Chapter 18
Product Review, Release, and Administration

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Abstract Once a cell or tissue product has been manufactured, a controlled process must be in place for review and release *before* distribution of the product. The procedure and documentation surrounding product review and release is both a microcosm of the Quality Assurance/Quality Control (QA/QC) structure and an encapsulation of the scientific data generated during manufacturing. Review and release attest that the entire system from accession of product into the laboratory, through removal of final samples for testing, to labeling and transportation of the finished product, has functioned as intended. This chapter describes the processes involved in the review of production and testing records and for product release.

Understanding Product Review and Release

The review and release procedure serves to confirm that cell therapy products have been manufactured following appropriate procedures under the prescribed conditions and have met all of the testing specifications required for clinical therapeutic use. If all aspects of production and testing are not as dictated by Standard Operating Procedures (SOPs) and policies, then a process must exist for exceptional release of the product. The exceptional release procedure summarizes how and why a product did not meet criteria, and the justification for its release. Cell therapy products also face the complication that the results of certain tests may not be available prior to product administration. The release procedure must, therefore, also include a mechanism to deal with results obtained after release and administration. In addition, since the only true measure of the product's function is restoration of some biological activity in the recipient, surrogate *in vitro* measures of the product's intended function *in vivo* must often be used for release.

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The adage that quality cannot be tested into a product is particularly true for cellular products. It is expected that as a product transitions from one developmental phase to the next (preclinical, Investigational New Drug (IND) phase, through licensure) the control of the manufacturing and testing process will become more stringent [1]. Likewise, the release process must become more robust.

A well-constructed review and release procedure has two components. The first component is record review. This demonstrates that appropriate documentation and associated control procedures are in place during all aspects of manufacturing. The second component is final product testing. This must show that the product meets predetermined specifications. As discussed above, the major challenge in release testing of cell therapy products is the frequent need for issue and administration before test results are finalized. As a result, final documentation of product characteristics is often delayed until after administration. Parameters that measure product function in the recipient, such as engraftment of hematopoietic cells (measured by rising absolute neutrophil count or hemoglobin) or functioning of pancreatic islet cells (measured by restoration of insulin production), may be the ultimate indicator of the success of processing and of functionality of the product, but these cannot be used as components of the formal review and release procedure.

Regulatory Issues

Cellular products in the United States can be either essentially unregulated or regulated as drugs, biologics, or devices, depending on tissue source of the cells, the degree of manipulation *ex vivo*, and the intended use of the product [2]. The level of regulation in turn dictates the rigor of review or oversight needed for product release, the type of release testing, and the person or entity responsible for ensuring that all criteria have been met. The degree of oversight is based largely on the perceived degree of risk (see Chapter 1 in this book). Less complex review and release criteria are required for Type 361 cellular products manufactured in facilities operating under Good Tissue Practice (GTP) regulations as described in Title 21, Part 1271 of the U.S. Code of Federal Regulations [3]. These are designed to ensure that the manufacturing process is controlled, and that products are handled in a manner that prevents contamination, cross-contamination, and introduction of transmissible disease agents.

A more stringent regulatory approach is in place for products manufactured under new drug and/or new device regulations (IND or Investigational Device Exemption (IDE)). In this case, manufacturing must be under Good Manufacturing Practices (GMP) as outlined in Section 351 of the Public Health Services Act ("Type 351 products") [4]. GMP regulations provide the framework for manufacturing of pharmaceuticals, blood components and blood products, and contain detailed sections covering product release. In addition, state and/or local laws may mandate supplementary requirements for release [5].

Products that fall outside the federal or state regulatory framework (e.g., bone marrow intended for autologous homologous applications) may be processed and issued without adherence to the full range of procedures described in this chapter.

However, it is clear that in the United States, manufacture of all products used clinically, even "unregulated" Type 361 products, and/or those not intended to proceed toward final licensure, should conform to the spirit of these regulations. Since most cellular processing facilities adopt the stricter interpretation of the regulations to ensure maximal safety for their patients, and to provide consistency in operations, this "regulatory creep" has resulted in a higher degree of control over all products. Facilities have recognized that use of standardized release procedures for all products generally increases laboratory efficiency. However, this universal approach also imposes an additional cost for documentation and labor in the review, and release of products which do not have to meet the stricter regulations.

