Investigational New Drug Applications for Cell Therapy Products

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1 Key Concepts

1. The FDA is the federal agency that decides which drugs, biologics, and medical devices are safe and efficacious, determinations upon which the agency decides if a product can be marketed in the USA.
2. The drug approval process in the USA is standardized by FDA review. It consists of preclinical testing and Phases I through IV of clinical testing.
3. The Investigational New Drug (IND) application is submitted by the study sponsor to the FDA to begin clinical trials in humans.
4. The IND should be amended as necessary. There are four types of documents used to amend the IND:
   - Clinical trial amendments.
   - Information amendments.
   - IND safety reports.
   - IND annual reports.
5. After sufficient evidence is obtained regarding the drug's safety and effectiveness, the sponsor will submit a New Drug application/Biologics Licensing Application to the FDA requesting approval of the agent for marketing.
6. An orphan drug is one that is used for the treatment of a rare disease, affecting fewer than 200,000 people in the USA, or one that will not generate enough revenue to justify the cost of research and development.
7. In addition, to review by the FDA, research clinical trials also require a review from Institutional Review Boards and as appropriate, Institutional Biosafety Committees.

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2 Introduction

The FDA monitors the manufacture, import, transport, storage, and sale of 25% of all goods purchased in the USA annually. The centers of the FDA involved in regulating biologics, drugs, and medical devices used in humans are as follows [1]:

- Center for Biologics Evaluation and Research (CBER).
- Center for Drug Evaluation and Research (CDER).
- Center for Devices and Radiological Health (CDRH) [2].

Since this chapter focuses on cellular therapies, we will focus on CBER which is where the majority of cellular therapies are reviewed. The FDA definition of cellular therapy products includes cellular immunotherapies, cancer vaccines, and both autologous and allogeneic cells used for therapeutic indications [3]. To date, although there is significant research in the use of cellular products as therapeutic treatments, less than 20 cellular products have been approved by the FDA [4]. Interestingly, a large number of cellular product INDs are submitted annually, and, in fact, in 2015, the number approached 250 IND submissions. Also interesting is that unlike drugs, where the vast majority of submissions are made by Biopharmaceutical companies, the majority of INDs for cellular therapies are submitted by noncommercial entities, primarily academic investigators and institutions [5].

3 History of Drug Development Regulation in the USA

For more than a century after the Declaration of Independence, drug products were not regulated in the USA. Available drugs were often ineffective, addictive, toxic, or even lethal. During this same period, physicians were not licensed and nearly anyone could practice medicine. The public was, for the most part, responsible for their own well-being when evaluating which products they would use.

The evolution of drug regulations in the USA is a study in human tragedy with medicinal crises resulting in the development of many of the laws regulating drug development, preparation, and distribution. Not until 1962, with the passage of the Kefauver-Harris Drug Amendment was there a requirement that a manufacturer had to demonstrate proof of efficacy, as well as safety, prior to marketing any new drug. [6]. Based on this and other laws, the FDA has assumed a large role in assessing the safety and efficacy of drug products prior to their distribution in the USA [7].

4 The Drug Approval Process

4.1 Preclinical Testing

The drug approval process in the USA is standardized by FDA review. It consists of preclinical testing and Phases I through IV of clinical testing. The first step in the process is preclinical testing [8]. This testing is conducted either in vitro (in a test tube or culture dish; outside of a living organism) or in vivo (within a living organism). Before filing an IND for an investigational new drug, preclinical studies should be conducted to establish feasibility of the use of the product and as possible to establish a safety profile supporting the use of the product in clinical studies. There are limitations to preclinical studies conducted in cellular therapies that relate rather specifically to difficulties identifying the appropriate animal species and animal models for cellular therapies. This makes traditional pharmacokinetic (PK) studies not feasible for cellular therapy products [9]. The FDA has provided specific guidance in this area entitled: Preclinical Assessment of Investigational Cellular and Gene Therapy Products [10].

4.2 Investigational New Drug Application

After the preclinical testing is completed, the sponsor will file an Investigational New Drug (IND) application with the FDA. The IND is the application by the study sponsor to the FDA to begin clinical trials in humans. As noted, the sponsor can be a biopharmaceutical company, but frequently in cellular therapy clinical trials, the sponsor will be an individual investigator who will file an IND and serve as a sponsor-investigator [5]. A commercial IND is one for which the sponsor is usually either a biopharmaceutical company or one of the institutes of the NIH. In addition, the FDA may designate any IND as commercial if it is clear that the sponsor intends the product to be commercialized at a later date. A sponsor-investigator IND is submitted when an investigator plans to use an approved drug for a new indication (i.e., one that is outside the package labeling) or an unapproved product in the context of a clinical trial. The IND requirements for the sponsor-investigator are generally the same as those for any other sponsor [11]. This caveat for commercial INDs relates to one of the information technology initiatives that the FDA has adopted in an attempt to facilitate the regulatory review process. Specifically, an important initiative of the FDA has been the development of systems allowing for electronic submission, management, and review of regulatory information [12]. The FDA mandated that all NDA, Biologics Licensing Applications (BLA), Abbreviated New Drug Application (ANDA), and Drug Master Files (DMF) be in the Electronic Common Technical Document (eCTD) format by May 2017 and all commercial Investigational New Drug Applications (INDs) be in eCTD format by May 2018 [13, 14]. This is a significant difference not only in how submissions are sent to the

FDA but also the format of those submissions. In this chapter we will focus on non-electronic submissions submitted in what is referred to as the ten-point format as specified in 21CFR312.23.

