subject is appropriate (from the minutes of Pharmaceutical Affairs and Food Sanitation Council discussions) [8]. GT includes in vivo and ex vivo applications of viral vectors and nonviral vectors, such as plasmid DNA. Therapies using unmodified viruses used as vaccines, recombinant proteins/peptides, siRNAs,

antisense oligonucleotides, RNA aptamers, and nucleic acid derivatives are not categorized as GT. On the other hand, the use of nonviral vectors designed to express the siRNAs or antisense RNAs is considered GT.

In Japan, although cell therapy (CT) is not clearly defined in the PMD Act and in the related Acts, the administration or transplantation of "processed" living cells derived from human or animal tissues/organs into a human subject is considered as CT. In contrast, established therapies/products such as organ transplantation, hematopoietic stem cell transplantation, and blood products are not regulated as CT, even if they consist of living cells. The technologies utilizing processed cells that are covered by the PMD Act and ASRM are defined as follows: (1) technologies intended for reconstruction, repair, or formation of structures or functions of the human body or (2) those intended for the treatment or prevention of human diseases.

"Processing" is defined by the PMD Act and ASRM as follows:

Processing of cells or tissues includes (1) artificial expansion/differentiation of cells and establishment of a cell line, (2) chemical treatment to activate cells or tissues, (3) modification of biological characteristics, (4) combination with non-cell/non-tissue components, and/or (5) genetic modification of cells conducted for the purpose of treatment of diseases or for repair or reconstruction of tissues. "Processing" does not include the following operations: (1) separation and cutting of tissues, (2) isolation of specific cells (except for isolation following biological/chemical treatments), (3) treatment with antibiotics, (4) washing, (5) sterilization by gamma ray, (6) freezing, (7) thawing, and/or other procedures that do not use cells for the purpose of gaining different structures and functions from the original cells.

Since the CT using genetically modified cells falls within both the definition of CT and GT (ex vivo GT category), regulations and scientific evaluations for both CT and GT apply to such products.

Currently, two cell therapeutic products, cultured autologous epidermis and cultured autologous cartilage, have been approved as medical devices, and no GT products have been approved in Japan. Therefore, in this chapter, the description of current regulatory frameworks deals mostly with clinical research of unestablished techniques and products.

Definitions of the terms used in this chapter are as follows [9, 10]:

"Clinical study" refers to a study conducted to investigate the clinical efficacy and safety of an investigational therapy, including both clinical research and a clinical trial.

"Clinical research" refers to a clinical study which is not intended to collect clinical data for a marketing authorization application (MAA) under the PMD Act. This type of study is conducted to gain scientific knowledge and establish various medical techniques.

"Clinical trial" refers to a clinical study intended to be used to collect clinical data for a MAA under the PMD Act.

2.2 *Outline of Regulatory Frameworks of GCT Clinical Studies*

Figure 1 provides an outline of health research regulations in Japan, regarding the conduct of clinical studies.

Two types of clinical studies are conducted in Japan. Some studies are conducted as clinical research in medical institutions, and other studies are conducted as clinical trials. Before conducting these studies, study plans must undergo different review systems depending on the type of GCT clinical studies. However, the Ministry of Health, Labour and Welfare (MHLW) has the authority to permit conducting both types of the clinical studies in Japan. MHLW will give approvals for providing the technologies under the national health insurance system or marketing products to the public based on the result of those studies.

In addition to GCTs in health research, GCTs in "medical care" are provided as private practices in clinics and hospitals through an agreement between a doctor and a patient. Although some of these "medical care" GCTs are not conducted for scientific purposes, this chapter counts them among health research in a broader sense of unestablished medical care practices.

In Japan, interventional treatments for patients are regulated by the Medical Service Act, the Medical Practitioners' Act, and related laws [11, 12]. In addition to these laws, before November 2014, for marketing authorization (MA), sponsors and medical institutes had to be compliant with PAL when they conducted clinical trials (Fig. 2a).

PAL was the law on manufacturing, marketing, distributing, and using of pharmaceuticals and medical devices [13]. Objects regulated by PAL were "products" that are pharmaceuticals and medical devices, and object-persons were manufacturers, MA holders, distributors, doctors, medical professionals, and so on.

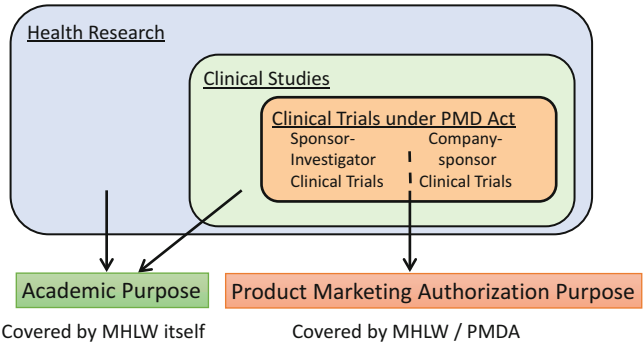

Fig. 1 Health research regulations in Japan. Health research includes both interventional studies and non-interventional studies. Clinical studies are basically interventional studies. Clinical trials are conducted for MAA under the PMD Act, including company-sponsor clinical trials and sponsor-investigator clinical trials

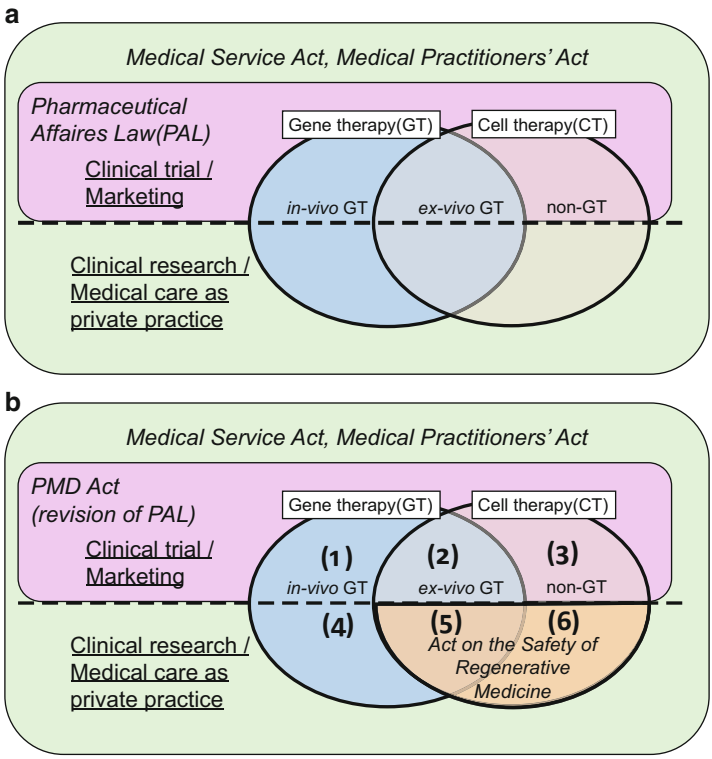

Fig. 2 Legislation for GT and CT. Legislation for GT and CT changed, (**a**) until November 24, 2014, (**b**) after November 25, 2014

The new legislations have introduced major changes to the regulatory frameworks. As of November 25, 2014, the PMD Act replaces PAL. ASRM has been introduced to cover the research areas not covered by the PMD Act and ensures the safety and ethicality of these new technologies (Fig. 2b). ASRM applies to cell therapies administered in medical practices using any processed cells, including cancer therapies with activated immune cells and the so-called stem cell therapies for cosmetic purposes.

2.3 Current Approved Products and Development Trends

There is currently no approved GT product in Japan. In Japan, over 40 clinical study protocols, mostly of clinical research, have been approved in the last 20 years, and about 20 protocols are ongoing as of December 2014 [14]. They include both in vivo and ex vivo GTs; approximately two-thirds of protocols are for in vivo GTs, and the rest are for ex vivo GTs. The majority of the protocols are for cancer therapy: the others include primary immunodeficiency, congenital metabolic disorders, and

severe limb ischemia. As for the gene delivery systems, the majority of the protocols use a retroviral or adenoviral vector, and the others use naked plasmids, plasmids in cationic liposomes, and herpes virus, lentivirus, adeno-associated virus, and Sendai virus (hemagglutinating virus of Japan) vectors.

For CT products, there are two products that have been approved for MA under the PMD Act in Japan. One is cultured autologous epidermis, and the other is cultured autologous cartilage, both of which are for homologous use. No allogeneic/heterologous products have been approved thus far. The National Institute of Health Sciences (NIHS) maintains a database on clinical research using stem cells in Japan on its website. Approximately 100 clinical study protocols have been approved for stem cell therapy research thus far [15].

3 Regulatory Procedures on GT and CT in Japan

Interactions with regulatory authorities are required at the following three stages in GCT product/technology development and marketing as GCT products:

(a) Prior to conducting a clinical study
(b) MAA
(c) Post-marketing

The GCTs can be divided into six patterns regarding required procedures, which are shown in Fig. 2b.

3.1 Conducting Clinical Studies

As mentioned above, the sponsor and the purpose of the clinical studies are essential to determine the regulations that apply at the stage of conducting clinical studies. As stated in Sect. 2.1, a clinical study conducted for the purpose of obtaining clinical data for a MAA is called a "clinical trial," and the study conducted by a researcher in a medical institution for scientific purposes is called "clinical research." The regulatory path for the former is shown in Fig. 2b(1)–(3), and the path for the latter is shown in Fig. 2b(4)–(6).

For both types of interventional clinical studies, the safety of patients and the ethical conduct of the study should be ensured. Evaluation of safety must be compliant with Japanese good clinical practice (J-GCP) and local implementation of ICH-GCP [16]. Clinical research studies are not required to be fully compliant with J-GCP, but the ethics of the study must be maintained, and a certain level of subject safety must be maintained.

Corresponding guidelines (GLs) that apply to the study design and the review bodies differ depending on the study type. For clinical trials, if clinical efficacy and safety are confirmed in the trials, the sponsor will then submit a dossier to MHLW

/Pharmaceuticals and Medical Devices Agency (PMDA) to obtain a MA. If MHLW grants a MA, the sponsor is permitted to provide their product to clinical facilities as a marketing authorization holder (MAH). In contrast, the results of a clinical research study are not equivalent to those from a pivotal clinical trial in the clinical data package for a MAA.

3.1.1 Procedures to Initiate a Clinical Trial

Before starting a clinical trial with a new product, a sponsor must submit a clinical trial notification to MHLW, consisting of a clinical protocol, an investigator's brochure, and materials for informed consent. Once the clinical trial notification is submitted, the sponsor must wait 30 days before initiating the clinical trial. During this period, MHLW/PMDA examines the study protocols and other documents submitted with the notification for assurance on the safety of the study subjects.

If any reasons for not starting the trial arise during the 30-day examination period, MHLW/PMDA asks the sponsor for appropriate modifications, and then, if necessary, MHLW/PMDA tells the sponsors not to conduct the trial until the changes are made. These procedures remain the same after November 25, 2014, except for format changes for notifications.

Prior to notifying about their clinical trial plan, sponsors are advised to consult with the Office of Cellular and Tissue-based Products (OCTP) of PMDA to confirm that the requirements or recommendations specified in applicable guidelines on ensuring of quality and safety of the investigative products are sufficiently met. This consultation should be at an early stage of product development. There is a consultation fee that the sponsor must pay for this meeting. In the case of academia or small companies, sponsors satisfying certain conditions, preferential reduction in the consultation fee may be given [17].

3.1.2 Starting Clinical Research

Under ASRM, CT technologies (Fig. 2b(5)–(6)) are classified into three categories based on potential risks that are dependent on (1) the cell source (autologous, allogeneic, embryonic stem cells/induced pluripotent stem cells, somatic stem cells, somatic cells), (2) type and extent of manipulation, (3) usages (homologous/non-homologous), and (4) other factors. The classification will be regularly reviewed and revised as necessary, based on opinions of the Health Science Council (HSC), one of the advisory bodies to the Minister of MHLW. Anyone who intends to provide CT technology to a human subject (except for investigators that conduct clinical trials) has to follow the procedure described below according to its category. A medical institution which intends to administer CT technologies must submit a provisional plan to the Certified Special Committee for Regenerative Medicine (certified by MHLW) and then notify MHLW of the plan. In case of Class 1 (high risk) use, MHLW will make a decision based on the opinions from the HSC within 90 days (Fig. 3).

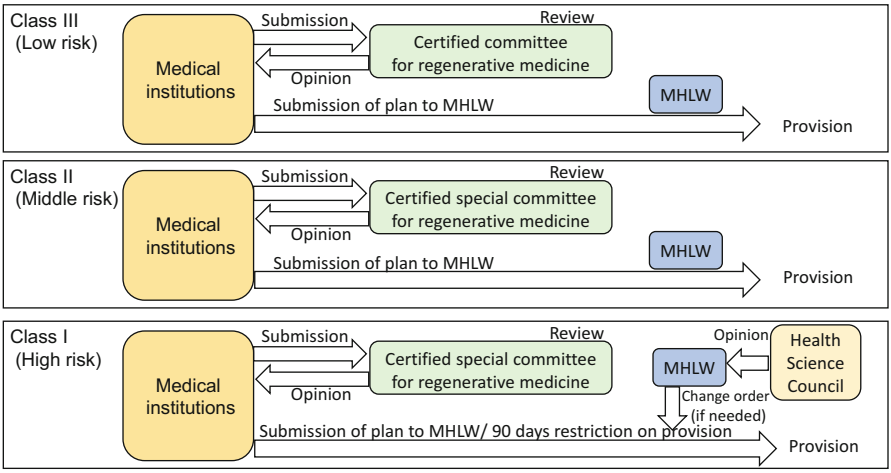

Fig. 3 Procedures to provide regenerative medicine under the new Act in Japan. CT technologies are classified into three categories based on potential risks. The categories are regularly revised based on opinions of the Health Science Council (HSC). Medical institutions which intend to administer CT technologies should submit a provisional plan to the Certified Special Committee for Regenerative Medicine (MHLW certifies the committee) and should then notify MHLW of this plan. In case of Class 1 (high risk) products, MHLW will make a judgment based on the opinions from the HSC within 90 days

The institution which provides the CT after notification to MHLW has to report annually to MHLW, including (1) the number of patients who were administrated processed cells, (2) incidence of diseases and disabilities related to CT administration, and (3) overall safety evaluation and scientific acceptability of the particular CT technologies, and has to submit the report to the Committee for Regenerative Medicine and MHLW.

Since every provision plan and annual report in each class have to be submitted to MHLW, MHLW will have an overview of all regenerative medical technologies provided in Japan. Based on the information, implementation status of regenerative medicine in Japan will be made public at an official website (in preparation as of December 2014). This action by the MHLW will make the regulation of CT in Japan more transparent to the public in Japan and worldwide.

The same procedure applied to both in vivo GT and ex vivo GT clinical researches up to November 24, 2014. However, because in vivo GTs are out of the scope of ASRM and ex vivo GTs are in the scope of ASRM, different procedures now apply to these two types of GTs. Since ex vivo GTs are handled as CT (Fig. 4), ex vivo GTs must follow the CT procedures. As of the end of December 2014, every ex vivo GT is classified as Class 1 (high risk), regardless of the cell source (e.g., autologous/allogeneic).

For a new in vivo GT technology, when a medical institute submits a clinical research plan to MHLW, MHLW consults with the HSC. The Gene Therapy Clinical Research Review Board, under the HSC, examines the plan. MHLW will consider the advice from the HSC and decide whether the medical institute can conduct the research.

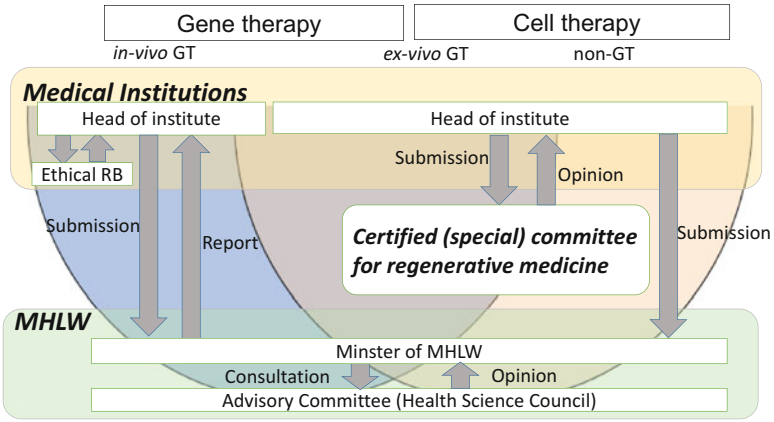

Fig. 4 It introduced the new review flow to cell therapies including ex vivo GT. On the other hand, the previous review flow has been applied to in vivo GT

For processing of the cells, it should be noted ASRM enables commissioning cell processing to facilities outside the medical institution, which had to be conducted within medical institutions before the new law took effect. Under ASRM, a business facility is required to obtain a license issued by MHLW prior to initiating cell processing at the demand of an institution. These business facilities are subject to licensing control by the government in order to ensure that they conduct effective quality control and assurance. All licensed facilities have to prepare annual reports, including the (1) number of manufacture of processed cells, (2) list of claims on the processed cells and the response to them, and (3) disease incidence, and submit the report to MHLW. This measure is expected to promote collaboration between the scientific community and industry from early stage, and it could accelerate the innovation in this area.