Although it is essential that staff responsible for all aspects of manufacturing and testing clearly understand review and release procedures, the ultimate responsibility for determining whether the product has met predetermined specifications usually depends on where the product falls in the regulatory continuum. As products progress toward licensure, release becomes the responsibility of fully mature Quality Assurance (QA) units. In the academic environment, the laboratory medical or technical director is usually responsible for all aspects of manufacturing; however, in practice, release is often handled by the manufacturing staff, especially during the early developmental phases or when processing is finished outside of regular working hours. Some professional standards, e.g., those of the Foundation for the Accreditation of Cellular Therapy (FACT) [6], only require that at least two "trained" personnel inspect the product and label, and leave the level of that training open to interpretation. However, even in early phase studies, it is recommended that manufacturing staff should be distinct from those with Quality Assurance/Quality Control (QA/QC) responsibilities (see Chapter 16 in this book). Use of the phrase "or designee" in product review and release SOPs allows the director to identify specific staff to review records and authorize off-hour product release.

In facilities with small numbers of staff, manufacturing, final review of records and labels, and release of the product may potentially involve the same individuals. If this cannot be avoided, there should be a separation in time and space between these activities.

As products move toward licensure this approach changes, since the complexity of release testing increases, and the differentiation between manufacturing and quality assurance activities becomes more rigorous [7, 8].

Institutional Review Boards (IRB) or Ethical Committees may also influence the type and timing of testing during all phases of product development. Most regulations and professional standards agree on the basic release test criteria for products in the earliest phases of clinical trials. These include assays for product identity, viability, and sterility. During later stages of clinical evaluation, additional assays, including potency testing, are required.

Product Review and Documentation

The dictum that unless an action is documented it has not happened is particularly important in product release. The pharmaceutical model of batch records for each

production cycle has been applied to cellular products; however, these currently differ from traditional pharmaceuticals, as they are patient specific and manufactured in very small lots. In addition, unlike a traditional drug, a cellular product that does not meet specifications may have to be used if medically necessary. There are, however, certain common elements in the documentation for any cell therapy product. These are listed in Table 18.1 [6, 9, 10].

Deviations that occur during manufacturing must be carefully reviewed by the quality program staff (QA). They must be managed in accordance with SOPs and their potential impact on product quality must be carefully assessed. There must also be a mechanism to report notifiable deviations to governmental agencies when required [5, 11].

Product release is often handled through a certificate of analysis (C of A) system (Table 18.1). The C of A summarizes the characteristics of the product, and the tests performed (Fig. 18.1), whether or not the results are available at the time of distribution. For this reason, a procedure for the addition of post-release test results and associated rereview of all documentation should be developed, as well as a mechanism to deal with postrelease test results that do not meet specifications.

The C of A details release specifications and results of each test, with the method used for testing and the assay sensitivity or acceptable range of results. Release specifications for test results are generally derived from the regulations, the IND or IDE, and the literature. As products move toward licensure, these specifications may be refined or become more stringent. Additional product information, such as details on vialing or packaging, storage conditions, and expiration date, may also be documented in the C of A. The certificate should be signed by the individual(s) responsible for its generation and review, and a copy is usually released with the product, while the original is retained by QA or in the patient chart as dictated by laboratory SOPs.

Review of the infectious disease status of the cell or tissue donor is an important component of the release process. In the United States, Part C of 21 CFR Part 1271 [12] requires that, with specific exemptions, donors must be classified as eligible or ineligible, as determined by infectious disease testing, assessment of risk behaviors, and clinical examination and history. Ineligible donors may be used under defined circumstances and with appropriate handling and labeling of the product, and notification of the intended recipient. Most U.S. centers have now developed systems to document that the patient is aware of the possibility of transmission of disease from a product obtained from a donor who has tested positive, has pending test results, or where the donor has known risk factors.