An IND is not required if the drug to be studied is marketed in the USA and all of the following requirements are met:

1. The clinical trial is not to be reported to the FDA in support of a new indication.
2. The clinical trial does not involve a different dose, route, or patient population that increases the risk to patients.
3. IRB approval and informed consent are secured.
4. The clinical trial will not be used to promote the drug's effectiveness for a new indication.

The FDA has developed a guidance document specifically to assist in determining whether or not an IND is required. However, in situations where it is unclear whether an IND is required or not, a call to the FDA is the best way to determine the appropriate way to proceed [15].

In recent years, there have been several therapeutic products including cellular therapies developed that depend on the use of an in vitro companion diagnostic device (or test) for their safe and effective use. It is important to note that in this situation, the in vitro device should be approved or cleared concurrently by FDA for the use indicated in the therapeutic product labeling. To be clear, this might require the clinical trial of the diagnostic device under an Investigational Device Exemption (IDE), while the therapeutic product is being studied under an IND. If the diagnostic device and therapeutic product are to be studied together to support their respective approvals (or clearance in the case of a device), both products can be studied in the same investigational clinical trial if the clinical trial has been developed and conducted in a manner that meets both IND and IDE regulations [16]. One other interesting issue related to devices is the use of a mobile app (i.e., a software application on a mobile platform such as an iPhone or Android) for the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body. In these situations, the mobile app can be considered to be a medical device subject to IDE regulations [17]. IDE regulations and components will not be further discussed in this chapter; however, the applicable regulations can be found in 21CFR 812, and the FDA has extensive guidance regarding these products and their development [18].

4.3 Contents of IND

As specified in 21CFR212.23, an IND application needs to contain the following information:

- **Cover sheet:** Form 1571 (available at the FDA website under Forms, http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm). This form

identifies the sponsor, documents that the sponsor agrees to follow appropriate regulations, and any involved clinical research organization (CRO). This is a legal document.

- **Table of contents.**
- **Introductory statement:** States the name, structure, pharmacologic class, dosage form, and all active ingredients in the investigational drug; the objectives and planned duration of the investigation should be stated here.
- **General investigational plan:** Describes the rationale, indications, and general approach for evaluating the drug, the types of trials to be conducted, the projected number of patients that will be treated, and any potential safety concerns; the purpose of this section is to give FDA reviewers a general overview of the plan to study the drug.
- **Investigator's brochure:** An information packet containing all available information on the drug including its formula, pharmacologic and toxicologic effects, pharmacokinetics, and any information regarding the safety and risks associated with the drug. It is important that this brochure be kept current and comprehensive; therefore, it should be amended as necessary. The investigator's brochure may be used by the investigator or other healthcare professionals as a reference during the conduct of the research clinical trial.
- **Clinical trial.**
  - *Objectives and purpose:* A description of the purpose of the trial (a typical Phase I objective would be to determine the maximum tolerated dose of the investigational drug, whereas a typical Phase III objective would be to compare the safety and efficacy of the investigational drug to placebo or standard therapy).
  - *Investigator data:* Provides qualifications and demographic data of the investigators involved in the clinical trial (may be presented on Form 1572 (available at the FDA website under Forms, http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm).
  - *Patient selection:* Describes the characteristics of patients that are eligible for enrollment in the trial and states factors that would exclude the patient.
  - *Clinical trial design***:** Describes how the clinical trial will be completed; if the clinical trial is to be randomized, this will be described here with a description of the alternate therapy including a description of the control group [19].
  - *Dose determination:* Describes the dose (with possible adjustments) and route of administration of the investigational drug; if retreatment or maintenance therapy of patients is allowed, it will be detailed in this section.
  - *Observations*: Describes how the objectives stated earlier in the clinical trial are to be assessed.
  - *Clinical procedures*: Describes all laboratory tests or clinical procedures that will be used to monitor the effects of the drug in the patient; the collection of this data is intended to minimize the risk to the patients.
  - *IRB approval for clinical trial:* Documentation of this approval is not required as part of the IND application process; however, Form 1571 does state that an

IRB will review and approve each clinical trial in the proposed clinical investigation before allowing initiation of those studies [2].

- **Chemistry, Manufacturing, and Control Data.**
  - *Drug substance*: Describes the drug substance including its name, biological, physical, and chemical characteristics; the address of the manufacturer; the method of synthesis or preparation; and the analytical methods used to assure purity, identity, and the substance's stability [20].
  - *Drug product:* Describes the drug product, including all of its components; the address of the manufacturer; the analytical methods used to ensure identity, quality, purity, and strength of the product; and the product's stability.
  - *Composition, manufacture, and control of any placebo used in the trial*: The FDA does not require that the placebo be identical to the investigational drug; however, it wants to ensure that the lack of similarity does not jeopardize the trial.
  - *Labeling*: Copies of all labels and labeling used for the drug substance or product and packages as it will be provided to each investigator. Labels in this context is the information affixed to the product and used to identify the contents, while labeling in this context relates to product information including prescribing information.
  - *Environmental assessment*: Presents a claim for categorical exclusion from the requirement for an environmental assessment (a statement that the amount of waste expected to reach the environment may reasonably be expected to be nontoxic).
- **Pharmacology and Toxicology Data.**
  - *Pharmacology and drug disposition*: Describes the pharmacology, mechanism of action, absorption, distribution, metabolism, and excretion of the drug in animals and in vitro.
  - *Toxicology*: Describes the toxicology in animals and in vitro.
  - A statement that all nonclinical laboratories involved in the research adhered to Good Laboratory Practice (GLP) regulations.