3.2 Marketing Authorization Application

When the efficacy and safety of the product are demonstrated in clinical trials, a sponsor will then submit a MAA to MHLW. Once the MAA is approved, continuous provision of the product is permitted to enable wide access of the product to the public under the PMD Act.

The PMD Act includes major changes to the product approval system. Two major changes are:

1. In addition to pharmaceuticals and medical devices, a new product category termed "regenerative medical products" was created for CT and GT products, and a specific chapter was dedicated to the category.

   Regenerative medical products are defined as (a) processed cells that are intended to be used for either (1) the reconstruction, repair, or formation of structures or functions of the human body or (2) those intended for treatment

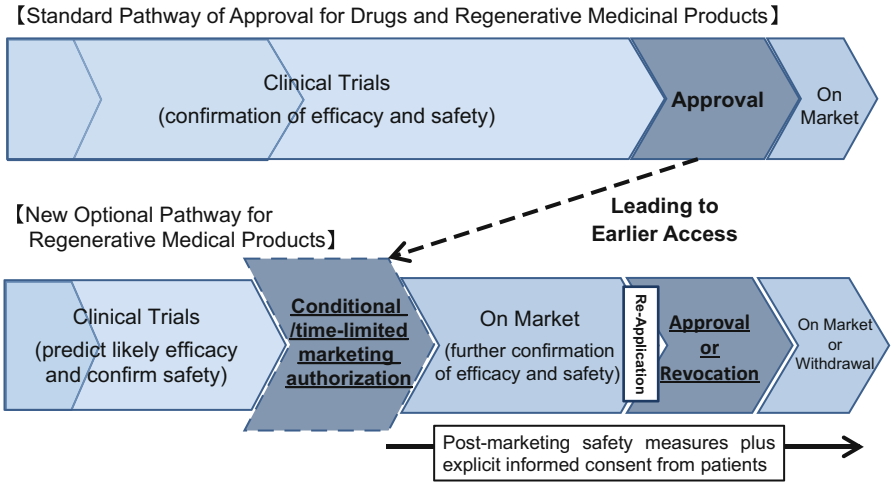

Fig. 5 Expedited approval system under the PMD Act. Under the traditional approval process of pharmaceuticals and medical devices, regenerative medical products must undergo lengthy clinical trials to confirm clinical efficacy before MA. The PMD Act has created a new scheme for regenerative medical products. If the results of clinical trial predict likely efficacy, the product will be given conditional, time-limited MA. Following conditional, time-limited MA, the product is subject to post-marketing safety monitoring in conjunction with surveillance and study to further confirm its efficacy and safety. MAH must submit an application dossier for the second MA. If the product failed to show its expected efficacy, MHLW may revoke its MA

or prevention of human diseases or (b) GT for therapeutic purposes. This definition is essentially equivalent to the definitions in the United States and European Union.

It is noted that GT products intended for therapeutic purpose are categorized as regenerative medical products under the PMD Act. As a result, a product consisting of a plasmid vector encoding an antigen of influenza virus for prophylactic use as a vaccine is not a regenerative medical product and therefore considered a pharmaceutical product. In contrast, CT products for prophylactic use are regenerative medical products.

2. Regenerative medical products can receive a time-limited approval with certain conditions after clinical data is obtained that is sufficient to predict likely efficacy and to confirm safety (Fig. 5). The time-limited conditional approval is introduced with consideration to such characteristics of these products as their heterogeneity in quality and the small patient populations, often resulting in a prolonged development.

After the conditional and time-limited MA, a MAH (i.e., a pharmaceutical company) will have to further confirm efficacy and safety of the product and submit an application dossier to MHLW for full approval within a specified time. The PMDA will review the application, and full approval would be granted by MHLW. If a MAH is not able to submit a reapplication within the time limit or efficacy and safety of the product are not proven, MA of the product will be revoked, and the product will be withdrawn from the market.

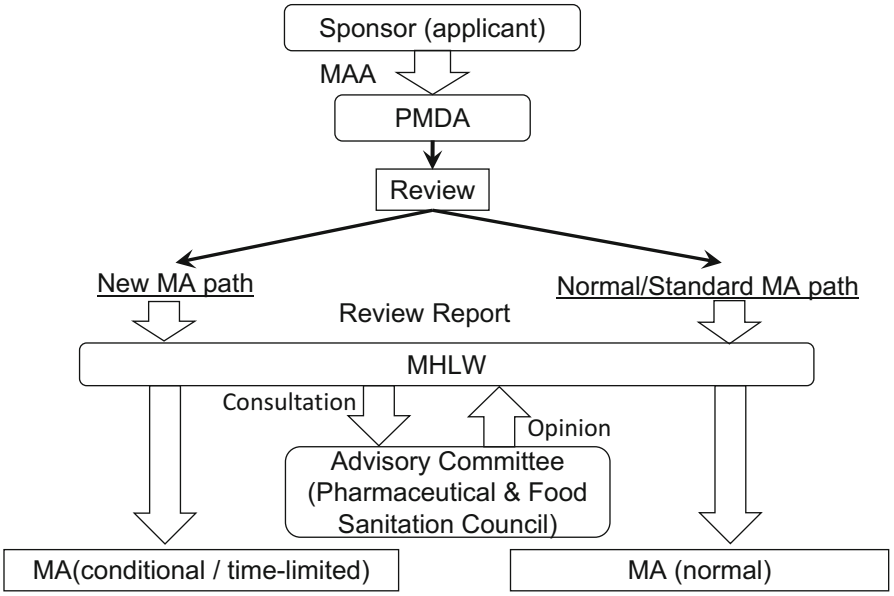

Fig. 6 Review flow for regenerative medicine under the PMD Act. The application submitted to PMDA will be classified for the normal MA or conditional, time-limited MA based on its nature of the target disease and characteristics of the product described in the application dossier

As for the conditions at the conditional and time-limited MA, it is assumed that the product will be used by physicians who have adequate knowledge and experience in regenerative medicine and MAH will collect follow-up data on all patients who received treatment with the product (these are only examples, not limited to these). The limited time interval for reapplication is 7 years from initial product MA as a general rule.

The newly introduced MA is granted not only depending on the heterogeneity in product quality but also on the target disease and the clinical importance of the product compared to pre-existing approved therapies. Although this conditional and time-limited MA allows expedited approval of regenerative medical products, it should be noted that this type of MA is only an option decided after MAA is reviewed and not all GCT products are eligible for this option (Fig. 6). Case-by-case approaches will take into account the nature of the target disease and characteristics of the product. Sponsors should consult with PMDA/OCTP at an early clinical stage.

3.3 Post-marketing

Regardless of a conditional and time-limited MA, after confirmation of the efficacy and safety in the clinical trials (and post-marketing clinical survey after conditional and time-limited MA), the reexamination period will be set after full MA. Reapplication after the reexamination period is needed like traditional pharmaceuticals in Japan.

It is obvious that the safety and efficacy of GT and CT products are not fully determined in the short period of clinical trials. Therefore, how to conduct long-term follow-up is one of the challenging issues with these products.

In Japan, the national registry system for regenerative medical products is under construction based on the MHLW working group discussion in July 2014 [18]. The system will be managed and maintained by PMDA, the details of which are not available at present.

3.4 Others

Environmental risk assessment is required for some types of GT products as an add-on procedure based on the "Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms" [19]. The competent authorities involved with this assessment at the stage of clinical studies and marketing are MHLW/PMDA and the Ministry of the Environment.

4 Guidelines

There are two sets of guidelines (GLs): one is for clinical trials and MAA [7, 20–32], and the other is for clinical research [33–37].

Specific to GT products, there is currently no guideline describing the clinical data package that is needed to achieve MA approval. Other existing GLs for pharmaceuticals such as ICH guidelines can be referred to an adequate extent as suited.

Revisions of GLs for GT, "GL for GT clinical research" and "GL for ensuring of quality and safety of GT products" (GL for GT clinical trials), are ongoing. They will be revised based on the current scientific knowledge.

Regarding the GL for GT clinical research, the committee that is responsible for revision of this GL met from 2013 to the second quarter of 2014 and produced a report in August 2014 (released for public comment in December 2014) [38]. The report proposed the following changes:

1. Added primary prophylactic use in the scope of the GL to harmonize with the GL for GT clinical trials.
2. Abolished the strict restrictions on "target diseases" to enable use of GT for subjects with chronic, non-life-threatening diseases.
3. Consistency with the GL for GT clinical trials in the quality and nonclinical areas.
4. Added recommendations for long-term follow-up.

Regarding the GL for GT clinical trials, the discussion about revisions to the existing document is ongoing. The contents are expected to become public in the near future.

As for the overarching GLs on CT products that were published in 2008 and 2012 [23–32], there is no official announcement about revising them. However, several GLs for the evaluation of individual products have been published or are in preparation under the MHLW [39, 40].

5 Future Perspective

This chapter summarizes the current regulatory situation of GT and CT in Japan and the domestic regulatory procedures for these product types from the viewpoint of regulators on clinical research and marketing authorization.

Development in the areas of advanced therapeutic medical products such as GT and CT is becoming very active in Japan due to the governmental policies implemented to ensure the safety of these products and to promote their practical clinical use. JSRM represented their welcome and newfound resolve in their statement in March 2014 [41].

In this innovative field, it is important for all stakeholders, including investigators, medical professionals, patients as well as general public, and regulatory authorities, to be aware that the use of flexible approaches which do not apply to traditional pharmaceuticals is admissible and necessary to foster these developing technologies.

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Regulatory Oversight of Gene Therapy and Cell Therapy Products in Korea

Minjoung Choi, Euiri Han, Sunmi Lee, Taegyun Kim, and Won Shin

Abstract The Ministry of Food and Drug Safety regulates gene therapy and cell therapy products as biological products under the authority of the Pharmaceutical Affairs Act. As with other medicinal products, gene therapy and cell therapy products are subject to approval for use in clinical trials and for a subsequent marketing authorization and to post-market surveillance. Research and development of gene therapy and cell therapy products have been progressing rapidly in Korea with extensive investment, offering great potential for the treatment of various serious diseases. To facilitate development of safe and effective products and provide more opportunities to patients suffering from severe diseases, several regulatory programs, such as the use of investigational products for emergency situations, fast-track approval, prereview of application packages, and intensive regulatory consultation, can be applied to these products. The regulatory approach for these innovative products is case by case and founded on science-based review that is flexible and balances the risks and benefits.

Keywords Gene therapy • Cell therapy • Ministry of Food and Drug Safety • Regulatory oversight • Regulation • Guideline

1 Introduction

The research and development of gene therapy (GT) and cell therapy (CT) products have been making rapid progress, offering great potential for the treatment of various serious diseases and for the regeneration of damaged tissues or organs. These efforts have led to considerable investment in such innovative therapies around the

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world. The early stages of this product area involved clinical studies that mainly focused on therapies for serious and life-threatening diseases, such as genetic diseases, cancers, AIDS, severe burns, and cardiovascular diseases. However, with the rapid development of science and technology and accumulated experience in the fields of GT and CT, therapeutic applications have expanded to include product intended to treat arthritis, diabetes, cutaneous ulcers, and various chronic diseases.

GT and CT products may require surgical operations, including invasive procedures for delivery to the target site. Medical aspects therefore also need to be considered, and the regulatory environments for GT and CT products may be influenced by the medical affairs law, medical environments, medical insurance coverage, and national policy support on development of advanced therapy medicinal products (ATMPs).

In Korea, the development of GT and CT products is mainly carried out by small- and medium-sized enterprises or venture companies. Compared to Europe and the USA, the number of patients available for clinical trials is fairly limited due to the relatively small population of Korea, which is about 50 million. Since in Korea the patients enrolled in clinical trials cannot be charged for the costs of both the investigational product and the treatment related to a clinical trial, there is a very heavy cost burden for clinical trials on such small- and medium-sized companies. Furthermore, the medical insurance coverage on these rather expensive products, determined by the national medical insurance system, also affects the development of GT and CT products. On the other hand, Seoul, the capital of Korea, has been credited with conducting clinical trials effectively since large populations and big hospitals with competent physicians are concentrated in this city. Under such circumstances, in order to facilitate providing safe and effective medicinal products to patients and especially to offer therapeutic opportunities to patients suffering from serious diseases that are difficult to treat with conventional therapies, several regulatory programs (see Sect. 3.2 of this chapter), such as expanded access to investigational drugs for treatment use or emergency use, conditional approval of New Drug Application (NDA), risk management plan (RMP), and prereview of application package, have been adopted. This chapter provides information on development of GT and CT products and regulatory overview of GT and CT products in Korea.

2 Regulatory Framework for Gene Therapy and Cell Therapy Products

2.1 Development of GT and CT Products in Korea

Since the first approval of a clinical trial for a GT product using a plasmid vector with VEGF gene in 2001, as many as 39 clinical trial protocols have been approved as of July 2014. About 50 % of protocols used plasmid vectors, while other

protocols used vectors derived from adenovirus, vaccinia, and retrovirus. The majority of the indications for GT Investigational New Drug (IND) Applications are cancers, and others include ischemic diseases and degenerative arthritis. However, there is no marketing-authorized GT product in Korea.

As of July 2014, 17 CT products derived from four mesenchymal stem cells (MSCs) and 13 somatic cells have been granted marketing authorization since 2001. Cell sources of somatic CT have included chondrocytes, keratinocytes, fibroblasts, osteoblasts, and immune cells. A total of 166 CT IND protocols have been approved for clinical trials, of which about 45 % are investigator-initiated trials (IITs). Prior to 2008, clinical protocols of somatic CT products were mainly approved; however, the number of stem cell IND protocols increased to about 45 % by 2014. In the early stage of stem cell therapy, bone marrow-derived MSCs were the most common source, but the percentage has since decreased to about 25 %, and the MSCs derived from adipose tissue, cord blood, or placental tissue have increased. Furthermore, stem cells derived from various kinds of tissues, such as neural stem cells, are being actively investigated.

2.2 Laws and Regulations for GT and CT Products

The Ministry of Food and Drug Safety (MFDS) regulates food, biological products, drugs, medical devices, and cosmetics. GT and CT products are categorized as biological products and, as with other drug products, are regulated under the Pharmaceutical Affairs Act (PAA) [1]. CT products regulated by the MFDS include somatic cells, stem cells, and combination products of such cells with scaffolds or other devices. Depending on product characteristics, these products are regulated under the PAA and/or the Medical Device Act [2]. Nine categories of human tissues derived from live or cadaveric donors (cartilage, bone, ligament, tendon, skin, heart valves, blood vessel, fascia, and amnion) are regulated under the Human Tissue Safety and Control Act [3]. They do not require pre-market approval but have to be registered at human tissue banks authorized by the MFDS and comply with good tissue practice (GTP). Research using cells, genes, and other kinds of materials of human origin has to be appropriately and ethically conducted to protect subjects, in accordance with the Bioethics and Safety Act [4]. Figure 1 shows the legislative basis for the regulation of medicinal products. The PAA defines the scope of medicinal product regulation. In order to enforce the PAA, the Enforcement Rule of Medicinal Product Safety [5] and various MFDS notifications have been developed. More than 30 MFDS notifications, including the Regulation on Review and Authorization of Biological Products (RRABP) [6], prescribe detailed procedures for review, approval, and management of medicinal products applicable to both chemical drugs and biological products including GT and CT products. In addition, the MFDS has developed many guidelines that provide recommendations on various issues and topics for industry and regulatory reviewers.

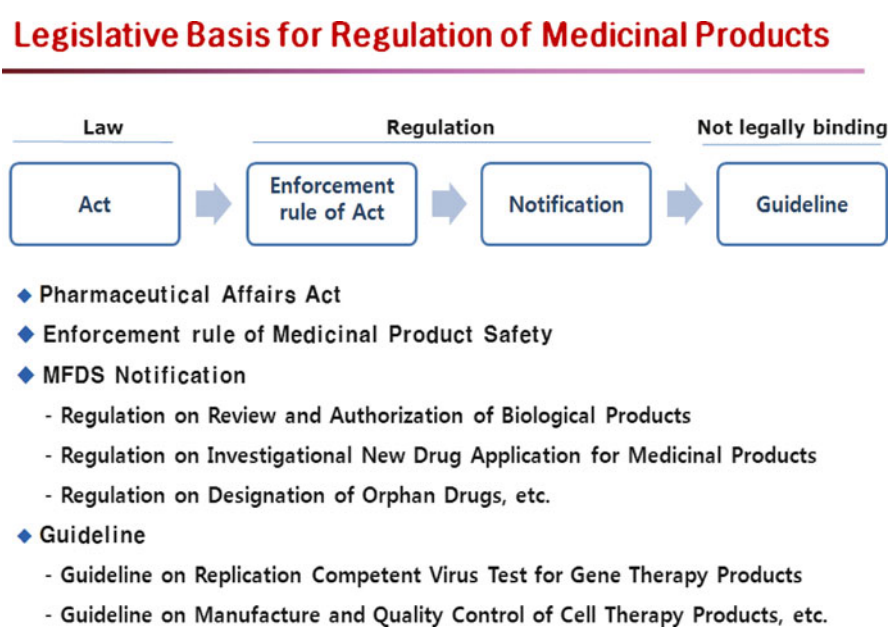

Fig. 1 Hierarchy structure of regulations enforced by the MFDS in Korea that apply to chemical drugs and biological products including GT and CT products

2.3 The Degree of Regulatory Oversight for GT and CT Products

In Korea, research on CT and GT has been actively conducted since the late 1900s and the early 2000s. In the early stage, GT or CT, especially autologous CT, was considered to be one of the medical procedures not requiring product approval. Following many discussions between regulators and investigators, GT and CT products were categorized as biological products regulated by the PAA. As a result, the definitions of a GT product and a CT product, regulatory requirements for clinical trial and marketing authorization, and others were prescribed in the RRABP (MFDS Notification).