Product Testing for Release

Practical and scientifically defendable release tests must be chosen [13]. There are few *in vitro* assays for functionality that reliably reflect likely cellular activity *in vivo*. Tests for the release of Type 361 products have not been specified and those

Table 18.1 Most common elements for review as part of product release

- Physician order for cell or tissue collection
- Informed consent for collection
- Informed consent for participation in study
- Donor eligibility assessment and supporting documentation
  - Donor risk questionnaire
  - Infectious disease test results with interpretation
    - Appropriate test kits and samples used
- Clinical history/examination
- Manufacturing records to ensure that proper procedures have been followed
  - Flowchart of manufacturing and testing process
  - Properly completed worksheets or batch records
  - Planned or unplanned deviation documentation
  - Listing of material, reagents, supplies, and equipment used
    - Copies of certificates of analysis for "critical" reagents, e.g., sera, enzymes, and growth factors
  - Cleaning and environmental monitoring records
  - In-process testing performed and results
  - Availability of appropriate staff training records
  - Information on in-process and final storage locations and conditions
  - Release testing performed and results
  - Label copy and label approval documentation
  - Review of tracking records to ensure that there has been no product mix-ups
  - Complete inventory of available product
- Certificate of analysis
  - Proper name of product
  - Identity of donor and/or intended recipient as appropriate
  - Required regulatory language, e.g. For Autologous Use Only
  - Expiration Date
  - Required storage conditions
  - Cautionary statements, e.g., Do not thaw and refreeze
  - Packaging information
  - Listing of all required testing
  - Method used for testing
  - Sensitivity (and specificity) of test method
  - Specification to be met for product release
  - Identity of test laboratory
  - Test result obtained
  - Appropriate "Reviewed by" and "Released by" authorization
- Physician order to issue product
- *Urgent medical need authorization* or regulatory approval documentation for use of nonconforming products if appropriate
- *Documentation of cross-checking of product identity* at time of removal from storage and transfer for administration
- Transfer/shipping documentation
  - Establishment and notification to all parties involved of requirement for product tracking
  - Removal from inventory with cross-check of product identity and integrity
  - Transportation records
    - How and when transported
    - Validated procedure used for transportation
    - Documentation of transportation container/equipment and labeling
    - Inclusion of instructions for receiving staff
    - Receipt documentation
    - Transportation temperature records
    - If shipped from external organization, procedure in place for reporting outcome of procedure

Not all elements are applicable to every type of cell therapy products.

CERTIFICATE OF ANALYSIS
GMP Cell Processing Facility
University of Anytown, Anytown, USA
Caution: New Drug-Limited by Federal Law to Investigational Use
Properly identify intended recipient and component
For Autologous Use Only

Non-Transduced Autologous EBV-specific Cytotoxic T Lymphocytes

Patient Name: **SAMPLE, Patient**
Medical Record Number# **P9999**
Hospital #: **12345678 Regional Medical Center**
Component Identification # **C2999.9**

TEST	LABORATORY	SPECIFICATION	RESULT
Lot # P9999C2999.9 Frozen: July 15, 2008 **$1x10^7$ T cells/ml/bag 10ml/bag in Plasmalyte** ***Store below -150°C Do not thaw & refreeze Expiration: July 24, 2013***			
Viability (Cell Product pre-cryopreservation) by dye exclusion	Quality Control Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	>70% viable	98% viable *(July 15,2008)*
Endotoxin (Cell Product) by Limulus Amebocyte Lysate Assay (K-QCL method)	Quality Control Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	<5.0 EU/ml	<2.0EU/ml ***<2.6EU/kg @ 70kg recipient weight*** *(July15,2008)*
Mycoplasma (Cell Product & Supernatant medium) By Points to Consider 1993 Assay	Quality Control Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	Negative	Negative *(August 15,2008)*
Sterility (Cell Product & Supernatant) by 21 CFR 610.12 assay	Quality Control Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	Negative	Negative *(August 15,2008)*
Immunophenotyping (Cell Product) by Flow Cytometry	Flow Cytometry Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	<2% $CD19^+$ Cells	0.1% $CD19^+$cells *(August 15,2008)*
HLA Typing (Donor and Cell product) by High resolution typing	Donor and Final Cell product must match **Donor** Deutsche Herzzentrum Berlin Transplanationsambulanz II Augustenburger Platz 1 Germany **Cell Product** Histocompatibility Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	**Donor** A*0301,1101 B*1510,5101 Cw*0304,1502 DRB1*1001,1501 DQB1*0501,0602 DRB3*Neg DRB4*Neg DRB5*0101 *(January 3, 2008)*	**Cell Product** A*0301,1101 B*1510,5101 Cw*0304,1502 DRB1*1001,1501 DQB1*0501,0602 DRB3*Neg DRB4*Neg DRB5*0101 *(July 30, 2008)*