The Letter of Authorization (LOA) to cross reference a DMF, IND, or NDA (referred to in item 9 on page 1 of Form 1571) is required when the investigational product (or some component of the investigational product) being used in the research is being supplied by a manufacturer other than the study sponsor. The original holder of the IND/NDA/DMF prepares the LOA. A LOA is frequently required when two companies are working together toward the development of a product.

Finally, proof of compliance with the requirements of ClinicalTrials.gov through submission of Form 3674 (available at the FDA website under Forms: http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm) is required as part of the IND [21].

4.4 Amendment of IND

The IND should be amended as necessary. There are four types of documents used to amend the IND:

5. Clinical trial amendments: submitted when a sponsor wants to change a previously submitted clinical trial or add a new clinical trial to an existing IND [22].
6. Information amendments: submitted when information becomes available that would not be presented using a clinical trial amendment, IND safety report, or annual report (e.g., new chemistry data) [23].
7. IND safety reports: Reports clinical and animal adverse reactions; reporting requirements depend on the nature, severity, and frequency of the experience. The following definitions are used to help evaluate adverse reactions.

- *Suspected adverse reaction:* An adverse reaction for which there is evidence to suggest a causal relationship between the drug and the adverse event.
- *Serious adverse event or serious suspected adverse reaction:* An event that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- *Unexpected adverse event or unexpected suspected adverse reaction:* An adverse reaction that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling but differs from the event because of greater severity or specificity.
- For serious and unexpected suspected adverse reactions, the sponsor must report the event to the FDA in writing within 15 calendar days. Those events that are serious and unexpected require notification of the FDA within 7 calendar days. The written reports should describe the current adverse event and identify all previously filed safety reports concerning similar adverse events. The written report may be submitted as a narrative or as Form 3500A (available at http://www.fda.gov/safety/medwatch/howtoreport/downloadforms/default.htm) [24, 25].

8. Annual Reports.

These are submitted within 60 days of the annual effective date of an IND. It should describe the progress of the investigation including information on the individual studies, summary information of the IND (summary of adverse experiences, IND safety reports, preclinical studies completed in the last year), relevant developments in foreign markets, and changes in the investigator's brochure [26].

Each submission to a specific IND is required to be numbered sequentially (starting with 000). A total of three sets (the original and two copies) of all submissions to an IND file (whether a new IND or revisions to an existing IND) are sent to the FDA [8].

4.5 IND Submission

Once submitted to the FDA, the IND will be forwarded to the appropriate review division based on the therapeutic category of the product. Examples of the different divisions include oncology products, hematology products, anti-infective products, and medical imaging products. Following submission, the IND and clinical trial will be assigned to a review team that includes the following individuals:

- The regulatory project manager (RPM): Contact information for the RPM is provided in the letter sent to the applicant acknowledging receipt of the application. This will be the sponsor's (see below) primary FDA contact person. Each application that is submitted is assigned an RPM. If the RPM is changed during the course of the review, the applicant is notified by the new RPM.
- A chemistry, manufacturing, and control (CMC) reviewer.
- A nonclinical pharmacology/toxicology reviewer.
- A clinical reviewer.
- Other reviewers as needed (e.g., statisticians, epidemiologists, site inspectors, patient representatives) [27].

The FDA has 30 days after receipt of an IND to respond to the sponsor. The sponsor may begin clinical trials if there is no response from the FDA within 30 days [28]. The FDA delays initiation of a new clinical trial or discontinues an ongoing clinical trial by issuing a clinical hold. Clinical holds are most often used when the FDA identifies an issue (through initial review or through later submissions) that the agency poses a significant risk to the subjects. After this issue has been satisfactorily resolved, the clinical hold can be removed, and the investigations can be initiated or resumed [29].

4.6 Inactivation, Withdrawal, and Termination of an IND

A sponsor may withdraw an IND at any time. To do so all clinical investigations under the IND must be stopped, all investigators must be notified, and all investigational product supplies must be returned to the sponsor or destroyed. If the IND was withdrawn for safety reasons, the FDA, all IRBs, and all investigators must be notified of the reason for the withdrawal [30].

An IND may be inactivated by the sponsor or by the FDA if no subjects are entered into the related clinical trials for 2 years or more. If an IND is placed on

inactive study, all investigators should be notified and all stocks of drug supplies should be returned to the sponsor or discarded. The sponsor will not be required to submit annual reports which an IND is on inactive status. The IND can be reactivated by the sponsor by submitting an IND amendment outlining the plans for the IND and any relevant protocols [31].