In Article 2 of the RRABP [6], a GT product is defined as "a genetic material or a medicinal product containing such genetic material intended to be administered to human beings for treatment of disease." A CT product is defined as "a medicinal product manufactured through physical, chemical, and/or biological manipulation, such as in vitro culture of autologous, allogeneic, or xenogeneic cells. However, this definition does not apply to a case where a medical doctor performs minimal manipulation (e.g., simple separation, washing, freezing, thawing, and other manipulations, while maintaining biological properties) that does not cause safety problems of the cells in the course of surgical operation or treatment at a medical center."

GT products are genetically modified vectors produced by recombinant technology or ex vivo genetically modified cells. In order to administer them to patients, approval

of an IND or an NDA must be obtained from the MFDS. Examples of GT products include genetically engineered plasmids, viruses (including conditionally replication competent virus by deletion), bacteria, cells, and siRNAs derived by recombination technology. However, chemically synthesized nucleic acids (such as siRNAs or antisense oligonucleotides), unmodified viruses (such as wild-type oncolytic viruses), and established continuous cell lines (such as HeLa cells and HEK-293 cells) are not categorized as GT products. Since new advanced products based on new concepts are being continuously developed, there may be a gray area of products difficult to clearly categorize as GT products. However, regardless of product classification, similar regulatory requirements may be applied to these products. DNA vaccines intended to prevent infectious diseases in healthy people are reviewed in the division in charge of conventional preventive vaccines, and DNA vaccines intended for use in cancer patients are reviewed in the division in charge of GT products within the MFDS.

For CT products, approval by the MFDS is required for use in clinical trials and for marketing when the cells are manipulated more than minimally, regardless of cell source (autologous or allogeneic cells) and use (homologous or nonhomologous). Although minimally manipulated cells are not regulated as CT products, when minimal manipulations are conducted in companies other than medical centers (in other words, other commercial organizations), those cells are considered as CT products, and product approval has to be obtained from the MFDS.

Regulations related to CT products have been established and revised several times according to the evolving situations since the definition of CT product was prescribed in the RRABP in 2001. In order to regulate autologous CT products that were not subject to regulatory oversight in the early 2000s, autologous CT products have been conditionally approved so that clinical study results have to be submitted after marketing authorization. Several CT products consisting of autologous keratinocytes for burns and autologous chondrocytes for cartilage defects have been approved as CT products. As various kinds of CT products have been developed, the degree of regulatory oversight has been reinforced. With emerging scientific development, research is in progress on embryonic stem cells, tissue-engineered products, induced pluripotent stem cells (iPSCs), and other ATMPs. Flexible and reasonable regulatory frameworks appropriate for these products are necessary to support development of ATMPs and to promote public health.

3 Regulatory Pathways for Gene Therapy and Cell Therapy Products

3.1 MFDS Organization Responsible for Regulatory Oversight of GT and CT Products

The Korea Food and Drug Administration (KFDA) was established in 1998, and its legal status was raised in 2013 to the MFDS to reinforce prospective and follow-up regulatory oversights. The MFDS consists of a headquarters and an affiliated

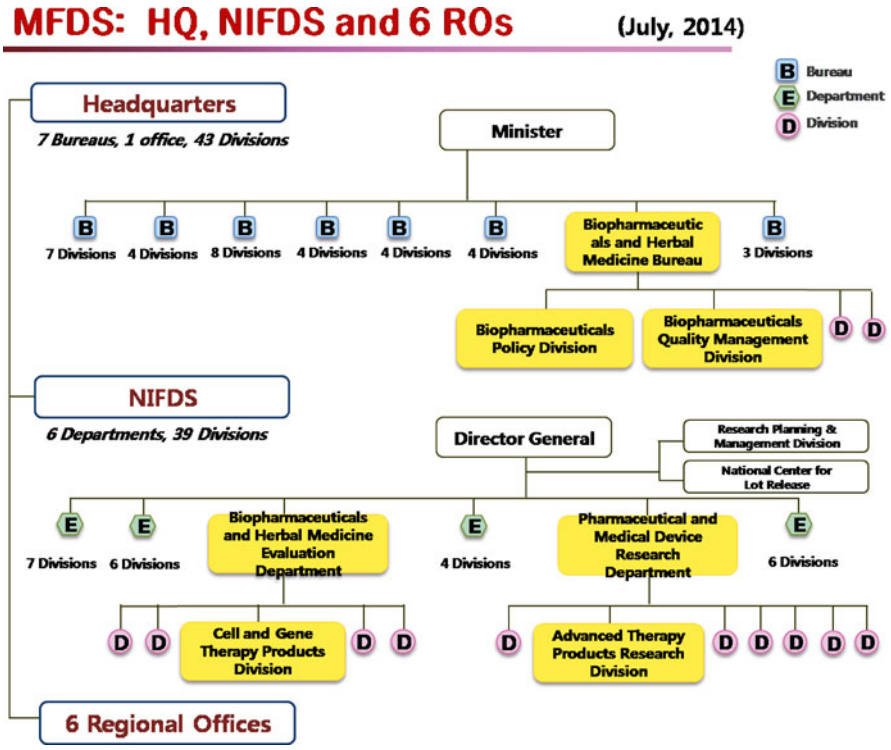

Fig. 2 MFDS organization showing offices responsible for regulation of biological products including gene therapy and cell therapy products

agency, the National Institute of Food and Drug Safety Evaluation (NIFDS), and six regional offices. Figure 2 shows the MFDS offices involved in regulatory oversight of GT and CT products. The Biopharmaceuticals and Herbal Medicines Bureau in the headquarters is responsible for developing policies and regulations, post-approval management, good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP) inspections of biological products and herbal medicines. Under the NIFDS, the Cell and Gene Therapy Products Division is responsible for marketing authorization and evaluation of IND and NDA dossiers for GT and CT products, and the Advanced Therapy Products Research Division is responsible for product testing and research related to the regulatory activities of GT and CT products and recombinant therapeutic proteins. Six regional offices are in charge of policy implementation, on-site inspections, and management of marketed products in the respective regions.

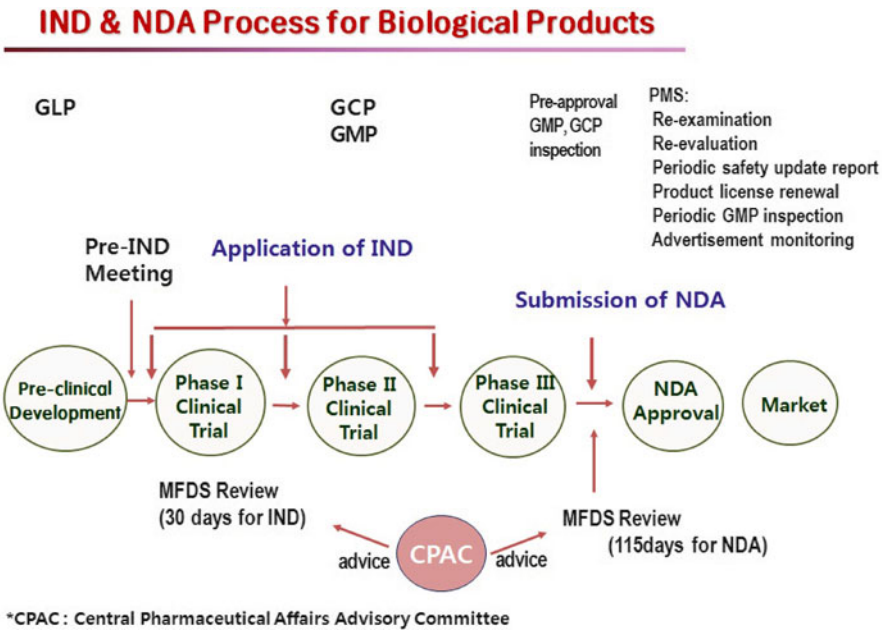

Fig. 3 Regulatory activities for Investigational New Drug (IND) Application, New Drug Application (NDA), and post-market surveillance (PMS)

3.2 IND, NDA, and Post-Market Surveillance (PMS) for GT and CT Products

As with other biological products, GT and CT products are subject to product approval in accordance with the PAA [1]. Therefore, use of these products in humans has to comply with regulatory requirements prescribed in the enforcement rule and notifications published under the PAA. Figure 3 summarizes IND, NDA, and post-approval controls of biological products. Regulatory requirements and procedures for an IND are prescribed in the Regulation on Approval of Investigational New Drug Application for Medicinal Products (MFDS Notification) [7]. The clinical protocol, along with documents related to GMP, quality, safety, and efficacy of the product, should be submitted. Regulatory requirements and procedures for submitting an NDA for GT and CT products are prescribed in the RRABP (MFDS Notification) [6]. In the RRABP, "Article 25: Safety & Efficacy Review Criteria," "Annex 2: Types of Information Required for Cell Therapy Products," and "Annex 3: Types of Information Required for Gene Therapy Products" prescribe the information needed to support the safety and efficacy of CT and GT products. In addition, criteria for review of specifications and test methods are provided in "Article 30: Review Criteria for Cell Therapy Products" and "Article 31: Review Criteria for Gene Therapy Products." If there are no available regulatory requirements or

procedures for review and approval of medicinal products, regulations and guidelines published in other countries may be referenced. The MFDS review time for an IND is 30 days and for an NDA is 115 days for biological products. The review process is suspended if applicants are requested to submit supplementary data; the process resumes when a complete response is submitted.

Investigational products have to be manufactured in compliance with GMP. Manufacturing sites for investigational products may be inspected prior to approval by the MFDS, especially when the site is newly established. If such products are manufactured in foreign countries, the GMP certificate and/or other production and quality control documents can be submitted instead. MFDS carries out pre-approval GMP inspection of the manufacturing site for granting marketing authorization.

For preclinical studies, toxicology data and safety pharmacology data must be generated in compliance with GLP. In Korea, GLP-compliant preclinical study testing facilities are designated for individual toxicology studies, and preclinical studies must be carried out by such facilities.

Clinical trials of investigational products must be conducted at hospitals designated as clinical trial institutions. The MFDS has designated about 170 hospitals as clinical trial institutions. A list of these hospitals is found on the MFDS website [8].

In addition to pharmaceutical firms (sponsor-initiated trial, SIT), individual investigators (investigator-initiated trial, IIT) can submit an IND. About 50 % of CT INDs are IITs. The IIT also must be approved by the MFDS and the same regulatory requirements and procedures as those for a SIT apply to the IIT. If an IIT for a CT product does not have significant safety issues and is intended only for academic research purposes, the IND may be approved by submitting (1) a clinical protocol, (2) the approval of the institutional review board (IRB) at the clinical institution, and (3) the written informed consent form for the clinical trial generated by more than five experts in the relevant field.

Many GT and CT products follow the route of an expanded access program, fast-track approval, or pre-review system, since these products are indicated for patients with serious and life-threatening diseases for which appropriate therapies are not available.

Expanded access to investigational drugs for treatment use or emergency use before marketing authorization is available. If clinical effectiveness of an investigational product currently being studied for a serious disease is observed in clinical trials, an application containing a treatment protocol can be submitted to the MFDS to permit an investigational product to be used in the treatment of patients not enrolled in the ongoing clinical trials. The investigational product can be used with the approval of the IRB and with the patient's informed consent. An application for administration of an investigational product in a patient in an emergency situation can be submitted to the MFDS if a medical specialist determines that the relevant patient has a serious or life-threatening condition, alternative treatment is not available, and the treatment effect cannot be realized if the opportunity to treat the disease is missed. A patient's informed consent and the manufacturer's intent to supply the product have to be submitted. After use of the investigational product for treatment

purpose or for an emergency situation, relevant information, such as adverse events, effectiveness, and safety follow-up observed in these patients, should be submitted to the MFDS.

If an investigational product at the clinical development stage (i.e., currently being used in a clinical trial or with sufficient supporting preclinical data) satisfies the requirements for designation as an orphan drug [9], an application for such a designation may be submitted to the MFDS. If a product is indicated for a disease which affects not more than 20,000 patients in Korea, and for which no appropriate treatment is available or safety and effectiveness are observed with the new product, such an application may be accepted. For orphan drugs indicated for life-threatening diseases, an application for product approval may be submitted on the basis of therapeutic exploratory clinical data. In such instances, product approval may be granted with the conditions of submitting therapeutic confirmatory clinical data and implementation of an RMP after marketing authorization. For anticancer products, if the purpose and design of the therapeutic exploratory clinical trial are similar to those of a therapeutic confirmatory clinical trial, the anticancer product may be approved on the basis of exploratory clinical data with surrogate endpoints, with the condition that therapeutic confirmatory clinical data shall be submitted after marketing authorization.

A pre-review system [10] allows applicants to submit portions of documents relating to quality, safety, efficacy, GMP aspects, and other issues to the MFDS prior to submission of the full IND or NDA package. During the review time of an IND and/or an NDA, the MFDS can hold a Central Pharmaceutical Affairs Advisory Committee (CPAC[1]) meeting to seek expert advice on scientific matters, as well as ethical issues.

In addition to a Periodic Safety Update Report, there are two specific pharmacovigilance systems, namely, the reexamination system [11] and the reevaluation system [12], to monitor the safety of medicinal products. It is impossible to identify all safety concerns of an investigational product during clinical trials, especially when there is a limitation on the number of patients. After marketing authorization, the license holder submits a reexamination plan to the MFDS and identifies any adverse events under routine medical treatment for a certain period of time. Data exclusivity is ensured during this period. For new medicinal products, 3,000 cases have to be investigated within 6 years; however, for CT products, reexamination plans are generally designed to investigate 600 patients in 6 years. Reexamination results, along with the safety data collected in Korea and foreign countries, are comprehensively reviewed and reflected in the product label. Another system is the reevaluation of products, which periodically reevaluates the safety and effectiveness of the approved products based on new scientific information from the labels of the comparable

[1] Central Pharmaceutical Affairs Advisory Committee (CPAC) provides advice to an MFDS request on issues related to medicinal products. The CPAC consists of five sub-committees categorized by subject. Committee members are composed of independent outside experts (e.g., medical doctors, pharmacists, professors, statisticians, lawyers) and consumer representatives.

products and from the published literature. This information is also reflected in the label. For products subject to reexamination, their product approvals have to be renewed at 5-year intervals on the basis of reevaluation results from the date when reexamination is completed.

Considering the limited clinical experience of CT products in Korea, safety information at the early stage of marketing is important. MFDS introduced a new system, which is under pilot study, in 2013 to reinforce the collection of safety information of CT products, which requires a license holder to investigate and report all cases of administration of the CT product, including off-label uses, for the first 2 years after marketing. In addition, in order to assure long-term follow-up of adverse events observed in patients who received ATMPs (thus also including GT products), measures for such long-term follow-up will be developed and employed in linkage with the RMP [5]. This RMP was recently introduced to require license holders to submit a comprehensive plan on product safety management focusing on risk mitigation and controls, including medication guides for patients and measures to ensure safe use, in order to minimize adverse events arising from the use of approved medicinal products.

Although ATMPs such as GT and CT products are being actively developed, appropriate evaluation of their safety, efficacy, and quality is a great challenge to manufacturers, as well as the MFDS, because of limited experience in this emerging field. The MFDS is trying to maintain consistency and transparency in their review work and support manufacturers by publishing guidelines in accordance with scientific developments.

4 Specific Considerations/Requirements for the Development of Gene Therapy and Cell Therapy Products

4.1 General Aspects

Although there are some specific aspects associated with GT and CT products due to their unique characteristics, general principles of the regulation of drugs or biological products can be applied to GT and CT products. GT and CT are new emerging fields for the treatment of many serious medical conditions. However, experience in these areas and understanding of the products' characteristics are quite limited around the world. Moreover migration, proliferation, differentiation, plasticity, and paracrine effects of stem cell therapy products after administration to patients may vary depending on cell source and the manufacturing process. To enable the reliable regulatory assessment of these products, the MFDS approach is case by case and founded on science-based reviews with flexibility, balancing risks and benefits. Many guidelines published in the USA and in the European countries provide considerations and requirements for development of biological products, including GT and CT products. However, some regulatory issues the MFDS has encountered had in reviewing GT and CT products are described here. Since most GT products under

development in Korea use plasmid vectors and the clinical experience is relatively limited, detailed considerations for various kinds of GT products will be developed by the MFDS as review experience is accumulated. Therefore, the subsequent sections will focus primarily on CT products.