Approved for Release for Autologous use ONLY by:

My signature Date: 29th August 2008
Quality Assurance, Anytown University Quality Assurance Department, Anytown, USA

Fig. 18.1 Example of certificate of analysis

used are basic, e.g., sterility. Type 351 products must meet a higher standard for product release. Listed in the CFR, these tests include sterility, mycoplasma contamination, purity, identity, potency, and others developed by the product manufacturer [14]. The test methods are specified for sterility, mycoplasma, and purity (pyrogenicity), but not for identity and potency.

The short shelf life of many cellular products poses a challenge when selecting release tests. Certain products may be cryopreserved providing the time in which to perform tests which require longer turnaround times for results; however, some products require release immediately after preparation, and prolonged testing cannot

be performed. In this situation, rapid tests must be used [15] if available. This is of particular importance if cells are required for intra operative procedures.

Sterility Testing

Sterility is a fundamental test requirement for cellular products. Since cellular therapeutics and some cell-derived products (e.g., lysates, semipurified extracts) cannot be filter-sterilized they must be handled aseptically throughout the manufacturing process. When manufacturing procedures are short, they do not allow sufficient time to obtain results from traditional tests for bacterial and fungal contamination. In these cases extra controls involving in-process testing during manufacturing are often set in place, and must be reviewed before product release [16]. Since the standard sterility test described in 21CFR 610.12 [17] uses a 14-day incubation, other tests for microbial contamination, such as microscopic examination following Gram staining (or other bacterial and fungal stains), should be used at release. While a Gram stain is rapid and easily performed, it suffers from the problems of insensitivity, sampling error, and operator variation.

Recent investigations have cultured cellular products using automated blood culture systems to shorten the incubation time [18]. While these results are promising, there is no consensus on which is the most reliable assay, and the Food and Drug Administration (FDA) often has asked that the 21CFR 610.12 method be used for IND or IDE studies; or that the rapid method must be formally validated locally against the CFR technique.

The small volume/cell number of some cellular products also hampers sterility testing, due to the inability to sacrifice a large enough sample for testing, or the problem of obtaining a sample that is representative of entire product. Under these circumstances supernatants from washes of the cell product may be used for testing, but the acceptability of supernatants has not been universally established for all types of cellular products. Another issue is that recipients of cellular therapy products are frequently immunosuppressed and, therefore, on broad-spectrum antibiotic coverage. The low rate of complications associated with infusion of contaminated products [19] suggests that this coverage may permit the use of products carrying a microbial burden. This approach should, however, be considered more as a "safety net" rather than as an acceptable practice.

Mycoplasma Testing

Mycoplasma testing is used for products that have been cultured *ex vivo* [20]. FDA-approved tests for this intracellular parasite are listed in 21 CFR 610.30, but the recommended "Points to Consider" method cannot provide rapid results.

There are several commercially available kits that can be used to detect mycoplasma by PCR within 24–48 hours [21, 22]. These, like the automated blood culture tests listed above, have not been approved by the FDA. Validation of

alternative test methods is essential since inconclusive or unreliable results necessitate repeating the test while cells deteriorate, or the intended recipient is kept waiting. Since few of these tests have received regulatory approval, proposals to use them in place of the approved method must be discussed with the regulatory agencies.

Purity

Purity is interpreted as meaning lack of contamination with endotoxin or other potential harmful materials added during manufacturing. Endotoxin, a component of the gram-negative bacterial cell wall, is both a cause of adverse reactions on infusion and an indicator of possible contamination with other bacteria. This highly stable material can be found not only in the lysed bacteria, but also as a residual contaminant of supplies and reagents used in manufacturing. Many tests for endotoxin have been developed; however, mainly the older and longer assays have been approved by regulatory agencies. Some rapid release assays that can be performed on site are now available [23], but many manufacturers still choose to send samples to commercial testing laboratories that use the more traditional testing methods. This can be costly in both time and money.