An IND may be terminated by the FDA for IND deficiencies, deficiencies in the conduct of an IND, or the IND remains on IND inactive status for 5 years or more. The FDA will notify the sponsor of the plan to terminate an IND, and the sponsor will have 30 days to provide a written explanation or provide a correction that allows the IND to remain in active or inactive status [32].

4.7 Phases of Clinical Trial

There are four phases of clinical trials. Clinical studies generally begin cautiously. As experience with the agent grows, the dose and duration of exposure to the agent may also increase. The number of patients treated at each phase of clinical trial, and the duration of the studies, can vary significantly depending on statistical considerations, the prevalence of patients affected by the disease, and the importance of the new drug. However, some general guidelines regarding the four phases of clinical testing are presented below.

4.7.1 Phase I

A Phase I trial is the first use of the agent in humans. As such, these studies are usually initiated with cautious (low) doses and in a small numbers of subjects. Doses may be increased as safety is established. A Phase I clinical trial will usually include 20–80 subjects who receive the investigational product. Phase I trials last an average of 6 months to 1 year. The purpose of a Phase I trial is to determine the safety and toxicity of the agent. Frequently these trials include a pharmacokinetic portion. These trials assist in identifying the preferred route of administration and a safe dosage range. When possible, these trials are initiated in normal, healthy volunteers. This allows for the evaluation of the effect of the drug on a subject who does not have any preexisting conditions. In situations in which this is not practical, such as oncology drugs, in which the drug itself can be highly toxic, these drugs are usually reserved for patients who have exhausted all conventional options.

4.7.2 Phase II

A Phase II trial is one in which the drug is used in a small number of subjects who suffer from the disease or condition that the drug is proposed to treat. The purpose of a Phase II trial is to evaluate the efficacy of the agent. Data from the Phase I trial,

in vitro testing, and animal testing may be used to identify which group of patients is most likely to benefit from therapy with this agent. Phase II trials usually treat between 100 and 200 patients and will average about 2 years in duration. Following Phase II trials, study sponsors will frequently assess these preliminary results and predicted marketability of the product prior to initiating the larger and more expensive Phase III trials.

4.7.3 Phase III

Phase III trials build on the experience gained during the Phase II trials. The purpose of a Phase III clinical trial is to further define the efficacy and safety of the agent. Frequently, in Phase III studies, the new agent is compared to current therapy. These trials are usually multicenter studies, generally treat from several hundred to 3000 patients, and the clinical trial will usually last about 3 years (although an individual subjects participation may be significantly shorter). Usually, some of the Phase III trials will be considered pivotal studies and will serve as the basis for the NDA/BLA for a medicinal product's marketing approval [33].

4.8 Biological License Application/New Drug Application

After sufficient evidence is obtained regarding the drug's safety and effectiveness, and Phase III trials have been completed, the sponsor will submit a BLA (in the case of drugs, it is referred to as an NDA) to the FDA requesting approval of the medicinal product for marketing. Except as noted for products being developed using accelerated approval pathways, the FDA requires the completion of two well-designed, controlled clinical trials prior to submission to the FDA. However, the sponsor will include information gathered from all of the clinical trials to show that the medicinal product is safe and effective and to describe the pharmacology and pharmacokinetics of the drug. The BLA/NDA will include all preclinical data, clinical data, manufacturing methods, product quality assurance, relevant foreign clinical testing (or marketing experience), and all published reports of experience with the medicinal agent (whether sponsored by the company or not). A proposed package insert will be supplied as well [34].

4.8.1 Review of New Drug Application

The BLA/NDA will be distributed to the same FDA review division assigned, while the product was under IND status. As noted, these divisions are based on the therapeutic group of the medicinal agent. The same reviewer may be assigned to review the IND and the BLA/NDA [10].

The speed at which the BLA/NDA will be processed is to some extent determined by the classification the drug receives during its initial review. Each agent is rated with a number-letter designation that evaluates two separate aspects of the agent. The number portion of the rating is associated with the uniqueness of the drug product (ranging from 1 for a NME to 7 for a drug that has already been marketed, but without an approved BLA/NDA), and the letter portion of the rating is associated with the therapeutic potential of the medicinal agent. The P (priority review) designation is given to drugs that represent a therapeutic advance with respect to available therapy, whereas an S (standard review) is given to drugs that have little or no therapeutic gain over previously available drugs. BLA prioritization is slightly simplified but similar [35].

During the review process, the FDA may utilize one of its prescription drug advisory committees to help review the NDA. These committees are composed of experts who provide the agency with independent, nonbinding advice and recommendations regarding the NDA. Currently the FDA has 31 advisory committees, many of which are composed of various panels. Examples of such committees include the allergenic products advisory committee and the cellular, tissue, and gene therapies advisory committee [36]. Within 180 days of receipt of an NDA, the FDA will review the application and send the applicant an approval letter or a complete response letter [37]. When an approval letter is sent, the drug is considered approved as of the date of the letter [38]. A complete response letter is issued to let the sponsor know that the review period for the drug is complete but that the application is not yet ready for approval. It will describe specific deficiencies and when possible, identify recommended actions that the sponsor might take to address those deficiencies. In response to the complete response letter, the sponsor amends the NDA, withdraws the NDA, or requests a hearing with the FDA to clarify whether grounds exist for denying the approval of the application [39].