4.2 Specific Considerations for the Manufacture of Gene Therapy and Cell Therapy Products

4.2.1 Maintenance of Aseptic Conditions

GT and CT products are exposed to potential contamination with infectious agents because materials of human or animal origin are used in the manufacture of these products. Because their active ingredients are living cells or nucleic acids which become unstable when exposed to heat or chemicals, the usual sterilization processes cannot be employed in the manufacture of these products. Maintenance of aseptic conditions in a manufacturing process is critical, and GMP-compliant facilities, equipment, personnel, environmental monitoring, and standard operating procedures (SOPs) are important factors [13]. Since cell culturing and differentiation are the longest steps in the manufacture of CT products, strict microbiological control is required.

4.2.2 Quality Control of GT and CT Products

Unlike conventional drugs, autologous CT products are manufactured for each patient on a small scale (i.e., one lot per patient), limiting the number of samples available for quality control of the lot. Since the final products are living cells and their shelf life is short, it is important to conduct strict in-process controls to ensure the quality of final products. When a sample amount has to be adjusted or samples have to be taken during the manufacturing process, it is important to take representative samples and include in-process tests in the release specifications of final product.

It is important to control impurities potentially derived from raw materials or production processes. Further, residues of ancillary materials used in cell culture and their toxic effects on the human body have to be considered. The safety and suitability of ancillary materials and excipients used in the manufacture of GT and CT products have to be ensured. Since most serum and growth factors used in cell culture and differentiation are derived from animals, they may be contaminated with bacteria, fungi, viruses, prions, or other adventitious agents. In general, use of pharmaceutical or GMP-grade reagents is recommended. If non-pharmaceutical reagents (investigational grade) have to be used, specifications for such reagents have to be established and a quality control program has to be developed to control potential hazards of such reagents.

During the manufacturing process, the genetic stability of active ingredients, such as cells or vectors, should be considered. If virus vectors are used in the manufacture of GT products, potential occurrence of replication-competent virus has to be assessed [14].

Specifications for identity, purity, potency, and cell viability have to be established on the basis of characterization data and intended clinical purpose (indication). However, for MSCs, the cell source (autologous/allogeneic, bone marrow, fat cells, placenta, and others), production method, and in vivo and in vitro characterization levels vary. Also, the mechanism of action of each type of cell is not completely understood, and the markers that sufficiently represent properties of certain cell types have not been identified. In order to establish specifications to ensure the safety, efficacy, and consistency of the final product, a wide range of properties of the product should be investigated, such as phenotype, genotype, gene expression, generation/induction of bioactive factors, and others.

Due to the unique properties of GT and CT products, their mechanisms of action are influenced by multiple factors. Therefore, it is important to employ various methods and validations to establish surrogate measures for potency that correlate with clinical outcomes. From the early stage of planning clinical trials, the therapeutic mechanism of the product has to be considered. This designing clinical trials in a manner that monitors the appropriateness of product potency is recommended.

Microbiological tests conducted during the manufacturing process and/or for the final products include sterility, Mycoplasma, and adventitious virus tests [15, 16]. However, even though microbiological tests may produce "acceptable results," it does not mean that all products in the relevant lot are free from microbiological contaminants. Therefore, microbiological test results have to be interpreted in parallel with environmental monitoring data and in-process control data. In the case that product administration to a patient occurs prior to knowing the microbiological test results, there has to be an investigation plan in the event that the microbiology test is positive.

As the clinical use of allogeneic CT products with cell banks is increasing, the ability to ensure the consistency of lots manufactured with cells obtained from different donors is another issue of concern.

4.3 Specific Considerations for Preclinical Studies of Gene Therapy and Cell Therapy Products

Preclinical studies of GT and CT products are very complex in various aspects when compared to other biological products or synthetic chemical drugs. Pharmacokinetic (PK) profiles of conventional drugs, such as absorption, distribution, metabolism, and excretion (ADME) pathways, are relatively simple, and assessment methods are well established to anticipate their pharmacological and toxicological reactions following administration. However, since genes and living cells are elements of the human body and show very dynamic reactions through exchange of signals with surrounding cells/tissues in the in vivo environment, traditional PK studies such as ADME cannot be applied to GT and CT products.

Appropriate animal models able to show pharmacological, toxicological, and physiological responses to GT and CT products similar to those in human beings have to be selected. If GT or CT products have to reach a specific target site to accomplish the desired effects, the delivery to a clinically relevant anatomical region of the animal has to be considered. Normal animals are generally used in conventional toxicology studies; however, when considering the xenotransplantation of cells into animals and the characteristics of stem cells, toxicology studies in immunodeficient animals and a combination of pharmacology and toxicology studies in disease model animals should be considered.

The preclinical study design, such as dose, schedule, route of administration, and dosage form, has to be determined with consideration of the product characteristics. Since the administered cells may show different physiological responses and rates of engraftment at different sites, the route of administration and the target site in preclinical studies have to represent those in clinical trials. If administration to the same anatomical site or surgical operation is impossible, other sites having similar microenvironments may be selected, or the use of large animals may be considered. In order to prevent immunological rejection, cells are administered into immunodeficient animals or analogous animal cells comparable to the investigational product may be administered to the relevant animal model. However, since responses in human beings cannot be fully predicted from preclinical results, scientific justifications and careful approaches are needed in the interpretation of preclinical data when they are applied to human beings.

Biodistribution studies of GT products are conducted to investigate (1) the insertion of genes into the host chromosome, (2) detection of genes in target and nontarget sites, (3) expression of a desired product, and (4) persistence of expression. In order to assess the biodistribution and engraftment of CT products, they are administered to immunodeficient animals or disease animal models through the proposed clinical route of administration, and their characteristic markers (genes or indicators) are evaluated to determine the amount and persistence at target sites and among other major organs. The biodistribution study can be conducted in combination with pharmacology or toxicology studies. In such instances, interpretation of biodistribution data in connection with pharmacological or toxicological data may provide useful information. Reproductive toxicity studies may be required in cases where vector presence is detected in the gonads [6].

Standard carcinogenicity assessments that are applied to drugs and other biological products are not needed for GT products. However, for immunomodulatory agents or GT and CT products associated with long-term expression of growth factors or growth factor receptors, a carcinogenicity study should be considered [6]. Stem cell therapy products may be associated with a risk of tumorigenicity owing to their inherent property of multipotency, the cell culture process, or other manipulations made during cell culture. In order to assess potential tumorigenicity, in vitro testing and in vivo testing are needed. The intended clinical product (not analogous animal cells) has to be administered through a clinical route with appropriate positive control cells in an appropriate animal model. The study design and inclusion of appropriate control cells to assess the tumorigenicity of stem cells in a preclinical study is an issue of concern.

4.4 Specific Considerations for Clinical Studies of Gene Therapy and Cell Therapy Products

General principles and requirements for clinical trials of conventional drugs also apply to clinical trials of GT and CT products. However, there are various regulatory challenges in implementation of clinical trials of GT and CT products due to (1) insufficient characterization, (2) insufficient understanding of mechanism of action, (3) lack of appropriate preclinical assessment systems, and (4) limited clinical experience.

Important considerations in the development of GT products include potential generation of replication-competent virus and insertional mutagenesis by integration of introduced genes into host chromosomes, resulting in cancer. In addition, the GT products prepared through genetic modification are not sufficiently investigated for potential adverse effects on the human body and the environment; therefore, in order to prevent biological risks resulting from spread and transmission of modified organisms in the course of product manufacture and use, a preliminary assessment has to be conducted to assure biosafety. Although efficacy of GT products has been demonstrated in animal models, satisfactory outcomes have not been realized in clinical trials because of low efficiency of delivery of currently used vectors to target cells, inability to selectively deliver the gene to the desired target cells, and insufficient expression in the human body. In addition, ethnic differences may also be important for GT products indicated for genetic diseases.

There are several specific issues in designing clinical trials of CT products. It is difficult to translate preclinical data into clinical design due to immune issues of xenotransplantation as well as species specificity. When appropriate dose levels for clinical trials on the basis of preclinical data are defined, the body weight of the animal model, biodistribution profile, route of administration, feasibility of production of the CT product and administration into patients, similar clinical cases, and other factors have to be considered. Since CT products are often administered by surgical procedures, standardized procedures and delivery design are important. If an invasive operation is included, it is difficult to establish the placebo control group and maintain the blinding condition. In such an instance, the clinical study has to be carefully designed, and study results also have to be carefully interpreted. Since the number of patients participating in clinical trials in Korea for GT and CT products is often limited owing to their serious disease and also the financial burden on a small venture company, it is not easy to interpret small-scale clinical data, and in particular adverse events cannot be sufficiently identified. Further, if the expected benefit of the product is due to regeneration or structural improvement, long-term observation is needed, making it more important to have an appropriate number of patients and an adequate clinical study duration. Unknown long-term risks due to limited clinical experience and concern over tumor or ectopic tissue formation with CT products and insertional mutagenesis with GT products have to be considered. In order to monitor for these possible adverse events, long-term follow-up of patients has to be considered; however, determination of the appropriate follow-up method, duration, intended category of products, indication, and other factors are also issues.

Since many clinical trials of GT and CT products in Korea are initiated by investigators who are relatively less familiar with regulatory requirements and procedures for clinical trial conduct and product approval than pharmaceutical companies, effective communication between investigators and the MFDS is important to assure appropriate conduct of preclinical and clinical studies.

5 Access to Relevant Guidelines and Regulations for Gene Therapy and Cell Therapy Products

The applicable laws, enforcement decrees, enforcement rules, notifications, orders, SOPs, guidelines, and handbooks for products regulated by the MFDS are found under the "Laws Information" menu at the MFDS website (www.mfds.go.kr). In addition, all laws and regulations can be found at the Korea Laws Center [17], which is run by the Ministry of Government Legislation. The MFDS has an "electronic service website" [18], where all types of applications can be electronically submitted. The IND and NDA information for various products, excipient information, and other information for manufacturers, as well as information on approved medicines, how to take medicines, Drug Utilization Review (DUR), and other materials for consumers, are also provided on this website.

6 Conclusion: Directions or Plans for the Future

The Korean government selected the advanced therapy healthcare industry as one of the next-generation growth engine industries and has thus provided extensive investment and R&D support in this area. The MFDS has also developed a regulatory framework that can flexibly respond to technological developments in the field of ATMPs, facilitate development of safe and effective products, and provide more potential therapies to patients suffering from severe diseases. The areas that the MFDS emphasizes to improve regulatory activities are as follows:

6.1 Strengthening the Aptitude of Regulators

In order to strengthen regulators' aptitude in the ATMP area, several short-term and long-term training programs for MFDS regulators in foreign countries have been promoted. Further, the MFDS holds workshops every year by inviting distinguished researchers and regulators from foreign countries to share scientific and regulatory issues and explore harmonization of regulatory policies. The MFDS has developed various guidelines for industry, as well as for regulators, to assure the development of safe and effective medicinal products and establish scientific and consistent

regulatory activities. The resources at the MFDS are limited; thus in order to provide guidance in a prompt manner, many new guidelines generated by MFDS in this area were developed by adapting published guidelines from the USA and Europe to the Korean perspective situation.

6.2 Interactive Communication with Industries and Researchers

In order to facilitate communication with industries that are developing biological products and to obtain comments and feedback on various issues encountered in the course of pharmaceutical development, a regularly held government-industry meeting called "Dynamic BIO" was organized, where problems in product development and opinions on possible improvements to the regulatory process are discussed. Recently, MFDS launched the "Priming Water Project" for GT and CT products, which consists of (1) expanding consultation opportunities at the early stage of product development, (2) providing intensive and customized support to promising products that are close to the commercialization stage, and (3) offering education programs for IND and NDA applications to researchers carrying out government-sponsored R&D projects.

6.3 International Cooperation

With the rapid development of science and technology, various kinds of ATMPs, such as iPSC-derived products and others, are under development in many countries. Not all regulatory agencies have enough resources to evaluate such innovative products appropriately, making it necessary to promote international cooperation such as (1) sharing of information on the GT and CT products in clinical trials and any associated adverse events, (2) establishment of international standards for GT and CT products, (3) publication of internationally harmonized guidelines, and (4) establishment of programs for information sharing and/or joint review of multinational clinical protocols, as well as other areas.

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Regulation of Cell and Gene Therapy Medicinal Products in Taiwan

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Abstract Owing to the rapid and mature development of emerging biotechnology in the fields of cell culture, cell preservation, and recombinant DNA technology, more and more cell or gene medicinal therapy products have been approved for marketing, to treat serious diseases which have been challenging to treat with current medical practice or medicine. This chapter will briefly introduce the Taiwan Food and Drug Administration (TFDA) and elaborate regulation of cell and gene therapy medicinal products in Taiwan, including regulatory history evolution, current regulatory framework, application and review procedures, and relevant jurisdictional issues. Under the promise of quality, safety, and efficacy of medicinal products, it is expected the regulation and environment will be more flexible, streamlining the process of the marketing approval of new emerging cell or gene therapy medicinal products and providing diverse treatment options for physicians and patients.

Keywords Taiwan Food and Drug Administration (TFDA) • Cell therapy medicinal products • Gene therapy medicinal products • Clinical trials • Investigational New Drug (IND) • New Drug Application (NDA) • Medical practice • New medical practice • Medicinal products • TFDA Guidance • Points to consider

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1 Introduction to the Taiwan Food and Drug Administration

The Taiwan Food and Drug Administration (TFDA) was established in 2010 and was integrated by the Bureau of Food Safety, the Bureau of Pharmaceutical Affairs, the Bureau of Food and Drug Analysis, and the Bureau of Controlled Drugs. Through organizational restructuring, the TFDA has been upgraded under the newly formed Ministry of Health and Welfare (MOHW) since 2013. As professionalism, service, quality, and innovation are the common core values of the TFDA, this agency comprehensively ensures the quality and safety of food and medical products and continues to safeguard the national health and to lead the nation to a new era of food and medicinal products management.

2 Regulatory History Evolution of Cell and Gene Therapies

In the early days (before the establishment of the TFDA on January 1, 2010), cell and gene therapies were regarded as a kind of "new medical practice," for which physicians or principal investigators (PI) needed to apply to the Bureau of Medical Affair for permission to conduct human trials according to the "Medical Care Act" and its related enforcement rules [1]. After many human trials, "new medical practice" confirmed to be safe and effective would have the opportunity to turn into "routine medical practice" to be routinely executed by physicians themselves in the hospital. Additionally, when medical institutions use cell or gene therapy products to treat human diseases, they are subject to follow the "Regulations on Human Trials" [2], "Regulations of Good Tissue Practice (GTP)" [3], "Guidelines of Application and Operation of Somatic Cell Treatment for Human Trial" [4], and "Guidelines of Application and Operation of Gene Treatment for Human Trial" [5], which were stipulated by the former Department of Health (now the MOHW).

Along with the breakthroughs in biotechnology, the data collated from previous human trials have gradually demonstrated the efficacy and safty of cell or gene therapy products for people in certain condition. Medically advanced countries have successively approved cell or gene therapy medicinal products, regulated as "biological drugs" or "medical devices." In order to remain abreast of the international developments, as well as meet the domestic industry demands, the cell and gene therapy products originally regulated as new medical practice by the Bureau of Medical Affairs were transferred to the TFDA on January 1, 2010. That is, the original "medical practice" management approach was changed to a "medicinal product" management approach. Manufacturers in this field must comply with the standards of the "Pharmaceutical Affairs Act" [6], "Regulations for Registration of Medicinal Products" [7], and "Regulations of Good Tissue Practice (GTP)" [3] and the requirements of the "Regulations of Good Manufacturing Practice (GMP)" [8].

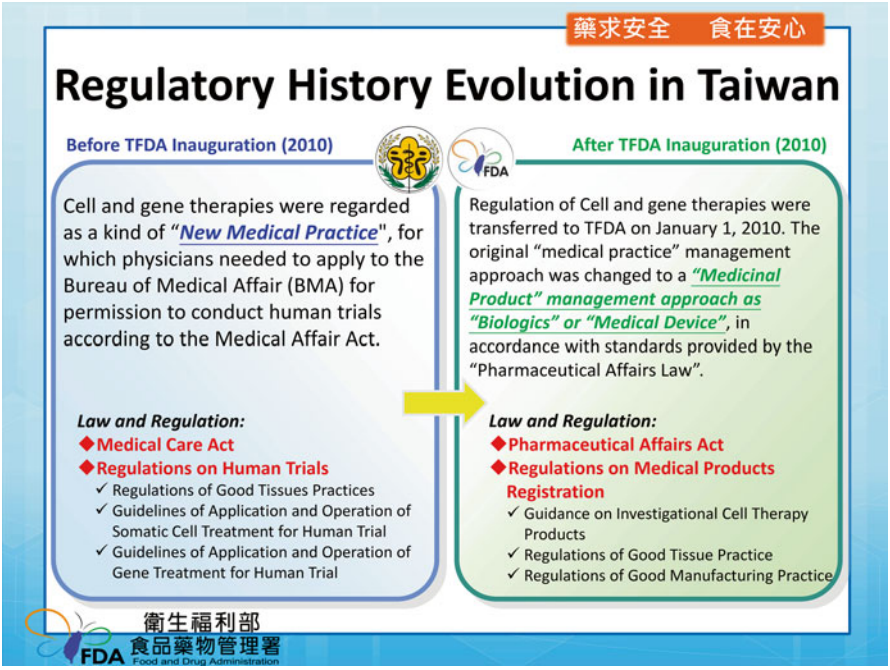

Fig. 1 Regulatory history evolution in Taiwan.