Viability

Cellular properties such as viability can be measured immediately by microscopic evaluation of cells stained with vital dyes such as Trypan blue, or by using flow cytometry and stains such as 7-AAD. In some products the cells required to exert the therapeutic effect may be a subpopulation remaining after destruction of other subpopulations. Under such circumstances it is important to determine the viability of only the effector population. This can be achieved most effectively by flow cytometry. The commonly accepted release specification for viability is >70%. For cryopreserved products the timing of viability assessment should be discussed with the regulatory agency. Most manufacturers measure viability pre-cryopreservation; however, increasingly there is a requirement for assessment at the time of thawing for administration.

Identity Testing

The identity of the cells in the product is frequently established by flow cytometric analysis for either surface phenotype, or identification of intracellular components. In certain circumstances testing of functional capacity (such as cytokine secretion) may also be used. Molecular techniques, such as PCR, can also provide extremely precise information on the genetic identity of cells present in the product. In many cases, the investigator responsible for the development of the product may be initially required to suggest the most appropriate assays for product release to

the laboratory manufacturing the clinical product. As the product moves along the regulatory pathway the responsibility for testing, test validation, and development of potency assays will fall to the quality unit (Table 18.2).

Table 18.2 Analytical tests for cell and gene therapy biological products

		Gene therapy products	
Test	Cell therapy products	Viral	Nonviral and antisense-oligonucleotide
Identity of biological substance	Surface marker determination	Restriction enzyme map	Restriction enzyme map
	Species	PCR	PCR
	Morphology	Immunoassay for expressed gene	Immunoassay for expressed gene
	Bioassay	Sequencing	Sequencing
	Biochemical marker		
Dose	Viable cell number	Particle number	Plasmid-DNA weight
	Enumeration of specific cell population	Transducing units (DNA hybridization assay)	Formulated-complex weight HPLC or capillary electrophoresis is assay using authenticated reference standard
	Total DNA	Total protein	
	Total protein	HPLC assay using authenticated reference standard	
Potency	Viable cell number (cells intended for structural repair)	Function of expressed gene (induction of secondary effect and other bioassays)	Function of expressed gene (induction of secondary effect and other bioassays)
	Bioassays: Colony-formation assay Function of expressed gene Induction of secondary effect (e.g., human leukocyte antigen (HLA) induction, secretion of cytokines, and up-regulation of surface marker)		
Purity	Percentage of viable cells	Residual host-cell DNA	Percentage of specific physical form (e.g., percentage supercoiled)

Table 18.2 (continued)

Test	Cell therapy products	Gene therapy products: Viral	Gene therapy products: Nonviral and antisense-oligonucleotide
	Percentage of transduced cells	Process contaminants (e.g., serum and cesium chloride)	Residual host-cell DNA
	Percentage of cells with specific surface marker	Residual helper virus	Residual RNA
	Process contaminants (e.g., serum)	Optical density ratio	Residual host-cell proteins
		Residual host-cell proteins	Residual solvents
		Viral protein profile (HPLC assay for defective or immature particles)	Optical density ratio
		Residual RNA	Process contaminants (e.g., cesium chloride and synthetic oligonucleotide by-products)
Safety	Mycoplasma	General safety	
	Sterility	Mycoplasma	Mycoplasma
	Pyrogen and endotoxins	Sterility	Sterility
	Adventitious viruses	Pyrogen and endotoxins	Pyrogen and endotoxins
	Residual virus (for transfected cells)	Adventitious viruses	
	Replication-competent vector virus (transfected cells)	RCV	

From United States Pharmacopeia USP 31-NF26 1046 Table 6.

Out-of-Specification (OOS) Results

The critical nature of some cell therapy products (e.g., hematopoietic cell grafts) are such that they may be required to sustain life in the intended recipient and alternative products may not be available. Under such circumstances it may be medically necessary to use products that do not meet release specifications (out of specification – OOS). This is usually described as release to meet urgent medical need. The use of such products requires medical justification and may additionally need approval from regulatory agencies and the informed consent from the intended recipient. Professional standards again give more operational guidance. FACT requires that a medical director authorize exceptional release for "nonconforming" product and that the patient's physician be informed and consent obtained to use of the prod-

uct. AABB standards additionally require identification of lot release tests, ranges of acceptable values, and actual product values. These provide the physician with appreciation as to where the particular product falls within the established ranges. This information is often provided by the C of A; however, AABB lists the review of specific items (e.g., red cell and HLA compatibility) required for release, and requires that the physician discuss risks of the use of nonconforming product (as do GTP regulations in their labeling requirements). All standards and regulations require special handling and careful documentation of the use on nonconforming products.

