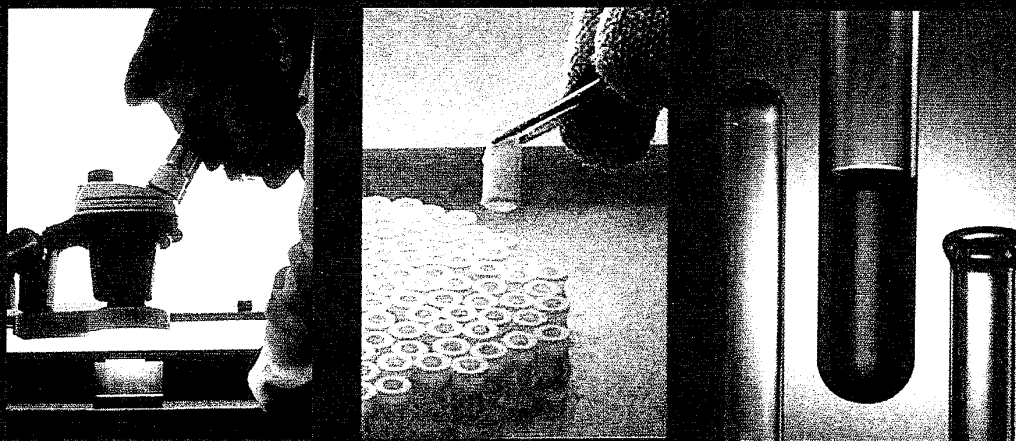


Biologics Development:

A REGULATORY OVERVIEW

T H I R D E D I T I O N



E D I T E D B Y

M A R K M A T H I E U

PAREXEL®

Biologics Development: A Regulatory Overview Third Edition

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CHAPTER 5

Clinical Testing of Biologically Derived Therapeutics

by

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As it does for other classes of products, the clinical development of biologically derived therapeutics involves the investigation of a product's safety and efficacy through the conduct of clinical studies. The goal of these studies is to generate sufficient data to support market authorization. To obtain market authorization in the United States, biologically derived therapeutics discussed in this chapter require the submission and FDA approval of a biological license application (BLA).

This chapter outlines the clinical development of biological therapeutics with a focus on the key phases of the clinical development process and, in particular, on key development issues and study design elements relevant to biological products. It also discusses specific issues relevant to the clinical investigation of related therapeutic biological products, including cellular and gene therapies.

It is important to note that the clinical development of biologically derived therapeutics will continue to adapt to new scientific discoveries and changes in regulatory requirements. Consequently, the application of some of the concepts discussed here will almost certainly evolve in the future as technology moves forward and FDA organizational and regulatory requirements change.

Phases of Clinical Drug Development

Clinical development proceeds through a series of phases that are defined in the Code of Federal Regulations (21 CFR 312.21). Each phase of clinical investigation has different objectives and design issues (see exhibit below). Rather than distinct steps, these phases can be considered milestones along the continuum of clinical development that begins with the first-in-humans study, continues through market authorization, and extends into the postmarketing phase. The development of therapeutics often follows a prospectively designed clinical development plan consisting of several well-designed and well-executed studies. Taken together, these studies will characterize clinical aspects of the biological product and generate scientifically valid clinical data that will support the efficacy claim when that therapy is administered to the indicated patient population.

As a roadmap to market authorization, the clinical development plan should be thoughtfully designed to generate clinical data that characterize specific aspects of the biological product that the sponsor hopes to include in the eventual product label. During labeling negotiations with the FDA, it is difficult for a sponsor to justify the inclusion of clinical claims that were studied in laboratory or preclinical testing but never investigated in the clinic. Thus, in addition to generating sufficient data to support the final indication, clinical study designs also should address clinically important questions of secondary interest and provide for the collection of appropriate data to describe the product as completely as possible in the label.

The clinical development plan should also reflect the lessons learned from prior clinical investigations or from regulatory experience gained during the development of products for the same or similar indications. Being the first to seek market authorization for a novel class of products or a product for an indication for which no therapies have been approved can be challenging. Inexperience in a particular field and the lack of regulatory precedents contribute to uncertainty regarding appropriate clinical trial design and regulatory standards.

Given the novelty of many biologically derived products, developers of these products should communicate with the FDA review team on a timely and effective basis throughout clinical development. Sponsor/regulator interaction allows the FDA to apprise developers of regulatory concerns, and allows sponsors to keep FDA informed of progress in clinical development.