The evolution of the regulatory history and the laws and regulations in Taiwan are summarized in Fig. 1.

In addition, the TFDA also released the "Guidance of Investigation of Human Cell Therapy Medicinal Products" [9] on September 7, 2014, to serve as reference for investigators in preparing application materials for clinical trials. Meanwhile, the TFDA also began to deliberate on the relevant regulations regarding the registration of cell therapy products and donor eligibility.

3 Law, Regulation, and Guidance

3.1 Guidance for Investigation of Human Cell Therapy Medicinal Products

The TFDA released the "Guidance of Investigation of Human Cell Therapy Medicinal Products" on September 17, 2014 [9]. The definition of cell therapy medicinal products refers to the administration of human autologous or allogeneic

cells to patients to achieve the purpose of treatment, prevention, or diagnosis of disease, while xenogeneic cell therapy products are excluded. Currently, it is not acceptable to propose xenogeneic cell therapy in Taiwan.

Apart from this, if cell therapy medicinal products are identified by the TFDA as meeting the following four conditions (A–D) at the same time, the review process may be adjusted to a fast-track pathway and thus may not need to be discussed by an advisory committee:

A. Minimal manipulation
B. Homologous use
C. Not used in combination with other articles (including other cells, medicines, and medical devices)
D. Does not cause a systemic effect

Minimal manipulation refers to a cell *operating process* (such as collection or procurement) or a cell *manufacturing process* (such as selection) which does not involve in vitro cell culturing and does not change the biological characteristics of the original cells during the operating or manufacturing process. Minimal manipulation includes centrifugation, cell separation, concentration, purification, and selective removal of peripheral blood B cells, T cells, malignant cells, red blood cells or platelets, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, filtering, or cryopreservation. Examples are the extraction of $CD34^+$ cells from peripheral blood and then infusing them back into the patients without in vitro cell culture or using a density gradient to remove specific cells from a mixed population of cells and then infusing them back into patients.

Homologous use refers to the donor's cells being used for the repair, reconstruction, replacement, or supplementation of the recipient's cells, where the function of cells in the recipient is the same as that in the donor. An example of nonhomologous use is implanting allogeneic adipose-derived stem cells (ADSCs) into a bone scaffold to fill or repair bony voids.

This guidance prohibits cell therapies that involve or affect human reproductive function, such as human cloning. If the cell source is from human embryos, it must comply with the requirements of the "Regulations of Ethical Issues in Human Embryonic Stem Cell Research" and the "Regulation of the Ethics of Human Embryo and Embryonic Stem Cell Research" promulgated by the former Department of Health (now the MOHW) on February 19, 2002, and August 9, 2007, respectively.

3.2 Guidance for Investigation of Human Gene Therapy Medicinal Products

The TFDA released the "Guidance of Investigation of Human Gene Therapy Medicinal Products (Draft)," in 2012. The definition of a gene therapy medicinal product refers to the therapeutic DNA (or genes) or cells containing such genes that are delivered into the human body with the purpose of treatment, prevention, or

diagnosis of diseases. There are some restrictions on performing gene therapy clinical studies. These include:

1. Limitation to diseases that are life-threatening or significantly affecting the quality of life
2. Having sufficient scientific basis for predicting the gene therapy to be an effective and safe treatment for a particular disease
3. The effects of the gene therapy which are predicted to be better than the current treatment method
4. The gene therapy treatment which is predicted to have its benefits outweigh its risks
5. Prohibiting to perform on human reproductive cells or any gene therapy that may result in genetic mutation of human germ cells

The field of gene therapy holds great promise for treating a wide array of illnesses, from genetically inherited diseases, such as cystic fibrosis or hemophilia, to heart disease, wound healing, graft versus host disease, or cancer. However, there are a number of safety issues associated with gene therapy medicinal products, some of which are unique to this area. Safety issues specific to gene therapy include the risk of exposure to a replication competent virus or vector, an immune response to the product, the toxicity associated with transgene expression, and inadvertent germline transmission of the vector. Gene therapy medicinal products may differ from the conventional medicinal products. In gene therapy, vector and transgene expression may persist for the lifetime of the patients. The "Guidance of Investigation of Human Gene Medicinal Therapy Products (Draft)" covers manufacturing and characterization information (including components and procedures), product testing (including microbiological testing, identity, purity, potency), final batch release testing, and product stability.

4 Application and Evaluation Procedures

4.1 Consultation Prior to an Application Submission

Prior to submitting an Investigation of New Drug (IND) or New Drug Application (NDA) for marketing, applicants shall apply to the Center for Drug Evaluation (CDE) for consultation, and upon completeness of the technology documents (such as protocol design, informed consent form) being confirmed, the applicants then submit the formal application to the TFDA along with the confirmed technology documents and administrative documents.

4.2 Online Registration

Applicants for an IND submission must register on the "Taiwan Pharmaceuticals Clinical Trials Information Network" [10] with a summary of the requested clinical trial program, including the information about the sponsor, the product's name/

ingredient/dose/dosage forms, the number of planned subjects, the trial's purposes/indications/hospitals/phase/estimated period, the main inclusion/exclusion criteria, and other details. In addition, the name of a contact person and telephone number need to be provided.

4.3 Evaluation Procedure

After receiving the IND or NDA application, the TFDA will establish the review team including reviewers in quality (manufacturing and testing), nonclinical, clinical, and statistics areas, to initiate the review process. These reviewers will also refer to an advisory committee for further discussion (refer to Sect. 4.4 below for more information). Finally, the TFDA will consider and evaluate the benefits and risks of the application and finally decide whether or not approve the application. Furthermore, for such IND or NDA applications, the TFDA will inspect the operating process and manufacturing process of cell or gene medicinal products in line with requirements of "Good Tissue Practice (GTP)."

4.4 Advisory Committee

The TFDA established the Advisory Committee for Regenerative Products on August 8, 2014. Because of the diversity of innovative biotechnology, the TFDA makes use of expert scientific advisory committees to complement its internal review process. These external advisors provide scientific advice, which contributes to regulatory decision-making. Expertise on the advisory committee often includes scientific, statistical, and clinical experts, as well as consumer or patient representatives.

5 Points of Considerations for Cell Therapy Medicinal Products

Although Taiwan has not yet approved a cell or gene therapy medicinal product for marketing, numerous clinical trials are being conducted in Taiwan. The following section will introduce considerations regarding cell therapy medicinal products.

5.1 Source Controls

5.1.1 Cells

If patients receive *autologous* cells, in which the specific pathogen screening and testing have not been implemented, or the results of the testing show positive reactions, the reviewers will evaluate whether the operating or manufacturing process

(such as cell culture) will introduce or spread pathogen virus or adventitious virus. In the case of *allogeneic* cells, the specific pathogen screening and testing of donors shall be implemented. Additionally, the serum type (such as major histocompatibility complex, blood types ABO), diagnosis, and clinical history of donors shall be recorded. The screening items include the detection of donors at high risk of infection of human immunodeficiency virus (HIV), hepatitis, degenerative spongiform encephalopathy (CJD), and tuberculosis. The testing items include type 1 and type 2 HIV; surface antigen and core antibody antigen of hepatitis B virus (HBV), hepatitis C virus (HCV), and cytomegalovirus (CMV); type 1 and type 2 human T-cell leukemia virus (HTLV); and *Treponema pallidum* and other relevant specific pathogens.

5.1.2 Reagents

The reagents used in producing (operating and manufacturing process) cell therapy medicinal products shall be listed in detail, including reagents required for cell growth, differentiation, selection, purification, etc. Furthermore, it is also necessary to note the amounts of residual of various reagents in the final product. If these reagents are known to be, or may be toxic to people, data from a validation study shall be provided to prove that these reagents have been removed from the final product. In addition, the use of penicillin or other beta-lactam antibiotics shall be avoided, to prevent patients from having allergic reactions. If such antibiotics must be used, appropriate exclusion criteria or caution shall be included.

5.1.3 Excipients

Inactive ingredients other than the active ingredient in the final product are known as excipients, such as human serum albumin or dimethyl sulfoxide (DMSO). All inactive ingredients and their final concentration in the final product shall be listed. For any excipients that have not been previously administered in humans, complete scientific documents containing manufacturing and control information, as well as nonclinical data for the excipients, shall be provided to support their quality and safety.

5.2 Process Controls

All the operating and manufacturing procedures of human cell therapy medicinal products shall be described in detail. The flowchart and the various inspections in the operating and manufacturing process shall be provided.

5.2.1 Cell Collection

The number and size of samples (such as tissue or cells) collected from the donor shall be specified, and the operating steps shall be described, such as the use of mechanical instruments or enzymatic digestion and the cell selection or separation equipment, including density gradients, magnetic beads, or fluorescence-activated cell sorting (FACS).

5.2.2 Cell Culture

The cell culture conditions shall be provided, such as the temperature, the time of cell culture, and the maximum passage number of cultured cells. When growth factors are added to the cell culture process, the potential growth of cell subpopulations shall be especially considered.

5.2.3 Final Harvest

If the final harvested cells have been centrifuged, the medium used and the washing conditions shall be described. Whether cells are frozen or immediately used in patients shall be specified. If storage is necessary, the method of storage, the conditions, and the period of storage shall be described.

5.2.4 Cell Modification

When cells are physically and chemically treated or genetically modified, the methods shall be provided. Moreover, the degree of change in cell properties caused by such modifications shall also be monitored.

5.2.5 Formulation

The formulation of the final product shall be described in detail. In addition, the density or concentration of cells in the final product and the conditions of shipment shall be clearly explained, so as to ensure that quality can be maintained.

5.2.6 Radiation Treatment

If cells need radiation treatment before they are transplanted into humans, related data shall be provided to show that these cells still retain the expected properties after the radiation treatment. In addition, the radiation equipment shall be calibrated regularly.

5.3 Product Testing

5.3.1 Sterility

The methods and results of sterility (such as microbiological testing, mycoplasma) testing shall be described in detail, for which the suitable methods shall be according to those stated in pharmacopeia such as USP and EP. If a non-compendia method is adopted, the appropriateness of this alternative method shall be confirmed and validated.

5.3.2 Identity

For cell therapy medicinal products, the implementation of identity tests is very important to ensure that the active ingredients remain the same. The identity tests include cell surface markers, gene polymorphism, etc.

5.3.3 Purity

Purity can be defined as the absence of other substances within the final product except those that are inevitably introduced as a result of the manufacturing process. The purity tests include testing for pyrogenic/endotoxin, protein, or peptide residues used to stimulate or regulate cell growth and reagent ingredients used in the manufacturing process, such as cytokines, growth factors, antibodies, serums, and unintended cellular phenotypes.

5.3.4 Survival Rate

The acceptable minimum release criterion for the survival rate of cell therapy medicinal products is 70 %. If this standard is not met, data shall be provided to show that the dead cells and cell debris will not affect the safety and efficacy of the product.

5.3.5 Release Testing

Release specifications include test items, test methods, and acceptance criteria. Testing for sterility, purity, identity, and the survival rate of the final product is important. For each batch, release testing shall be implemented. The results of the release testing shall be obtained prior to the product being used in patients. If it is not possible to obtain the complete results of release testing (such as sterility tests) prior to administrating the cell therapy medicinal product into patients, the

investigators or manufacturers shall provide alternative methods to test the final product and describe the notification process if the final product is not in conformity with the specifications of the acceptance criteria after administration to patients.

5.3.6 Stability

If cell therapy medicinal products need to be cryopreserved, various parameters of the stability studies shall be developed to ensure that the stability of products can be maintained during the refrigerated preservation. In addition, it is necessary to conduct the comparative analysis to compare the stability of products before and after cryopreservation. If the product needs to be transported from the manufacturing location to the hospital, the delivery time and conditions (such as temperature) shall also be described.

5.4 Nonclinical Studies

5.4.1 Animal Species Selection

Ideally, selecting an animal model with human disease is the best study design, yet not every cell therapy medicinal product has an appropriate suitable animal model of the human disease. For cell therapy medicinal products, small animal models may not be suitable; therefore, large animal models whose physiological and immune system may be more similar to that of humans shall be considered.

5.4.2 Cell Distribution

The general pharmacokinetic studies of absorption, distribution, metabolism, and excretion (ADME) are not fully suitable for human cell therapy medicinal products; however, the performance, distribution, survival, and persistence of cells which enter into the human body shall still be investigated.

In consideration of the safety issue of using cells labeled with radioactive markers or fluorescent reagents to track the distribution of cells in humans, it is difficult to obtain information on the distribution of the cell therapy medicinal products in the patients. Hence, determination of whether the transplanted cells are distributed in expected or unexpected anatomic locations and the persistence of the cells shall be evaluated in animal studies. If there is an abnormal or unexpected distribution of cells in the animals, an assessment of whether or not development of abnormal tissues or any safety issues occur shall be determined.

5.4.3 Tumorigenicity

If cell therapy medicinal products contain stem cells, the possibility of tumor formation shall be considered.

5.4.4 Immunogenicity

If the allogeneic cells are used in the treatment, nonclinical studies to evaluate antigenicity and immune toxicity shall be conducted.

5.5 Clinical Trials

The overall considerations regarding clinical trials of cell therapy medicinal products are essentially the same as that for the pharmaceutical products. However, the protocol designs are slightly adjusted according to the characteristics of the cell therapy medicinal products, such as the source, or activity of the cells.

Generally speaking, the early stages of clinical trials focus on (1) donor eligibility, (2) source and specifications of cells, and (3) the compliance with "Good Tissue Practice (GTP)." However, the late stages of clinical trials or a future NDA marketing application will require more relevant documents and literature to prove the consistency of product using the final manufacturing process. Cell therapy medicinal products shall also comply with regulation of the "Good Manufacturing Practice (GMP)."

5.5.1 The Clinical Population

The selection of the appropriate clinical population is based on the therapeutic purpose of the cell therapy medicinal product; this principle is the same as that used in selecting subjects for clinical trials of pharmaceutical products. Generally speaking, cell therapy medicinal products have a higher and/or uncertain degree of risks than conventional pharmaceutical products; therefore, the inclusion of healthy subjects is not recommended.

5.5.2 The Dose Selection

"Dose" refers to the number of cells in each administration that the patient receives. If there is little or no clinical experience, the initial dose shall be determined according to results of animal studies and the dose estimation method from animals to humans shall be explained. In principle, single-dose administration is preferred; however, the appropriateness of multiple-dose administration depends on the

characteristics of the cells. If multiple-dose administration is potentially necessary to achieve the objectives, assessment as to whether the administered cells usually remain active in the human body is important. Therefore, appropriate time intervals and frequencies of product administration are required. When other medicines are required before or after administering cell therapy medicinal products (such as chemotherapy), the basis and reasons for use of the combination regimen shall be provided. For first-in-human trials, the time intervals between administrations within cohorts shall be staggered, allowing enough follow-up time to confirm the acceptable risk range of former subjects, and then continue administration to the next subject.

5.5.3 Tracking and Monitoring

Some cell therapy medicinal products, depending on their characteristics, have specific safety issues, such as immunogenicity, formation of new cancer, and ectopic tissue regeneration; thus, special tracking and monitoring following administration are important. Investigators or manufacturers need to establish a tracking and monitoring system for the purpose of long-term evaluation of safety of cell therapy medicinal products. The scope of the safety monitoring shall cover expected and unexpected effects. It is recommended that this aspect of the clinical protocol be based on the animal data, previous clinical trial experiences, and experiences with similar cell products. The follow-up period of patients shall be at least 1 year; however, for cell therapy medicinal products with uncertain mechanism(s) of action, a longer follow-up period shall be considered.

For cell therapy medicinal products with a high level of safety uncertainty, the cessation rules shall be established to define what procedures shall be performed (e.g., suspension of the study for all subjects, study closure, etc.) when certain events (such as unexpected subject deaths) take place during the trial to avoid exposure of more subjects to risk. For example, how many cases of serious adverse reactions caused by acute infusion of the product are required before suspension of the study for all subjects? The study shall not restart until the relevant data are analyzed by investigators and the risks are identified.

6 Reviews and Considerations for Gene Therapy Medicinal Products

The TFDA has limited experience with the evaluation of clinical trials for gene therapy medicinal products. Although the TFDA released the "Guidance of Investigation of Human Gene Therapy Products (Draft)," in 2012, the current opinions on the contents of this document from investigators and manufacturers are diverse. The TFDA will continue to participate in international conferences, study international regulations, and review the experiences on the review of gene therapy medicinal products and will announce the final version in the near future.

7 Regulatory Challenge

The greatest challenges to regulatory management of cell or gene therapy medicinal products lie in the long-term potential risks that may occur after administration to patients. For example, will the implanted cells proliferate in the body? Will these cells have carcinogenic risks over a long period of time? Will the administered vector insert into the "germ cell" and be passed on to the next generation? Therefore, the quality and safety of these emerging products are very important issues of concern to the TFDA regulators.