4.9 Expanded Access to Investigational Drugs for Treatment Use

The FDA has historically received considerable criticism relative to the time taken for product review. They have implemented many initiatives to address these criticisms. The most recent initiative implemented by the FDA is referred to as "expanded access to investigational drugs for treatment use." The expanded access rule clarifies existing regulations and adds new types of expanded access for treatment use. Specifically, the rule allows for investigational drugs to be used for treatment in patients with serious or life-threatening diseases where there is no other comparable or satisfactory alternative therapy. The FDA defines immediately life-threatening conditions as those where death is likely to occur within a matter of months or in which premature death is likely without early treatment. Serious conditions are defined as those associated with morbidity that has substantial impact on day-to-day

functioning [40]. The rules specify different requirements for expanded access for individual patients in emergencies; intermediate-sized patient populations; and larger populations under a treatment clinical trial or treatment IND [41].

The FDA must determine that, in addition to the patient having a serious or immediately life-threatening disease for which there is no satisfactory alternative therapy, the potential patient benefit must outweigh the risk and that the requested use will not interfere with clinical investigations that could support marketing approval of the expanded access use. In all cases, an expanded access submission to the FDA is required. The submission may be a new IND or a clinical trial amendment to an existing IND (see the above explanation). Except as justified by emergency use guidelines further discussed in this chapter, all other regulations governing new INDs and clinical trial amendments, including regulations regarding clinical trial initiation, adverse reaction reporting, and annual reports, are identical to that described for standard INDs and described elsewhere in this chapter [42].

For individual patients, submission requirements must include information adequate for the FDA to determine that the risk to the person from the investigational drug is not greater than the probable risk from the disease and that the patient cannot obtain the drug under another type of IND. Treatment is generally limited to a single course of therapy for a specified duration unless the FDA expressly authorizes multiple courses or chronic therapy. Individual patient expanded access submissions can be made in accordance with the standard submission requirements for an IND as outlined elsewhere in this chapter, or they may be submitted utilizing Form 3926. In this type of submission, the FDA does allow for emergency procedures if the patient must be treated before a written submission can be made. In that situation, the FDA may authorize the emergency use by telephone. The sponsor must agree to submit an expanded access submission within 15 business days of the FDA's authorization of the use [43]. In addition, although the FDA must authorize emergency use of a test article (investigational drug), 21CFR56.104 allows for treatment to occur without prospective IRB approval in situations where there is insufficient time to obtain such review. In such situations the emergency use must be reported to the IRB within 5 days after the treatment. Newer guidance from the FDA allows an investigator submitting an individual patient expanded access IND to request a waiver from full IRB review under 21CFR56.105 when the investigator obtains concurrence by the IRB chairperson or another designated IRB member before treatment use begins [44].

For intermediate patient populations, there must be sufficient evidence that the drug is safe at the dose and duration proposed for treatment and that there is at least preliminary clinical evidence of the effectiveness of the drug. The sponsor must also indicate whether the drug is being developed and define the patient population. If the drug is being studied in a clinical trial, the sponsor must explain why the expanded access patient population cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in those patients [45].

The treatment IND, or treatment clinical trial, is a way the FDA has allowed for increased accessibility of experimental drugs for widespread treatment use. The drug must be investigated in a clinical trial under an IND designed to support a

marketing application for the expanded access use, or if all clinical trials have been completed, the sponsor must be actively pursuing marketing approval of the drug for the expanded access use. When the expanded access use is for an immediately life-threatening disease, the available scientific evidence (usually clinical data from Phase II or Phase III trials) must provide reasonable assurance that the drug may be effective for the expanded access use and would not expose patients to significant risk [46].

5 Right to Try

The Right to Try Act was signed into law May 30, 2018. This law is another way for patients with life-threatening conditions without other alternatives, and unable to participate in a clinical trial, to obtain access to certain unapproved treatments. Right to Try treatments are those that are defined as eligible investigational drugs according to the following criteria:

- A Phase I trial has been completed.
- The product is not FDA approved for any use.
- An application has been filed with the FDA that will form the basis for a claim of effectiveness, and an IND has been submitted to the FDA.
- Active development of the product is ongoing and has not been discontinued by the manufacturer or placed on hold by the FDA.

Neither the FDA nor an IRB reviews the Right to Try Act uses. A physician working with a patient will contact the sponsor of the investigational product to determine if it is an eligible investigational drug under the Right to Try Act. The Right to Try Act does not require a sponsor to provide an eligible investigational drug to an eligible patient [47, 48].

6 Cost of Using Investigational Drugs

The FDA allows the manufacturer to charge for an investigational drug under certain conditions. The sponsor must obtain prior written authorization from FDA to charge for an investigational drug. In order to charge for an investigational drug, the sponsor must provide evidence that the drug has a potential clinical benefit that would provide a significant advantage over available products, demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe, and demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The sponsor may only charge recovery costs for direct cost attributable to making the investigational drug, including raw materials, labor, nonreusable supplies, and equipment used to manufacture the drug or costs to acquire the drug from another

manufacturer or to ship and handle the drug. In addition, for expanded access studies for intermediate-sized patient populations or treatment IND/clinical trials, a sponsor may recover the cost of monitoring the expanded access IND or clinical trial, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access IND [49–51].