FDA guidance documents are among the tools available to assist sponsors in planning and coordinating clinical investigations.^{1,2} In addition to several guidance documents on the development of products for cancer, guidance documents for rheumatoid arthritis,³ imaging agents,⁴ and chronic cutaneous ulcers⁵ have proven useful in the development of recently approved biologically derived products.

The amount of clinical data necessary to assess a biological product's safety very much depends upon the intended patient population and the availability of effective therapies for the targeted indication. Patients with severe or life-threatening illnesses or who have inadequate treatment options are generally more willing to accept greater levels of risk in order to experience clinical benefit. For these patient populations, the amount of safety data may be considerably less than that needed for patient populations with non-life-threatening diseases that require chronic treatment. In their respective pivotal studies, for example, rituximab (RituxanTM) was evaluated in 296 patients with relapsed or refractory non-Hodgkin's lymphoma, and trastuzumab (HerceptinTM) was evaluated in 222 chemotherapy-experienced patients with metastatic breast cancer over-expressing HER2. In contrast to these patient populations with life-threatening malignancy, patients with psoriasis have non-life-threatening diseases and available treatment options. The safety databases for two recently approved biological products for patients with chronic plaque psoriasis were much larger: 1,350 patients for alefacept (AmiveveTM) and 2,762 for efalizumab (RaptivaTM). For each product, safety and efficacy were evaluated in two Phase 3 studies in which the experimental therapy was administered to roughly 700 to 800 patients.

Because biologically derived therapeutics are often intended to treat patients whose disease significantly increases the risk of death or severe morbidity, many products have been approved on the basis of a single adequate and well-controlled clinical study, usually a Phase 3 study. The CBER/CDER 1998 guidance entitled, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*⁶ describes situations in which a single adequate and well-controlled clinical study may be acceptable to the FDA in supporting a product's efficacy. It is important to note, however, that the FDA's willingness to rely on a single study for initial market authorization will generally be limited to situations in which a study

demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and in which confirmation of the result in a second trial would be impossible for practical or ethical reasons. As illustrated in the preceding example, for biological products intended to treat patients with less severe or chronic diseases (e.g., patients with psoriasis or rheumatoid arthritis), a larger clinical database, usually derived from two or more pivotal studies, will be required to substantiate the clinical results and to assess adequately the risk/benefit ratio in the intended patient population.

Increasingly, clinical development plans for biologically derived therapeutics should also include an evaluation of safety and efficacy in pediatric patient populations. Under the FDA's 1998 Pediatric Rule, BLAs for new biological products were required to include investigations in pediatric populations unless the FDA granted a waiver or deferral of pediatric studies.⁷ Waivers were granted to products intended to treat diseases that rarely, if ever, occur in children (e.g., breast cancer, Alzheimer's disease) or when there was strong evidence that the product would be ineffective or unsafe in children. Deferral of pediatric studies allowed such studies to be completed following market authorization.

In an October 2002 ruling, however, the U.S. District Court held that the FDA lacked the statutory authority to require that industry conduct pediatric studies, thereby preventing the agency from enforcing the 1998 Pediatric Rule. Following this court ruling, the FDA has remained active in encouraging firms to propose and undertake clinical studies in pediatric populations. In November 2003, Congress passed The Pediatric Research Equity Act of 2003 (S650) to provide the agency with clear statutory authority to mandate pediatric clinical studies when necessary to ensure the safe and effective use of drug and biological products in children. The legislation was signed into law in December 2003.

Phase 1 Phase 1 studies are designed to assess the safety of a biologically derived therapeutic when administered for the first time in humans or to evaluate the product's safety in a new patient population. Because the primary objective of Phase 1 studies is to evaluate the safety of different doses, these studies tend to enroll a limited number of study participants and are closely monitored for safety events. In addition to safety, Phase 1 studies are designed to evaluate the pharmacokinetics, pharmacodynamics, and immunogenicity of the different doses being investigated.

Design Issues

Phase 1 studies are usually designed as open-label, dose-escalation studies that enroll sequential cohorts of patients. Although each cohort may include patients who receive a placebo, a placebo control, while useful, is not a critical element in Phase 1 studies because safety and effectiveness can be compared across cohorts.