8 Conclusion

The development of cell or gene therapy medicinal products in Taiwan is relatively slower than in the USA and Europe; however, along with the Taiwan government's developing biological medicinal products as a national key project, many research institutes and industries have also already actively invested manpower and material resources in this field. There are seventeen manufacturers engaged in the development of cell or gene therapy-related products in Taiwan, and most of them are primarily focused on the study of umbilical cord stem cells, immune cells, and adipose stem cells. There are also certain manufacturers that are developing and providing stem cells following in vitro culture for treatment of various diseases.

This chapter presents the current regulatory approach for cell and gene therapy medicinal products in Taiwan. In the near future, the TFDA is considering constructing a risk-based regulatory strategy for cell and gene therapy medicinal products. However, at the present time, for possible commercialization of any cell or gene therapy medicinal product, the TFDA will continue the consultation system to assist the developers of these products and to assure that the demands associated with the development of such medicinal products are met.

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Regulatory Oversight of Cell- and Tissue-Based Therapeutic Products and Gene Therapy Products in Singapore

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Abstract The regulatory environment for cell- and tissue-based therapeutic products and gene therapy products is rapidly evolving and drug regulatory agencies are working towards establishing a risk-based system in the regulatory framework. Similarly in Singapore, a risk-based tiered approach has been applied whereby clinical trials and product licence of high-risk cell- and tissue-based therapeutic products (substantially manipulated products, products intended for nonhomologous use or combined products) and gene therapy products are regulated as medicinal products under the Medicines Act. There is no legal definition for cell- and tissue-based therapeutic and gene therapy products. The current working definition for a cell- and tissue-based therapeutic product is an article containing or consisting of an autologous or allogeneic human cell or tissue that are used for or administered to, or intended to be used for or administered to, human beings for the diagnosis, treatment, or prevention of human diseases or conditions. Gene therapy products are included under the current biological medicinal product definition.

Keywords Cell- and tissue-based therapeutic product • Gene therapy product • Good manufacturing practice • Clinical trial certificate • Product licence

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1 Introduction

The Health Sciences Authority (HSA) was formed on 1 April 2001 as a statutory board of the Singapore Ministry of Health. HSA's vision is to be the leading innovative authority protecting and advancing national health and safety, with a scope of work that spans a wide spectrum of scientific and professional functions: the Health Products Regulation Group (HPRG), the Blood Services Group, and the Applied Sciences Group. These functions support other regulatory and compliance agencies in protecting public health and safety in Singapore.

HSA's mission is:

- To wisely regulate health products to meet standards of safety, quality and efficacy
- To serve the administration of justice through its capabilities in forensic medicine, forensic science and analytical chemistry testing
- To secure the nation's blood supply by ensuring a safe and adequate blood supply for public and private hospitals

The HPRG strives to create a more conducive and smart regulatory environment in providing safe and timely access to health products and supporting the development of the biomedical sector. It ensures that drugs, innovative therapeutics, medical devices, and other health-related products are wisely regulated and meet appropriate safety, quality, and efficacy standards. The HPRG also contributes to the formulation of national drug policies.

2 Regulatory Framework for Cell- and Tissue-Based Therapeutic Products and Gene Therapy Products

2.1 Definition

Currently in Singapore there is no legal definition for a cell- and tissue-based therapeutic (CTT) product and a gene therapy (GT) product. Both CTT and GT products are regulated as biological medicinal products. A biological medicinal product [1] (a biologic) refers to products derived from biological systems, which include:

- Whole cells or organisms, e.g., whole virus/bacterium used as a vaccine
- Part of organisms, e.g., subunit vaccines, blood/serum-derived products
- Macromolecules extracted from or produced by organisms, e.g., proteins, nucleic acids, proteoglycans, cytokines, and growth factors
- Biotechnology products, e.g., recombinant hormones, enzymes, and antibodies

but does not include:

- Metabolites from microorganisms, e.g., antibiotics
- Macromolecules produced by chemical synthesis, e.g., peptides/oligonucleotides produced by chemical synthesizers

Table 1 Risk classification for cell- and tissue-based therapeutic products

	Degree of manipulation	Intended use	Combined or use with drug, biologic, or device
High risk	Substantial	Nonhomologous	Yes
	Substantial	Nonhomologous	No
	Substantial	Homologous	Yes
	Substantial	Homologous	No
	Minimal	Nonhomologous	Yes
	Minimal	Nonhomologous	No
	Minimal	Homologous	Yes
Low risk	Minimal	Homologous	No

The working definition for a CTT product is as an article containing or consisting of an autologous or allogeneic human cell or tissue that is used for or administered to, or intended to be used for or administered to, human beings for diagnosis, treatment, or prevention of human diseases or conditions.

2.2 CTT Product Classification

A risk-based phased approach is being adopted so as to allow tiered levels of regulatory oversight (Table 1). The products are classified as either high or low risk based on three criteria as listed below:

1. The first criterion is the degree of manipulation during the manufacturing of the products. The product will be considered as substantially manipulated when the manufacturing processes include, but is not limited to, cell expansion, encapsulation, genetic modification, or any processing that alters the biological, physiological, or metabolic properties of cells, or structural characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.
2. The second criterion is if the product is intended for homologous use, that is, whether the CTT product performs the same basic function in the recipient as in the donor.
3. The last criterion for a high-risk CTT product is if the product is to be combined or used in conjunction with a drug, biologic, or device.

Currently only high-risk CTT and GT products are regulated, while the low risk CTT products will be regulated at a later phase during the development of a new regulatory framework for cell, tissue, and gene therapy products. Stakeholders are highly encouraged to submit a brief description of the product and manufacturing process for product classification during the early stage of product development.

2.3 Current Legislations

CTT products are regulated as medicinal products under the Medicines Act since February 2009, and the GT products since 2005 under the same Act. The Medicines Act [2] was gazetted in 1977 to provide a comprehensive control on:

– Licensing of activities such as manufacture, import, wholesale supply
– Registration of medicinal product
– Prohibition on false or misleading advertisements

Conduct of clinical trials in Singapore is regulated by the Medicines Act 1975 and the Medicines (Clinical Trials) (Amendment) Regulations 1998 [3]. In addition, the Singapore Guideline for Good Clinical Practice (GCP) has to be observed in the conduct of local clinical trials; this document sets ethical and scientific standards for the conduct of clinical trials [3].

In addition to the above, stakeholders should also read other applicable laws governing pharmaceutical products in Singapore, which include the following:

- Poisons Act (Chapter 234) [4]
- Misuse of Drugs Regulations—subsidiary legislation under the Misuse of Drugs Act (Chapter 185) [5]
- Sale of Drugs Act (Chapter 282) [6]
- Medicines (Advertisement and Sale) Act (Chapter 177) [7]

The HSA accepts reference to relevant international guidelines and standards such as the International Conference on Harmonisation (ICH), Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), and specific guidelines and standards published by HSA's reference agencies (see below), in the assessment of application for a product licence and clinical trial certificate (CTC). Stakeholders are advised to check the HSA website for latest updates on regulatory requirements for medicinal product registration and CTC applications [8].

3 Regulatory Pathway

3.1 Product Licence

A product licence is required for a CTT product to be supplied in Singapore. Applicants are encouraged to discuss the submission and documentary requirements in a pre-submission consultation with the HSA prior to submission of a licence application. As per current policy, application for a CTT product licence is to be submitted as New Drug Application via the abridged dossier evaluation route. This means that the product needs to be evaluated and approved by at least one of HSA's reference agencies namely, Australian Therapeutic Goods Administration,

European Medicines Agency (EMA), Health Canada or the United States Food and Drug Administration (USFDA). The review process involves a series of steps as depicted in Fig. 1.

The application dossier should be submitted in a common technical document (CTD) format; either ICH or The Association of Southeast Asian Nations (ASEAN) CTD (Table 2). Module 1 should include a comprehensive table of contents, an introduction of the application, proposed product labels, approved labels from HSA's reference drug regulatory agency, the proof of approval, authorization letters, good manufacturing practice (GMP) certification/proof of GMP compliance, and

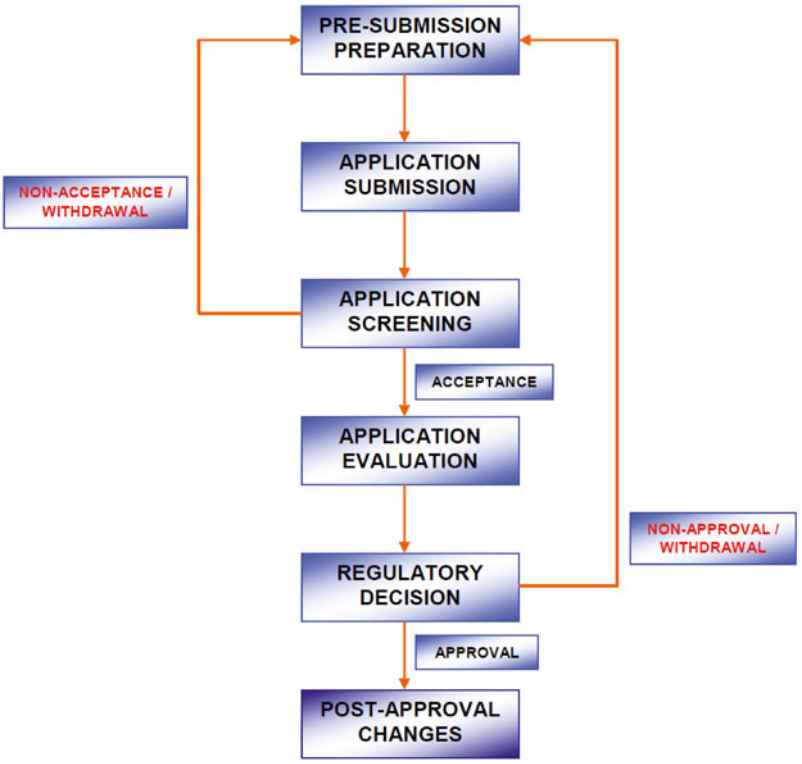

Fig. 1 Singapore HSA registration process for a medicinal product licence application

Table 2 Dossier submission format for Singapore HSA?

Module 1	Administrative documents and product information
Module 2	Common technical document overview and summaries
Module 3	Quality documents
Module 4	Nonclinical documents
Module 5	Clinical documents

declaration on rejection, withdrawal, and deferral. Module 2 should contain a quality overall summary, overview, and summaries of both the nonclinical and clinical documents. Module 3 should document the complete quality information of the product, while Module 4 captures all the nonclinical study data. The clinical studies provided in Module 5 should generally be conducted using the CTT product submitted in the application and in the appropriate patient population for the proposed indication(s) and/or dosing regimen(s). Risk management plans submitted to the EMA, risk evaluation and mitigation strategies submitted to the USFDA, and/or other relevant documents pertaining to such purposes should be included in Module 5. The need to implement a risk management plan in Singapore would be identified on a case-by-case basis during the review process.

The screening process will determine the completeness of the dossier for evaluation. The target processing timeline for screening is 25 working days before the first communication, in the form of an input request or acceptance/non-acceptance notification. The target evaluation timeline is 270 working days from the date of acceptance of the dossier to issue a regulatory decision, excluding all stop-clocks. Upon product approval, the licence holder shall be responsible to maintain the product's quality, efficacy, and safety throughout the product life cycle. The authority must be notified of any post-approval changes, which shall be subjected to regulatory approval [1].

More detailed information on product registration can be obtained from the guidance document, "Guidance on Medicinal Product Registration in Singapore" [1].

3.2 Clinical Trials

The objectives of clinical trials regulation are:

- To ensure the safety and quality of the investigational medicinal product administered to clinical trial subjects.
- To ensure that the scientific evidence is adequate to demonstrate product safety and efficacy.
- To ensure that the participants' rights and interests are adequately protected and they are not exposed to undue risk, and that the safety and efficacy data collected are credible.

In Singapore, CTT and GT product clinical trials are approved as an individual clinical trial application. Besides ethics approval of clinical trials from the healthcare institutional review board, the HSA issues regulatory approval in the form of a CTC. The CTC is issued in the name of principal investigator who is a locally registered medical or dental practitioner. It is specific for each study protocol, and for each institution or site involved in the study. The guidelines on CTC application, submission process and documentary requirements are provided on the HSA website [9]. The target evaluation timeline is 60 working days from the date of acceptance of a CTC application for evaluation to regulatory recommendation, excluding stop-clocks.

The investigational medicinal products that the HSA has evaluated thus far include T cells, NK cells, dendritic cells, mesenchymal stromal cell (MSCs), and MSCs grown on scaffold, as well as non-viral or viral gene vectors. These products are mostly being investigated for oncology and regenerative medicine indications. Detailed information on all active clinical trials, including CTT and GT product trials can be obtained from the HSA Clinical Trials Register [10].

The list of possible investigational CTT and GT products include the following:

1. CTT products:
   (a) T cells, NK cells, dendritic cells, chondrocytes, keratinocyte and fibroblasts, pancreatic islet cells, hepatocytes, neuronal cells
   (b) MSCs, cells derived from embryonic stem cells, cells derived from induced pluripotent stem cells and other progenitors
   (c) Cells/tissues grown on a noncellular material (scaffold or matrices)
2. GT products:
   (a) Replication-incompetent gene vectors (non-viral and viral)[1]
   (b) Genetically modified cells
   (c) Genetically modified virus[2]
   (d) Genetically modified bacteria

These products are investigated to treat disorders/diseases including cancer, enzyme/factor deficiency, neurodegenerative, retinal, immune deficiency and modulation, cardiovascular, pulmonary, metabolic, orthopaedic indications, among others.

Further, there are other potential applications of novel technologies in CTT and GT products such as development of induced pluripotent stem cells and 3D printing that could potentially generate living organs/tissues including reproductive tissues. These potential applications require specific and extended safety and ethical assessments relevant to the clinical indication.

4 Regulatory Review

The regulatory review of CTT and GT product clinical trials includes chemistry, manufacturing and controls (CMC), pharmacology and toxicology studies, as well as clinical study design. Complete information on product development, applicable pharmaceutical/genetic development, toxicological, pharmacological, and clinical data should be submitted in support of a CTC application.

[1] Non-viral vectors: nuclear acid (DNA, siRNA, shRNA, and mRNA) cloned into an expression vector in combination with non-viral components, for example lipids, polymers, etc.; viral vectors: adenoviral, adeno-associated, poxiviral, retroviral-derived (lentiviral, Moloney murine leukemia viral) and others.

[2] Oncolytic virus, adenovirus, measles virus, stomatitis virus (VSV), reovirus, Newcastle disease virus, poxvirus, Sendai virus, and others.

4.1 Chemistry, Manufacturing, and Controls

The quality dossier should document detailed information on the CMC throughout all stages of product manufacturing. For the cell source, the donor needs to undergo screening and panel testing for Human immunodeficiency virus antibody (HIV-1, HIV-2); Hepatitis B virus surface antigen, Hepatitis C virus antibody, and Syphilis [11]. If cell lines are used, information such as origin, source, cultivation history, characterization of both master and working cell banks should be documented. The cell lines should be subjected to evaluation of the risk of viral contamination [12, 13], and free from bacterial, fungal, and mycoplasma contamination. For products using a gene therapy vector, the description on the construction of the gene construct, vector diagram, and gene sequences should be submitted. If oligonucleotides are used, the derivation and sequence should be described. Whenever possible, clinical grade reagents should be used throughout the manufacturing of the product. If no clinical grade reagents are available, the next highest available reagent grade should be used. If scaffolds or cell matrices are a component of the finished product, their chemical, biological, physical, and mechanical properties as well as biocompatibility with the cellular components, should be addressed.

A detailed description of the entire manufacturing process starting from collection of cells/ tissues; production; harvest and final formulation should be provided. The in-process sampling and testing at various critical manufacturing steps monitor the manufacturing progress and quality attributes of the product intermediates. Information on construction materials and compatibility studies to demonstrate suitability of the container closure system for the product should be submitted.

The finished product should be characterized in terms of cell viability, cell number, sterility, identity, purity, and potency [14–16]. The product should be tested for absence of contaminants such as aerobic bacteria, anaerobic bacteria, fungus, and mycoplasma. The product identity can be determined by assays for cell surface markers or the presence of the gene vector. The purity aspect should quantitate the desired cell population in the product and ensure that unwanted cell types, endotoxin levels, residual impurities generated during the manufacturing process are maintained within the acceptable range. The potency assay is the measure of biological activity based on the proposed mechanism of action of the product and should correlate with the expected clinical response. Stability data should be submitted to support the proposed storage condition and shelf-life.

4.2 Pharmacology and Toxicology

The common issues observed in CTT and GT product clinical trial applications are as follows: (1) the dossier is insufficiently detailed to help in the assessment of product safety; (2) the preclinical studies are often not designed to answer the potential toxicity issues and (3) the published animal or human study data used as sole support for initiation of a clinical trial may not be directly relevant to the investigational product. Hence, it is important that the nonclinical team within the

research institutes and the industry stakeholders collaborates with the clinical development team in planning critical toxicology studies because of multiple factors that contribute to determine the clinical study design. Sponsors and investigators are encouraged to initiate early discussion with HSA in designing preclinical studies to support clinical trials for the purpose of developing a reasonable safe product to benefit target disease population.