7 Expedited Review for New Drugs

As previously noted, the FDA has received considerable criticism for slow review times. Over the past two decades, the FDA and the federal government have initiated many reforms and initiatives designed to address these criticisms. Included in these reform acts are the Prescription Drug User Fee Acts (PDUFA); the Food and Drug Administration Modernization Act (FDAMA) of 1997; the Food and Drug Administration Amendments Act (FDAAA) of 2007, the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 signed into law on July 9, 2012; and most recently the twenty-first Century Cures Act, signed into law in December 2016 [52–56]. These acts and other initiatives have resulted in expedited review pathways as follows:

9. Priority review: The FDA determines a drug will potentially provide a significant advance in medical care and sets a target to review the drug within 6 months instead of the standard 10 months.
10. Fast-track review: The FDA determines that a drug can treat unmet medical needs. Fast-track speeds new drug reviews, for instance, by increasing the level of communication the FDA allocates to developers and by enabling developers to use a rolling review process such that portions of an application can be reviewed ahead of the submission of the full application.
11. Breakthrough therapy: Allows for expedited development and review of drugs which are intended to treat serious conditions and which may demonstrate a substantial improvement over available therapy.
12. Regenerative Medicine Advanced Therapy (RMAT) designation: The CBER gives this designation to certain human gene therapies and xenogeneic cell products if it determines being that the product is intended for use in serious or life-threatening illness and preliminary clinical evidence indicates that the drug has the potential to address an unmet medical need for such disease or condition. RMAT designation includes all the benefits of the fast-track and breakthrough therapy designation programs [57].

These designations relate directly to an IND and become an integral part of the review of the product being studied under the IND.

Aside from looking at review times, the FDA has also been concerned about the increasing difficulty in drug and biologic development. To attempt to address this issue, the FDA launched a new initiative in March 2004 called the Critical Path Initiative. Having identified an increasingly large gap between laboratory

discoveries and new treatments for patients with serious diseases such as diabetes, cancer, and Alzheimer disease, the Critical Path Initiative is the FDA's attempt to facilitate modernization of the sciences and improve regulatory decision-making. The FDA has been working with the public, the pharmaceutical industry, other regulatory agencies, and academia to identify projects that they feel are most likely to help the drug development process from test tube to bedside [58].

More recently, as a result of FDASIA, the FDA has increased their focus on patient engagement [55]. A notable example of this initiative is a patient advocacy-initiated draft guidance submitted to the FDA to help accelerate the development and review of potential therapies for Duchenne syndrome. A major point of emphasis was that the parents of children affected by Duchenne syndrome were willing to accept a higher-risk profile for potential therapies even those in that may improve patient quality of life without prolonging life [59, 60].

Overall, the goal of all of the abovementioned initiatives is to review priority drugs in 6 months and standard drugs within 10 months, with an emphasis on improving consistency and transparency of the review process [61].

8 Phase IV Post-Marketing Surveillance

After the drug has been approved, post-marketing studies may be initiated. They are conducted for the approved indication but may evaluate different doses, the effects of extended therapy, or the drug's safety in patient populations that were not represented in premarketing clinical trials. The final phase of clinical trial is referred to as Phase IV trials. These Phase IV trials may be requested by the FDA, or they may be initiated by the sponsor in an attempt to gather more data on the safety and efficacy of the drug or to identify a competitive advantage of the drug over other available therapies.

9 Risk Evaluation and Mitigation Strategies (REMS)

In some situations, the FDA may actually approve a product with restrictions limiting use to certain facilities or providers or limiting the patient population to only those who have demonstrated certain performance on specified medical procedures [62, 63]. Specifically, the FDA has started to utilize Risk Evaluation and Mitigation Strategies (REMS) when they determine that safety measures are needed beyond the labeling to ensure that a drug's benefits outweigh its risks. REMS can be required before or after a drug is approved. REMS are developed by drug sponsors; however, the FDA reviews and approves them. Factors that are considered in determining the need for a REMS include the following [64]:

- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
- The expected benefit of the drug with respect to the disease or condition.
- The seriousness of the disease or condition that is to be treated with the drug.
- Whether the drug is an NME.
- The expected or actual duration of treatment with the drug.
- The estimated size of the population likely to use the drug.

The REMS may include the following components: a medication guide (patient package insert) and a communication plan (for providing key information to health care providers). The FDA may also require elements to assure safe use (ETASU) if the drug has been shown to be effective but is associated with a specific serious risk. Sample ETASU components include required training or certifications for healthcare providers, limitations on healthcare settings where the drug can be infused, dispensing the drug only with evidence of safe conditions (e.g., specific laboratory results), monitoring of drug use by the patient, and enrollment of the patient on a registry. The REMS must be assessed for adequacy at least by 18 months, 3 years, and 7 years after approval [65]. As an example, the product Axicabtagene Ciloleucel (trade name YESCARTA) was approved to treat certain types of non-Hodgkin lymphoma. The product however may cause side effects that are life-threatening and require intensive interventions including treatment with the product tocilizumab. Due to these risks, the drug was approved with a requirement for a REMS. The goal of the FDA-mandated REMS is to ensure that individuals who prescribe, dispense, and administer YESCARTA are aware of how to manage the toxicities, ensuring that hospitals and their associated clinics that dispense the product are certified and have onsite access to tocilizumab. The REMS therefore requires that hospitals and their associated clinics must be enrolled in the YESCARTA REMS program to be able to dispense YESCARTA. Additionally, all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA must be trained on the REMS program requirements and must successfully complete a YESCARTA REMS program knowledge assessment [66, 67].