Product Release, Transportation, and Shipment

Administration of products may consist of a number of phases that should be described in standard operating procedures. These should cover the removal of the product from manufacture and inventory or storage, transportation within and/or shipping between facilities, instructions for and documentation of administration, possible adverse reactions, possible return to inventory, complaints and recalls, handling of positive test results received following administration, and communication of outcome results to the collection/production facility in the case of shipped products. Many of these are addressed by governmental regulations and professional standards and will be product-dependent. In most cases the key element is to develop a system of documentation that clearly records not only everything that happens to the product during manufacturing, but also all events after the completion of manufacturing and testing to final disposition. This system must be able to account for all of the material that was manufactured and to deal with potential complications, such as adverse reactions to administration, recalls, and complaints.

The administration of a product requires a formal documented request (prescription) from the intended recipient's physician. This specifies precisely the product to be administered, the dose to be given, and the date and time of the administration. Additionally it may request some supplementary manipulation of the product, such as thawing, washing, and so on. Under such circumstances it may also be necessary to perform additional release testing following the manipulation.

Products will generally require transport or shipping to the site of administration under conditions that have been validated to maintain cellular viability and functional integrity. Movement of product may be done under the custody of trained couriers, or by commercial shipping companies. Regardless of whether trained couriers accompany products, some formal demonstration that appropriate temperature range has been maintained during transit should exist. The temperature will be specific to the type of product, ranging from ambient to <–150°C (attained by the use of liquid nitrogen "dry" shippers). The use of recording thermometers during transportation has become the norm and these are now available for most widely

used temperature ranges. Professional standards from FACT and AABB address transportation and describe the labeling to be used and precautions to be followed to ensure safe and timely shipment between and within facilities. In the United States, federal regulations address the nature of the accompanying records and establishment of tracking and tracing capability between all parties involved in the manufacture, testing, release, and administration of the product. Instructions should be provided that describe handling of the product on arrival, contact information in case of delay or delivery problems, transfer to on-site storage, preparation for administration, and follow-up (e.g., adverse events and engraftment). Additional national and international standards and regulations address the use and labeling of appropriate shipping containers and provision of customs declarations when appropriate. This information is usually readily available from commercial shipping and courier companies.

Administration

Product administration should be clearly described and include instructions on procedures to be followed in case of problems (e.g., the rupture of a product container during thawing). The staff performing the administration should also have access to a document (often referred to as the Circular of Information or Instructions for Administration) that describes the indication and contraindications for product use, product format, and possible adverse reactions. In the United States a Circular of Information (COI) for cell therapy products has been jointly developed by a number of professional organizations [24]. The COI is intended to be generic, so is often supplemented by product and institution-specific information. Adverse reactions to administration should be anticipated and potential remedial actions described. In some cases these are expected, as is the case when products containing dimethylsulfoxide are infused. Under such circumstances the acceptable range for these reactions can be described to reduce unnecessary documentation and follow-up. Governmental regulations usually mandate reporting of serious adverse reactions to regulatory agencies within a specified timeframe and require some form of attribution. In the United States the regulations for products under IND and IDE (Type 351 products) are detailed and specific. For Type 361 products the FDA requires reporting of specific biological product deviations on products that have been administered [11].

Conclusions

Product release is one of the most critical components of cell therapy product manufacturing. As was stated earlier, quality cannot be tested into a product postmanufacturing, but is the result of a properly engineered production process. The release procedure, however, provides the final opportunity to ensure that the product was

manufactured as specified using a controlled and auditable procedure and is safe for administration. The variety of cellular products and potential applications is already enormous and our ability to test them in a predictive manner is still limited. Their manufacturing processes and testing procedures still differ radically from those used for pharmaceuticals. This makes it all the more important to ensure that these potentially very promising medicines are released using a process that ensures, at very least, their safety. As the field progresses, we must continue to work with the regulatory agencies to develop faster assays that better predict clinical outcome.

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