Similar to drugs, pharmacology studies of CTT and GT products should demonstrate the scientific proof-of-concept (POC), and toxicity studies should address the potential safety issues of the product. These studies are designed to: (1) build the scientific justification; (2) recommend a safe starting dose; (3) support patient eligibility criteria; (4) provide monitoring parameters for the targeted patients, and (5) recommend duration of safety follow-up. There are multiple factors that determine the design of preclinical studies, such as product type, formulation, target disease population, route of administration (ROA) and clinical endpoints. Thus, preclinical study design should be customized for each product by taking into account the above mentioned factors. Often, pharmacology and toxicology assessments are designed in the same study that provide the information on the POC and general safety profile of the product. Sometimes, stand-alone toxicology assessments are required to address potential safety issues before initiation of a first-in-human study and/or additional toxicity assessments may be required to address specific safety issues observed from early clinical trials. However, generally the best way to characterize the product would still be in an appropriate animal model of disease or injury, although acknowledging that the model does not always mimic all aspects of the immunologic, anatomic, and human disease process. The limitation of animal models in predicting the risk of immunogenicity, genotoxicity and carcinogenicity should be discussed. The justification with supporting in vitro and/or in vivo data should be provided for selected animal models.

The in vitro and in vivo assessments generally include the following.

1. *Product characterization*:

   - CTT products
     - Karyotype and phenotype stability
     - Proliferation, differentiation, engraftment capacity, and duration of survival
     - Biological activity and comparable bioactivity of cells grown on noncellular material
     - Dose required for pharmacologically relevant response
   - GT products
     - Biodistribution of vector and transgene kinetics
     - Vector genome stability, profile of integration, and integration site analysis
     - Potential for vector transfected cell-related genotoxicity
     - Potential for vector release and germline transmission
     - Dose required for pharmacologically relevant response

   The product characterization profile should be considered in the evaluation of safety in animal models.

2. *Safety evaluation in animal models*:

   The type of cell, serotype of virus, and the viral vector construct have different safety profiles. Parameters that have an impact on the safety of CTT products are diverse, including cell source, ability to proliferate/differentiate, immunogenicity and tumorigenicity. Parameters that have impact on the safety of GT products include in vitro and the extent of in vivo replication competence of the viral vector, in situ integration, and cellular transformation related to persistent transduction, and genetically modified cell-related genotoxicity. Therefore, safety studies should be designed to analyze these risks. The focus of safety evaluation for CTT and GT products are listed as follows.

   - CTT products
     - Undesirable cell types, chimerism, and dominant clonal survival
     - Trafficking to non-target tissues
     - Homing with existing physiology
     - Undesirable immunogenicity, e.g., graft-versus-host disease (GVHD)
     - Tumorigenicity
     - Transplant risk associated with ROA, surgical procedure and anatomic site seeding
   - GT products
     - Persistence in non-target tissues
     - Undesirable effect of the transgene
     - Undesirable immunogenicity, e.g., autoimmune diseases
     - Genotoxicity/carcinogenicity

3. *Animal model selection and recommendation*:

   (a) Identify the ability and the limitation of animal models
   (b) Selection of models with similar biological response to humans
   (c) Mimic clinical treatment scenario as closely as possible (finished product formulation, ROA, timing of administration, dose regimen, etc.)
   (d) Determine the number of animals for providing adequate safety data
   (e) Allow adequate duration of study and recovery period for evaluation of toxicity
   (f) Use control groups (placebo, sham, and positive) as necessary
   (g) Use of the 3Rs (Refinement, Reduction, and Replacement) of animal use in research
      - Reduction: use of single species and nonterminal studies when justified
      - Refinement: incorporation of pain management, nonterminal imaging
      - Replacement: use of in vitro studies when available
   (h) Ensure Good Laboratory Practice (GLP) compliance for toxicology studies

The USFDA guidance on preclinical assessment of investigational cellular and gene therapy products is a good reference for preclinical assessment of CTT and GT products before initiating a clinical trial [17].

Table 3 Characteristics of cell- and tissue-based therapies (CTT), gene therapies (GT), and drug (small molecule) therapies

	CTT	GT	Drug therapies
Safety margin	Maximum feasible dose (MFD)	Maximum feasible dose (MFD)	Maximum tolerated dose (MTD)
PK	Time course of cell; trafficking; site seeding for intended activity; non-target site seeding	Time course of biodistribution; level of persistence of vector; transgene expression; integration into genome	Exponential decay of drug concentration vs. time
$T_{1/2}$/clearance	Days/months/years/ lifetime	Days/months/years/ lifetime	Minutes/hours/days
Dose	Far less precise	Less precise	Precise
	Viable cell number; enumeration of specific cell populations; total DNA, RNA and protein	Viral particle number; transducing unit; total protein	Weight; concentration
Dose administration	Number of cells; volume; rate, route and number of administrations; cell or cell/noncellular material stability	Particle number; volume; rate, route and number of administrations; vector/ transgene stability	Weight/ concentration; volume; rate, route and number of administrations
Dose extrapolation	Number of cells delivered, initially retained, or eventually incorporated; cross species validation (body weight or body surface area), previous human experience with similar products	Number of particles delivered, initially retained, or eventually integrated; cross species validation (body weight or body surface area); previous human experience with similar products	Weight/ concentration delivered; distribution; metabolism; excretion; cross species validation (body weight or body surface area)

4.3 Clinical Trial Design

The standard clinical trial development design for conventional drugs may not always be suitable for CTT and GT product trials. The factors listed in Table 3 dictate many complicated aspects and uncertainty of these groups of products as compared to conventional drugs i.e., small molecules.

Further, traditional Pharmacokinetics (PK)/Pharmacodynamics (PD) modelling that is performed for drugs does not translate well for CTT and GT products because assessments of PK/PD are recognizably different when compared to drugs, as elaborated in Fig. 2.

In vivo proliferation/replication of CTT and GT products to some degree may be robust to achieve substantial PD effect, however there are potential risks related to abnormal amplification, non-target site seeding and genomic integration. The PD studies, such as immune response, engraftment, transgene expression are expected

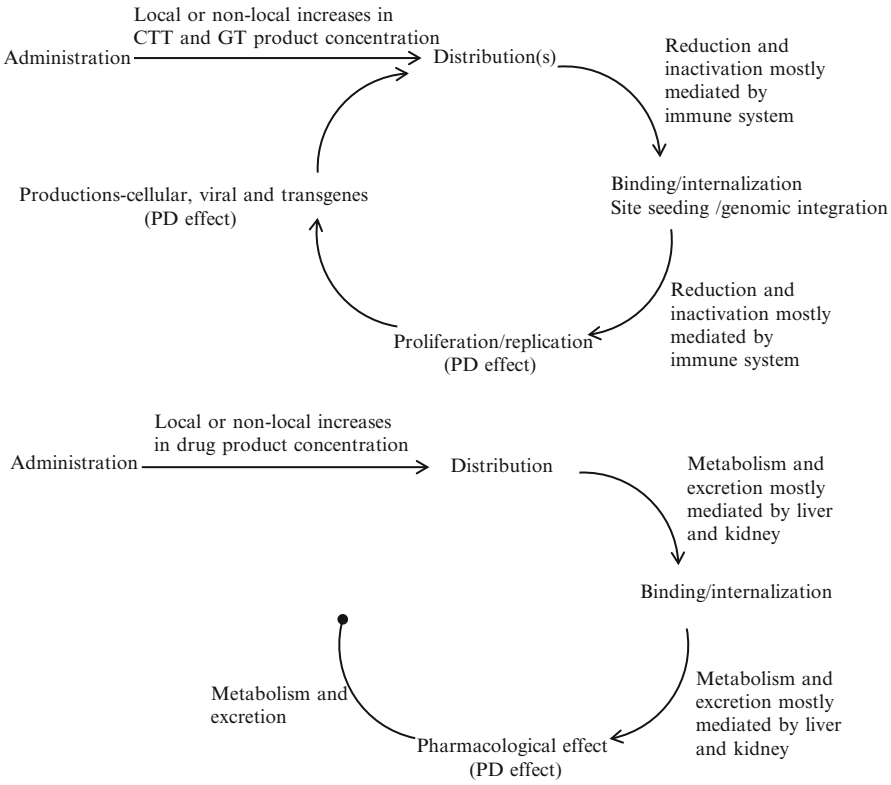

Fig. 2 PK/PD of CTT product, GT product, and drug product

as alternative objectives. The risk assessments of CTT and GT products should cover the entire product development program, including:

1. *Product risk*: Besides the source of product and product manufacturing attributes, CTT and GT products are heterogeneous and the possibility of unidentified cells, unchecked cells, cellular residuals/viral particles, and by-products may exert a disproportional effect and thus a safety concern. The in vivo clearance of CTT and GT product sometimes involve immune rejection or other unanticipated immunological responses.
2. *Patient risk*: Patients with the target disease that will receive the CTT or GT product are often seriously ill or have a life-threatening illness. Such individuals may require standard of care and medication which could potentially interact with the investigational product. The prophylactic medications or elimination of the subject's own immune cells by conditioning regimen impose an additional risk of immune suppression. In addition, the difference in the subjects' genetic background has substantial effects on various biological activities, which can be associated with different levels of risk. Unlike drug trials, the risk from premedication, concomitant medication, and product administration are too significant to allow participation of healthy volunteers in clinical studies.

3. *Administration risk*: The risk of CTT and GT product administration can be greater than conventional bone marrow transplant or organ transplant in some cases, because some anatomical sites of administration, for example, intracardiac, intraspinal, and intracranial, pose significant risk to the subject. Some additional risks can also arise from inaccurate target site seeding and distribution of the product. The incorporation of an investigational delivery device or other noncellular materials often adds complication to the transplant. Evaluation of novel transplant risks in animal models should be considered to predict the risk of the delivery procedure and to evaluate the need for a risk mitigation strategy.
4. *Viral spread risk*: The administration of certain GT products to patients raises the possibility of transmission of product-based viruses and bacteria, for example, oncolytic virus from treated to untreated individuals and spread to the environment. Applicable international guidances on viral shedding studies, including how and when shedding data should be collected as well as how shedding data can be used to assess the potential for transmission, have been used as a guide in assessing the environmental risk impact for GT products [18, 19].

In Singapore, investigational CTT and GT products are largely in early phase studies with a very small percentage involving large-scale phase 3 trials. There are mixed reports, both positive and negative results, on the early phase trials that are often not sufficiently informative to proceed with confirmatory phase 3 trials. Therefore, obtaining adequate and useful information from early clinical trials is important for successful CTT and GT product development. The consideration and assessment of some aspects of early clinical trial design are provided as follows.

1. *Dose and dosing regimen*: The goal of a starting dose selection is to administer a pharmacologically active dose that is reasonably safe. In a conventional drug study, the no observed adverse effect level (NOAEL) obtained from toxicity studies in appropriate animal models are used to calculate the human equivalent dose and establish a safety margin. However, this approach may not be fully employed to estimate the potential safe start dose for CTT and GT products because there are some confounding factors such as:

   (a) A maximum feasible dose (MFD) is often administered as the highest dose level in animal toxicology studies because further escalation of the dose to achieve the maximum tolerated dose (MTD) is not feasible due to the limitations of anatomic feature of animals and dosage formulation. The selected dose regimen based on the animal MFD may therefore not be optimized for the clinical protocol.
   (b) The preclinical testing using the same ROA as for humans is expected to demonstrate the safety of the administration procedure when the product is delivered via a special device, such as using a catheter to deliver cells into the brain or the heart. However, the risks may be unpredictable if the device cannot be used in or is not available for the animal models.
   (c) Some CTT and GT products are human-specific; the results from animal toxicity studies may not accurately predict toxicity in humans due to immune inactivation or rejection of the product.

In some cases, the recommendation of a safe starting dose is empirical by taking into account clinical experiences for similar products. When such an approach is applied, the evaluation of product similarity to justify the dose may include the cellular characterization or vector construct, the manufacturing process, analytical testing, pharmacologically relevant response, and in vivo toxicity endpoints.

With these issues, a starting dose and dose escalation plan proposed for early phase clinical trials to identify the MTD may not be achievable or if achievable, dose escalation to higher than the MTD may not be appropriate because the predictability of therapeutic effect vs. toxic effect from preclinical studies is not very reliable. Nevertheless, the approach of dose finding is often to optimize a dose range to identify safe doses and establish safety profile. Thus, it is important that sponsors provide sufficient preclinical data, including biologically active dose ranges, minimum effective dose, MFD, and the NOAEL to support the clinical trial design. The sponsors should also provide the rationale to support the clinical dose escalation plan.

Further, CTT and GT products can potentially proliferate, replicate, and/or remain in body for a long period. Therefore, the concentration vs. time curve applied to drugs is not applicable for CTT and GT products, especially considering that the current available technologies for the dosage of CTT and GT product are far less precise than that for drug products (Table 3). Hence, the development of a reliable assessment of exposure vs. time course in relation to a pharmacologically relevant response for CTT and GT products will be useful.

2. *Target disease population*: The target population is the most critical consideration for the design of a successful clinical trial. This consideration may go beyond the demographic, histopathological, and biochemical characteristics, which are routinely used as selection criteria for drug trials. In many cases, the genetic and phenotypic diversity of a disease are expected for the target population, even for a monogenic disease or a specific type of cancer. These impose a major challenge in achieving the goal of choosing an appropriate therapeutic regimen. A well-established genetically determined difference for a disease pathophysiology is the basis for patient selection. Thus, genomic and proteomic tests are prospectively used as criteria to select patients by which the therapeutic effect would be more likely to be observed than in unselected patients. This approach may increase the chance of success, especially for a disease with a small sample size.
3. *Safety monitoring and follow-up*: The efficacy of CTT and GT products are sustainable because many of these products have the ability to proliferate/replicate in vivo. The clinical manifestation of acute and chronic systemic toxicity, local toxicity and administered site reaction can be severe and unpredictable, e.g., cytokine release, GVHD, autoimmune disease, and risk associated with transplant, such as death, haemorrhage, infection, and complications of graft failure. Thus, the safety monitoring for CTT and GT products during clinical trials should be based on potential product-specific adverse outcomes. The protocol defining specific safety monitoring evaluation and stopping rules should be

developed prior to implementing dose escalation. Monitoring and follow-up may be needed over a prolonged period depending on the nature and characteristics of the product and the targeted patients. For some GT trials, observing subjects for delayed adverse events is required [20]. For some CTT trials, observing subjects for oncogenicity and immunogenicity is also recommended.

The USFDA draft guidance on considerations for the design of early phase clinical trials of cellular and gene therapy products can be a good reference for the design of early phase clinical trials [21].

5 GMP Inspection of Manufacturers

In Singapore it is recognized that there are significant manufacturing risks for CTT and GT products that have been subject to substantially manipulation and therefore decided to incorporate compliance with GMP standards as part of the regulatory requirements for application for a Manufacturer's Licence or CTC application. In other words, the local manufacturers that produce substantially manipulated CTT and GT products for commercial purpose or for use in clinical trials are subjected to GMP inspection.

PIC/S is an informal arrangement among the national pharmaceutical regulatory authorities in the field of GMP for medicinal products. It is dedicated to harmonize the GMP inspection procedure through common GMP standards, by providing training opportunities to inspectors, and encouraging collaboration and networking among the pharmaceutical regulatory authorities. It was established in 1995 and the Singapore HSA has been a member authority since 2001. Therefore, Singapore HSA uses the PIC/S GMP standard in GMP inspections of manufacturers of substantially manipulated CTT and GT products.

The PIC/S GMP standard was established with the aim to promote uniformity in licensing and regulatory decisions, to remove trade barriers between countries and to ensure continued maintenance of high-quality standards in the development, manufacture, and control of medicinal products. The PIC/S GMP standard itself consists of Part I and Part II, and accompanying annexes [22]. Part I specifies the basic requirements for intermediate and finished medicinal products. Part II provides guidance regarding GMP for the manufacturing of active pharmaceutical ingredients, while the annexes provide supplementary guidelines for specific products and manufacturing aspects. The GMP requirements applicable to the manufacture of substantially manipulated CTT and GT product can be found in Part I and in relevant annexes.

Similar to the manufacture of conventional medicinal products, problems like contamination (including cross contamination), a mix-up in material, intermediate and finished products can occur in any manufacturing step of CTT and GT products. However, unlike most of the conventional medicinal products, most, if not all, of the starting materials and reagents used in the manufacture of CTT and GT product support microbial growth by nature. Furthermore, since these products cannot be

terminally sterilized, control measures to prevent contamination of material and products during the manufacturing process become paramount important to assure product quality, and that leads to the emphasis of controlling the risk of contamination during the GMP inspection.