10 The Orphan Drug Act

The Orphan Drug Act was passed in 1983 and provides incentives for manufacturers to develop orphan drugs. An orphan drug is one used for the treatment of a rare disease, affecting fewer than 200,000 people in the USA, or one that will not generate enough revenue to justify the cost of research and development. There are currently more than 7000 rare diseases impacting approximately 30 million Americans [68].

The Orphan Drug Act is administered by the FDA's Office of Orphan Products, and the related program has enabled the development and marketing of over 600

drugs and biologic products for rare diseases since its inception in 1983 [69]. Of note, although to qualify for consideration as an orphan drug, a product must be under evaluation as part of an IND; the review and approval process for an orphan drug designation is separate from that of the IND. The orphan drug designation (also known as the orphan status) is awarded only if both the drug and the disease meet certain qualifications.

The orphan drug designation provides the following incentives:

- **Tax incentives***:* The sponsor is eligible to receive a tax credit money spent on research and development of an orphan drug.
- **Waive filing fees:** The sponsor is eligible to file for a waiver from the application fee associated with the review of an NDA.
- **Clinical trial assistance***:* If a sponsor can show that a drug will be used for a rare disease, the FDA will provide assistance developing the preclinical and clinical plan for the product.
- **Grants and contracts***:* The FDA budget may allot money for grants and contracts to be used in developing orphan drugs. The current annual budget for orphan drug grants is $15 million with $ten million for ongoing noncompete renewals and $five million to fund new projects annually. The orphan grants process has been used to bring more than 60 products to marketing approval [70].
- **Marketing exclusivity***:* The first sponsor to obtain marketing approval for a designated orphan drug is allowed 7 years of marketing exclusivity for that indication, but identical versions of the same product marketed by another manufacturer may be approved for other indications.

The Orphan Drug Act does not provide advantages for the drug approval process. Sponsors seeking approval for drugs that will be designated as orphan drugs must still provide the same safety and efficacy data as all other drugs evaluated by the FDA. Exceptions to the rules governing the number of patients that should be treated in the clinical trials may be made based on the scarcity of patients with the condition. Additionally, because in many cases there are no alternative therapies for the disease, the drug may be given a high review priority during the NDA process [71, 72].

11 Transparency of Drug Development

First initiated in response to components of FDAMA, the National Institutes of Health (NIH) developed a web-based system that offers information about ongoing clinical trials for a wide range of diseases and conditions. The site is available at http://clinicaltrials.gov. Initially intended as a system to provide a registry of clinical trials, it allows potential study subjects to search for studies for particular diseases and identify treatment centers that offer enrollment into those studies. The FDA requires that for studies being conducted under an IND, the sponsor verifies that the study is posted to the system through submission of Form 3674 to the IND

[73]. Requirements for postings have become increasingly more stringent over time. In 2016, both the FDA and NIH implemented initiatives intended to further enhance the availability of clinical trial information. Both entities require registration of all applicable studies in the system within 21 days after enrollment of the first participant. The difference is in the scope being related to the definition of an applicable study. The FDA defines an applicable clinical trial as any clinical trial, including an FDA-regulated product, but excludes Phase 1 or small feasibility device studies. In contrast, the NIH defines an applicable clinical trial as all clinical trials funded by NIH, including only behavioral interventions. Both the NIH and FDA require reporting of results from applicable studies no later than 12 months after the primary completion date (the date that the last participant but reached the primary objective). Results reporting includes not only information about the subjects (demographics and participant flow) but also information about adverse events, outcomes, and statistical analyses [74, 75].

12 Institutional Reviews

In additional to review of the investigational product by the FDA, institutions will have required reviews as well. The review processes may include a review by an Institutional Review Board (IRB), Institutional Biosafety Committee (IBC), and a Scientific Review Committee. Review by these committees are considered to be complementary processes within institutions and approval as required by all of them before a clinical trial can be activated.

12.1 Institutional Review Board/Institutional Ethics Committee

The Institutional Review Board (IRB), known outside of the USA as the Institutional Ethics Committee, is a committee formed to review proposed clinical trials and the progress of such studies to ensure that the rights and welfare of human subjects are protected. The US regulations governing the protection of human subjects include Title 45 Part 46 of the Code of Federal Regulations (CFR), which was designed to make uniform the protection of human subjects in all federal agencies; Title 21 Part 50 of the CFR sets forth FDA guidelines for appropriate informed consent; and Title 21 Part 56 of the CFR sets forth FDA guidelines for the IRB [76–78]. IRB review can be accomplished in two ways, either review by a locally constituted (usually institutionally based) IRB or reliance on a single IRB. The IRB must contain at least one member who has specialized knowledge in a scientific area (in situations where drugs and biologics are being reviewed, this is usually a physician) and at least one board member who has a specialty in a nonscientific area such as law, ethics, or