Often, Phase 1 studies will first evaluate the safety of a single dose in a dose escalating fashion to determine the maximum tolerated dose (MTD). An evaluation of repeat dosing will be conducted either as a separate Phase 1 study or will be incorporated into the original Phase 1 study design as a second component whose conduct depends upon the safety data for the initial single doses evaluated (i.e., acceptability of the single dose's safety data to allow administration of repeat doses).

Obviously, sufficient preclinical toxicity data are necessary to support both the initial single and repeat dose investigations.^{8, 9} In some cases, however, the preclinical evaluation of biologically derived therapeutics is not feasible (e.g., cellular therapies evaluating human cells such as CD34⁺ hematopoietic cells and autologous tumor cells). For these types of products, the sponsor and FDA must discuss the degree to

which an investigational product's safety can be extrapolated from clinical experience with similar products or other types of available data.

The Phase 1 study design should incorporate a measurement of the investigational product's biological activity along with its pharmacokinetics to determine the optimum biologic dose (OBD). Biological prod-

General Characteristics of Studies during Different Phases	
Phase 1	- First-in-human studies for novel, biologically derived therapeutic products, or similar evaluation in a new patient population - Primary objective is safety - Explores safety of different product doses or dosing regimens - Assesses pharmacokinetic and pharmacodynamic measurements - May provide early evidence of effectiveness - Generally open-label, single dose, dose escalation design - For biological products, commonly conducted in patient population
Phase 2	- Hypothesis-generating studies in larger number of patients than Phase 1 - Expands safety and efficacy information regarding specific product dose or dosing regimen initially evaluated in Phase 1 - Explores potential endpoints, study population, and disease characteristics for the design of Phase 3 studies - Generates clinical data intended to support Phase 3 studies - Generally randomized, blinded, with or without a control
Phase 3	- Pivotal studies intended to support BLA for market authorization - Generates information for product labeling - Assesses risk-benefit relationship in intended patient population - Generally randomized, double-blind, controlled design; often placebo-controlled - Endpoints selected to support clinical benefit
Postmarketing Studies	- Collects additional clinical data in approved or closely related patient populations - Studies to which the sponsor committed at market authorization (see Chapter 12) - Studies required for accelerated approval - Registries and studies as part of risk management program

ucts may have a non-linear dose-response curve in which the MTD can be higher than the OBD. The lack of a direct correlation between dose and response may result from the naturally dynamic activity of a biological product. The pharmacodynamic effect of many biological products, for example, involves product-protein or product-receptor interactions that cause cellular or protein activity and subsequent clinical response.

Most gene therapy products are designed to demonstrate effect with gene expression following cell uptake, which makes correlating pharmacokinetics with biological activity difficult. Thus, clinical response often depends on a series of inter-related biological steps or cellular functions whose activities may vary among different disease states or in the presence or absence of disease.

A critical component of the safety evaluation for biologically derived therapeutics involves the assessment of the product's immunogenicity (see below). In Phase 1 studies, serum should be collected and analyzed to assess antibody development to the biological product following both single and repeat administration. The development of antibodies should be correlated to the occurrence of safety events. In addition to monitoring for acute events, researchers should monitor study participants for delayed safety events for at least 28 days following the administration of study agent. Because antibody development may alter the biological product's serum concentration or biological activity, the immunogenicity data should also be analyzed to determine effects on the biological product's pharmacokinetics or pharmacodynamics.

Since the risks associated with the investigational product are either unknown or were not characterized in the new patient population, the Phase 1 study design generally incorporates the use of predefined toxicity limits that will restrict dose escalation or trigger the discontinuation of the clinical study. Although the types and severity of all adverse events must be closely monitored, toxicities seen in the preclinical studies and any known product-class effects will help identify dose-limiting toxicities (DLT) of particular interest. In addition, the definition of DLTs will depend upon the nature of the study participants—that is, significantly lower grades or levels of DLTs may be acceptable in healthy volunteers or relatively healthy patient populations, while slightly higher grades of DLTs may be acceptable in patient populations with more severe or life-threatening diseases.

Frequently, Phase 1 studies for biologically derived therapeutics are conducted in the intended patient population rather than healthy volunteers. Because healthy populations cannot derive any therapeutic benefit by being exposed to biologically derived therapeutics, there are natural sensitivities to exposing such populations to theoretical or unnecessary risks. One particular concern is that the exposure to biologically derived therapeutics may trigger antibody development. The risk of antibody development to a native protein, which could theoretically result in a secondary deficiency state or the risk of antibody formation to a portion of a monoclonal antibody, may be considered unacceptable in healthy volunteers.