A holistic approach is undertaken in the GMP inspection process to assess whether the risk of contamination has been adequately managed within the manufacturing facility. The approach encompasses essential areas ranging from design to operational perspective. Examples include:

- Design and qualification of biosafety cabinet, cleanrooms and heating, ventilation and air conditioning (HVAC) system
- Monitoring systems for particulates and bioburden within biosafety cabinets and cleanrooms
- Maintenance system for biosafety cabinets and HVAC system, including HEPA (high-efficiency particulate air) filters
- Training system for personnel, including qualification of aseptic and gowning procedures
- Controls of ancillary material to be used, including those in cleanrooms
- Sanitization and disinfection system
- Aseptic process validation study
- Cleaning validation study (where applicable)

In addition to contamination, the inspection assesses the level of compliance with GMP requirements on various aspects such as the quality management system, production control, quality control, traceability, outsourced activities, complaints and recalls, etc. In short, the manufacturers have to demonstrate to the inspectors that their quality system, as a whole, can ensure that the manufacturing process is carried out in a defined and controlled manner to produce CTT and GT products that can consistently meet the predetermined product specifications, as approved by the regulatory authority.

Moving forward, when more experience is gained through GMP inspections and from collaboration with reference regulatory authorities, there are plans to publish guidance document(s) related to GMP requirements for CTT and GT products. Hopefully such documents will provide the necessary guidance to manufacturers, especially the smaller manufacturers residing within healthcare institutions, and will enable sharing what the HSA has learned with other regulatory authorities in Asia.

6 Future Directions

A new stand-alone regulation for CTT and GT products as a subsidiary legislation under the Health Products Act (HPA) is being drafted. The HPA was enacted in 2007 to regulate the manufacture, import, supply, presentation, and advertisement of health products (Table 4) and of active ingredients used in the manufacture of health products [23].

Table 4 Definition of a "health product" and "health-related purpose" in the Health Products Act

A "health product", as defined in the HPA, means any substance, preparation, or device—
(a) that—
• is represented for use by humans;
• whether because of its presentation or otherwise, is likely to be taken for use by humans; or
• is included in a class of substances, preparations or devices which are for use by humans or are ordinarily intended for use by humans
solely or principally for a health-related purpose; and
(b) that falls within any of the categories of health products specified in the First Schedule;
"health-related purpose" means a therapeutic, preventive, palliative, diagnostic or cosmetic purpose, or any other purpose for the promotion or preservation of human health and well-being, and includes the following:
• preventing, diagnosing, monitoring, treating, curing, or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or the symptoms thereof, in humans;
• compensating for any injury or handicap in humans;
• investigating, modifying, or replacing any part of the human anatomy or any physiological process in humans;
• testing the susceptibility of humans to any disease, disorder, or ailment;
• influencing, controlling, or preventing conception in humans;
• testing for pregnancy in humans;
• inducing anaesthesia in humans;
• destroying or inhibiting microorganisms that may be harmful to humans; and
• cleansing, fragrancing, deodorizing, beautifying, preserving, improving, altering or restoring the complexion, skin, hair, nails or teeth of humans

Cell, tissue, and gene therapy product regulatory environment is still evolving but in a rapid pace. The new regulation in the HPA will further foster HSA's vision to be a leading innovative authority protecting and advancing national health and safety in the fast growing field of cell, tissue, and gene therapy products.

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The Regulatory Pathway for Advanced Cell Therapy and Gene Therapy Products in Brazil: A Road to Be Built

Daniel Roberto Coradi de Freitas

Abstract The regulation of cell therapy and gene therapy products is a major challenge for the Brazilian state. From a legal point of view, the legislative apparatus, including constitutional, prohibits the marketing and patent of human substances. From the point of view of the organization of the state bureaucracy, the responsibilities for the regulation of research and application of these technologies in humans may involve up to four different institutions. The National Agency for Health Surveillance (ANVISA) has been the protagonist in structuring the regulation of cell therapy and gene therapy in Brazil, and steps have been taken to ensure quality of these products. However, obstacles such as the commercialization of these therapies and the need to determine whether these products will be regulated following the assumptions adopted in Brazil for drugs and biological products or for human blood and tissues still remain.

Keywords National Agency for Health Surveillance • ANVISA • Brazil • Cell therapy • Center for Cell Technology • Clinical trial • Gene therapy • Good manufacturing practice • Quality control • Regulation

1 Efforts to Regulate Cell Therapy and Gene Therapy Products: Legal Obstacles and Multi-agency Responsibilities

If blood transfusion is considered the first cell therapy administered to humans, cell therapy regulation in Brazil started in the 1950s. The first innovative regulation beyond blood transfusion was established in 2004 when bone marrow transplantation was included in a regulation encompassing blood products, the National Agency for Health Surveillance (ANVISA) Board Resolution #153 of 2004 [1].

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Table 1 Government funding for cell therapy research in Brazil from 2005 to 2012

Grant	Year	Amount (million US dollars)	Number of projects
MiHeart trial	2005	7.5	5
RFA	2005	5.8	45
RFA	2008	6.4	52
CTCs	2008	22.7	8
Cell therapy network	2008	1.4	1
Brazil and Argentina cooperation	2011	8.0	10
RFA	2012	5.0	30
Total		56.8	151

Source: Data kindly provided by Dr. Antonio Carlos Campos de Carvalho, Director of the Department of Science and Technology, Secretariat of Science, Technology and Strategic Supplies, Ministry of Health of Brazil

Since 2002, the Brazilian Ministry of Science and Technology and the Ministry of Health have stimulated basic and clinical research in the field of cell therapy. One of the first government efforts was the founding of the Millennium Institute of Tissue Bioengineering (IMBT), which brought together scientists and research projects from various regions of the country. Following this action, several research funding applications (RFAs) were launched by the Brazilian government (Table 1). The first, known as the MiHeart trial, supported a randomized multicenter study of a cell therapy in patients with acute myocardial infarction, chronic ischemic heart disease, dilated cardiomyopathy, or Chagas cardiomyopathy. The RFA 2005 included 45 projects that involved basic research (47 %), preclinical trials (29 %), and clinical trials (24 %). The RFA 2008 included 52 projects that were 32 % basic research, 62 % preclinical studies, and 6 % clinical trials [2]. Finally, the RFA 2012 included 30 projects that were 14 % basic research, 72 % preclinical trials, and 14 % clinical trials (Dr. Antonio Carlos Campos de Carvalho, personal communication). As a result, over 15 Centers for Cell Technology (CCT) were created around the country, groups of researchers dedicated to studying the field of cell therapy were established, and the number of published articles about cell therapies developed in Brazil increased in the last 12 years [2], from 73 in 2000 to 493 in 2012 (Dr. Antonio Carlos Campos de Carvalho, personal communication).

The year 2005 was very important for the regulation of cell therapies in Brazil. The Brazilian Congress approved Law #11,105 on March 25, 2005 [3], which included topics related to genetically modified organisms (GMOs) and approval of the use of embryonic cells for research (including clinical trials). The Brazilian president published Decree #5591 on November 22, 2005 [4], which declared that ANVISA will regulate the research, production, and use of products derived from embryonic cells. This law aroused the interest of Brazilian society regarding cell therapy products. However, the General Prosecutor of the Republic of Brazil asked the Brazilian Supreme Court to suspend authorization of the use of embryos for these research purposes. The Supreme Court granted the request for an injunction, and the verdict that occurred in May 2008 stated that the existing law was constitutional and valid.

The Supreme Court deliberations contributed to the delay of the regulatory process for cell therapies, including the embryonic issue. Although the governmental stimulus for cell therapy research has been strengthened since 2002, ANVISA created a working group to draft an advanced cell therapy regulation, which was released in 2007 [5]. As a result, ANVISA published the ANVISA Board Resolution #9 of March 16, 2011 [6], which is the first health regulation for cell therapy in Brazil. This regulation is discussed further in Sect. 2.2 of this chapter.

Until 2009, all ANVISA efforts to regulate cell therapy were concentrated in blood, bone marrow, and reproductive cells. The implementation of ANVISA Board Resolution #9 of 2011 has resulted in the establishment of standards for production, stocking, and distribution of advanced cell therapy and cell derivatives. However, the regulations for the conduct of clinical trials and marketing authorization of cell therapies were not enforceable by ANVISA due to the question of the constitutionality of the commercialization of human substances, including cell therapy and cell derivatives. Article #199, Paragraph 4 of the Brazilian Constitution forbids the commercialization of any human-derived product [7]:

> Paragraph 4. The law shall provide for the conditions and requirements which facilitate the removal of organs, tissues and human substances for the purpose of transplants, research and treatment, as well as the collection, processing and transfusion of blood and its by-products, all kinds of sale being forbidden.

In addition, according to Brazilian Law #9279 of May 14, 1996, a patent cannot be granted for "all or part of living beings and biological materials found in nature, or even if isolated, including the genome or germplasm of any natural living being and the natural biological processes" [8].

This constitutional issue involving cell therapy thus remains an active area of discussion in ANVISA. Two public technical-scientific events have been held to discuss this topic. The first event was a workshop titled "Paradigms for Regulation of Advanced Products based on Human Cell and Tissue" occurred in December 2010 and served as preparation for the second meeting. Participants in this workshop included representatives from universities, CCT, as well as international guests from United States Food and Drug Administration, Ministry of Health from Austria, and a member of the European Union/Committee for Advanced Therapies. The second event, the National Seminar on Regulation in Advanced Cell Therapy, was held in October 2011 and was attended by scientists, regulatory personnel from the Brazilian ministries (Health, Industries and Commerce), lawyers, and a member of the parliament. Two different positions were discussed at this second meeting.

- One group's position is that the cell therapies should be regulated as transplants of tissues and organs or blood transfusions in Brazil, where ANVISA defines the general requirements for safety and quality for collecting, processing, storage and distribution of these products. No market authorization would be necessary, and the evaluation of clinical efficacy and intended use should be the responsibility of the Federal Councils of Medicine and Odontology. Therefore, commercialization would still be prohibited, but these products could be considered for patients, hospital, health insurance, and the public health system (the Unified

Health System [SUS]) to pay for production costs (collection, processing, distribution, injection, or infusion).

- Another group's position is that advanced cell therapies should be regulated as medicines, and they should be subject to review and approval by ANVISA, from the conduct of clinical trials to market authorization. Commercialization should be allowed, as it is now permitted for human albumin, immunoglobulin, and other blood derivatives. A constitutional modification should not be necessary since the constitutional principle of the "right to health" should override the prohibition on marketing since this prohibition would impede the use of this new technology by the Brazilian people.

Although this debate was not solved in these meetings and a consensus among the participants was not reached, these discussions reinforced the important role and leadership of ANVISA in the regulation of cell therapy.

The challenge and the complexity involved in formulating a body of regulations about advanced cell therapy and gene therapy products were recognized by the ANVISA Board Directory. This resulted in the publication of Ordinance #1700 on December 12, 2012 [9], creating the ANVISA Chamber for Advanced Cell Therapy (CAT). The ANVISA CAT is responsible for advising the ANVISA Board Director in establishing regulations for advanced cell and gene therapies, including clinical trials. It has representatives from various sectors of society, including the Ministry of Health, scientific societies, researchers, patient groups, the National Research Ethics Committee (CONEP) of the National Health Council and the Federal Councils of Medicine and Odontology.

Since 2013, the ANVISA CAT has been working on a draft regulation for clinical trials for advanced cell therapies. In Brazil, clinical trials for medicines undergo a bicameral evaluation (submitted to ANVISA for safety and efficacy evaluation and to CONEP for ethical evaluation). ANVISA has proposed the same model for clinical trials involving advanced cell therapy and gene therapy products.

It is important to mention that if use of a GMO is involved, the National Technical Commission for Biosafety (CTNBio) needs to be included as a regulatory institution, according to Law #11,105 [3]. The CTNBio, which is part of the Ministry of Science and Technology, is a collegiate multidisciplinary consultative and deliberative group that provides technical and advisory support to the federal government regarding the formulation, updating, and implementation of the biosafety of GMOs and their derivatives. This commission is also responsible for establishing technical safety standards and technical advice for granting permission for activities involving research and commercial use of GMOs and their derivatives, based on an evaluation of the risk to human health and to the environment. It is composed of 27 Brazilian citizens with Ph.D. degrees that are appointed by the Minister of State for Science and Technology, Health, Environment, and others. These citizens must be recognized for their technical competence, remarkable performance and scientific knowledge, and outstanding professional activities in areas of biosafety, biotechnology, biology, human and animal health, or the environment.

2 The Health Regulatory Framework for Advanced Cell Therapy Products in Brazil

2.1 Hematopoietic Stem Cell Regulations for Bone Marrow Transplant

Hematopoietic stem cell from bone marrow and umbilical cord blood specifically used for bone marrow transplant are under regulation of ANVISA Board Resolution #56 of December 16, 2010 [10]. This is not considered until now as advanced cell therapy and it is not a scope of this chapter.

2.2 Advanced Cell Therapy Product Regulations: ANVISA Board Resolution #9 of 2011

The ANVISA Board Resolution #9 of 2011 [6] provides technical standards for the operation of the CCT that involve human cells and their derivatives, for clinical trials and for approved intended use. The objective of this regulation is to establish technical and sanitary requirements for the collection, processing, storage, quality control tests, disposal, release for use, and transportation of human cells and their derivatives for use in clinical trials and therapy.

The resolution applies to all institutions or commercial establishments, public or private, carrying out activities with human cells and their derivatives for the purpose of clinical trials and approved intended use, with the exception of the following:

(a) Basic research and preclinical use
(b) Hematopoietic stem cells for use in conventional bone marrow transplants
(c) Stem cells, germinal tissue, and human embryos for reproductive purposes

This resolution defines the CCT as the responsible party throughout the production cycle of the cells and their derivatives, to include the collection, processing, storage, quality control tests, disposal, release for use, and transportation of cell therapy products.

This resolution does not address the conduct of clinical trials or evaluation of intended use of the product. It asserts that the release for use should precede the authorization by CONEP for the conduct of a clinical trial and by the Federal Councils of Medicine or Odontology that should evaluate the efficacy of intended use.

Each CCT can be licensed to work as Type 1 or Type 2 according to its activities. The Resolution specifies that the CCT is classified as Type 1 only when activities performed are with fresh or cryopreserved adult human cells for autologous use. The cultivation and substantial manipulation of cells are not permitted in a Type 1 CCT.

Substantial manipulation is defined as all processing of biological material that does not set minimal manipulation. Minimal manipulation is defined as the processing of biological material in a manner that does not alter the original relevant characteristics of the cells.

In addition to those performed by a Type 1 CCT, a Type 2 CCT performs more complex activities such as manipulation of human embryonic stem cells, allogeneic use, cultivation, and substantial manipulation. If a Type 1 CCT plans to develop activities not included as minimal, it needs to ask for a Type 2 CCT license.

A quality control process for the cells is a prerequisite before releasing the product for human use. The CCT is responsible for ensuring the safety and quality of the cell therapy products by performing the following controls:

(a) Microbiological testing
(b) Tests for infectious diseases
(c) Pyrogenicity tests, when appropriate
(d) Counting and cell viability
(e) Cell phenotyping, when appropriate
(f) Genetic control (i.e., cells in culture, expanded, genetically modified, and/or transduction proteins)
(g) Functional tests, when appropriate
(h) Identification of human leukocyte antigens (HLA), when appropriate

In order to collect data about the activities performed by each CCT, ANVISA requires an annual production report informing the amount of the following:

(a) Biological specimens or samples received for processing
(b) Biological specimens or samples processed for cryopreservation
(c) Total of biological products (cells or derivatives) released for therapeutic use
(d) Biological products (cells or derivatives) that were discarded and the reason for disposal

A Good Manufacturing Practice (GMP) Certification issued by ANVISA is not needed for CCTs, unlike what is required for manufacturers of vaccines and biological medicines. However, as with the regulation for blood banks and tissue banks, although a GMP Certification issued by ANVISA is not necessary, a quality assurance system must be in place in all CCTs to ensure GMP according to the requirements of ANVISA Board Resolution #9 of 2011 [6].

2.3 Gene Therapy Products

At this moment, there is no ANVISA regulation targeting gene therapy products for human use. However, any activities involving GMOs must be authorized by CONEP (for clinical trials) [11] and CTNBio (for basic research, preclinical studies, and clinical trials) [3].

3 Conclusion

The development of advanced cell therapies in Brazil has progressed rapidly in the last decade. Since 2005, a total of 56.8 million US dollars toward various grants to enable active research in this field has been funded by the Brazilian government (Table 1). These investments have resulted in an increase in scientific production, patents, and clinical trials in Brazil, with the eventual goal of benefiting the health of the Brazilian population.

The current regulatory framework for advanced cell therapy and gene therapy products is intended to handle the challenge of regulating products for which multiple institutions are involved (each with different, sometimes overlapping, responsibilities) and to overcome the unsolved questions about the commercialization of advanced cell therapies and gene therapies. These topics can become a disincentive for private investors and for the creation of new research groups in the future.

This multifaceted range of institutions involved, in addition to the laws and constitutional issues, reflects the complexity involved in the regulation of advanced cell therapies and gene therapies in Brazil. However, despite the challenges, ANVISA has achieved progress in this area and has been a protagonist in discussions regarding the regulation model that should be adopted by the Brazilian society.

Disclaimer The stream of arguments, findings, and conclusions are the author's entire responsibility, not necessarily expressing the institutional definitions of the ANVISA, Ministry of Health, and the Federal Government of Brazil.

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