religion. Additionally, the IRB must contain at least one individual who is not affiliated with the institution where the research is being conducted. The membership of the IRB varies between institutions. Common members of IRBs include physicians, pharmacists, nurses, lawyers, clergy, and laypeople. Scientific membership of a locally constituted IRB can vary between institutions but will generally reflect the expertise of the scientific community at the institution. An institution that focuses only on cancer may have an IRB composed only of oncologists. However, a more general hospital will have membership inclusive of multiple disciplines and specialties. Locally constituted IRBs are generally utilized to review internally initiated clinical trials, although their scope is not limited by law. Reliance on a single IRB is more likely to occur in situations where a clinical trial will be conducted at more than one institution or when a study has an external sponsor. In this situation, the institution can enter into an agreement stating that they will rely on the review of a clinical trial as provided by another IRB. This is called *reliance* on a single IRB of record. Current law requires a single IRB review of many federally supported clinical trials including those being conducted by the National Cancer Institute (NCI). The single IRB can be for profit, or they can be constituted by other organizations including the Federal government, but in any case, although the specialties and expertise represented on the committee may closely mirror that of a locally constituted IRB, their members are more likely to be from different geographic areas. As with locally constituted IRBs, single IRBs can also be developed specifically to review certain types of research, and as an example, COG clinical trials are reviewed by the National Cancer Institute (NCI) IRB. The intent of reliance on a single IRB of record is to decrease duplicative review processes at individual institutions while still maintaining human subject protections. However, frequently institutions require administrative review of the clinical trial by the IRB or the Office of Research including a review of the consent form and a requirement for standard, institution-required verbiage to be included.

The IRB reviews new studies, amendments to existing studies, and serious adverse events that occur during the conduct of a study and provides an annual review of all studies that are active at the institution. The IRB reviews these submissions to ensure that the following requirements are met:

- The risks to subjects are minimal.
- The expected risk/anticipated benefit ratio must be reasonable.
- Equitable subject selection is utilized.
- Informed consent must be received from each participant (or his or her legally authorized representative).
- Informed consent must be documented in writing unless a modified approach is justified according to very specific criteria spelled out in the regulations.
- Data must be monitored to ensure subject safety.
- Patient confidentiality must be maintained.
- If appropriate, additional safeguards against coercion must be included in studies that include vulnerable subjects (children, prisoners, pregnant women, mentally disabled people, or economically or educationally disadvantaged persons).

- IRBs are also involved in evaluating research conflict of interest (COI). Although this is a shared responsibility for the institution, the IRB, and the investigator (and staff), the IRB has the responsibility for evaluating whether or not financial interests may impact the protection of human subjects. The IRB will have a mechanism for reporting COI, policies for managing or eliminating such COI, and as deemed necessary require that such conflicts be provided to potential study subjects as part of the informed consent process [79].

12.2 Scientific Review

Some institutions divide their review of proposed clinical research into two separate processes, IRB review as described above and scientific review. Scientific review committees are not mandated by law but are required by some funding agencies including the NCI [80]. As a result, this type of committee review is common in institutions that conduct a high volume of interventional clinical trials and is a common component of review at cancer centers. Timing of scientific review is not mandated; however, most institutions require scientific review prior to review by an IRB as this optimizes the content of the study prior to submission to the IRB. Scientific review committees include experts knowledgeable in the types of research being conducted and will generally include not only physicians but also surgeons, radiologists, statisticians, pharmacists, and nurses who work in areas of research. The typical committee usually includes about 20 scientists and specialists. Patient advocates/laypeople are frequently asked to serve on these committees as well to provide insight into logistical issues that may impact the desire of the patient to participate or the feasibility of the study.

12.3 Institutional Biosafety Committee

For clinical trials that include gene therapy (also called gene transfer), review by a local *Institutional Biosafety Committee* (*IBC*) is also required as specified in the NIH guidelines [81]. Gene therapy clinical trials use techniques that are novel and include potentially irreversible risks to the subject and their progeny (in cases of germline [egg or sperm] alteration). Gene therapy products also include the risk of inadvertent transfer to other individuals including healthcare workers, family members, and even the general public. For this reason, IBC review is intended to provide a local review of all research that includes gene transfer into any human. The use of a single IBC to cover research across multiple institutions is uncommon. IBC review is highly scientific in nature, and the requirements for submission of a project to the IBC will vary among institutions; however, in all cases the IBC is required to review:

- The source of the genes being used.
- The nature of the genes being used.
- The way in which the gene might be introduced into the cells of the patient.
- The mechanisms used for gene containment.
- The training plan for personnel involved in the project.
- The plans that exist for handling accidental spills and personnel contamination resulting from contact with the product.

Each of these components of a clinical trial including the actual gene transfer has a risk profile that requires consideration by scientific experts through the IBC review process. IRB and IBC reviews are considered to be complementary processes within institutions, and approval is required by both entities before a gene therapy clinical trial can be activated.

13 Conclusions

Clinical trials that utilize drugs, biologics, and devices in the USA are largely controlled by the FDA and by local IRBs although additional reviews may be required. A thorough understanding of the regulations governing those entities is extremely helpful when conducting clinical trials as failure to comply with the regulations can result in serious consequences including loss of funding, inability to publish, and restrictions in the ability to engage in further clinical research.

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