Other products whose bioactivity is disease-specific are evaluated in the intended patient population (e.g., a tumor-specific therapeutic vaccine or a monoclonal antibody directed against a tumor-specific receptor vaccine will be evaluated in patients with the targeted cancer). Since gene therapies, in which an inserted gene is intended to alter the disease process, pose unnecessary risks to healthy volunteers, these products are evaluated only in the intended patient population.

Despite the risks, Phase 1 studies for some biological products are conducted in healthy volunteers. In all cases, sponsors must provide sufficient preclinical data and a rationale to support proposals that Phase 1 studies be undertaken in healthy volunteers. When Phase 1 studies are conducted in healthy volunteers,

safety events can be correlated with the study drug without the confounding influence of an ongoing disease process. In such cases, study participants can be enrolled and the study can be conducted in a more controlled setting at a single center than studies conducted in the intended patient population. Consequently, data collection is more uniform, and the studies can be conducted over a shorter period.

Phase 2 Due to limited resources and industry's desire for the rapid clinical development of biologically derived therapeutics, Phase 2 is a phase whose borders often overlap with those of Phase 1 and Phase 3 studies—that is, firms frequently conduct them as part of combined Phase 1/2, Phase 1b/2, or Phase 2/3 study designs. Because Phase 2 studies play an important role in the characterization of the therapeutic product, the abbreviation—or even omission—of these studies is often regrettable. Often, the design of and clinical data derived from Phase 1 studies are insufficient to permit the sponsor to identify the optimal dose or dose regimen, or to help the sponsor design a successful Phase 3 study that will support market authorization. Additionally, Phase 1 studies are generally too small to permit the sponsor to estimate the biological product's effects, which is important in calculating an adequate sample size for the Phase 3 studies. Such estimates are needed to provide some assurance that the critical Phase 3 studies have sufficient statistical power to allow an adequate comparison of the safety and efficacy of the biological product and the control.

Therefore, one of the goals of Phase 2 studies is exploring the effect and degree of effect that selected doses or dose regimens have on the investigational product's safety and efficacy, and to provide the information necessary for the selection of the appropriate dose or dose regimen that will be evaluated in Phase 3 studies. Phase 2 studies are also used to better define or clarify the appropriate patient population, clinical endpoints, and safety issues that could affect the design of Phase 3 clinical studies. When a sponsor plans to use a single large, multicenter Phase 3 clinical study to support approval, results from a well-designed Phase 2 study will provide supportive evidence for the Phase 3 study results. Lastly, from a practical perspective, Phase 2 studies permit sponsors to assess feasibility issues and fine-tune their Phase 3 study plan (e.g., feasibility of measuring certain endpoints and improving methods for data collection to avoid missing data).

Design Issues

Phase 2 studies are generally randomized, blinded studies that evaluate a larger number of patients than Phase 1 trials. These studies often include a control group that is administered either a placebo or an active treatment for comparison. For some indications, such as oncology, the Phase 2 study may have a single-arm design. In contrast to those in many Phase 1 trials, Phase 2 study participants are patients with the disease for which treatment is intended.

The dose or dose regimens evaluated in Phase 2 studies are chosen following an assessment of the Phase 1 study results. The Phase 2 study should be designed to collect and analyze additional pharmacokinetic, pharmacodynamic, and immunogenicity data. These data will provide a better understanding of the product's safety and exposure-response and exposure-toxicity relationships. Two guidance documents—the FDA's industry guidance entitled, *Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Application* (2003) and ICH's *E4: Dose Response Information to Support Drug Registration*—that discuss study designs and data analysis may be useful in designing these aspects of studies for biological products.^{10, 11} When feasible, population pharmacokinetic analyses may be useful as well, particularly for analyzing exposure-response in subpopulations.¹²

The assessment of the biological product in a larger number of study participants provides a better estimate of the product's clinical effectiveness compared to placebo or other therapies. As noted, such esti-

mates will be useful measures in determining a reasonable size for the Phase 3 studies (i.e., the so-called “power calculations”). The Phase 2 study design can incorporate an analysis of clinical response in subsets defined by covariates that may help the sponsor determine the appropriate study population for Phase 3. These covariates could include baseline patient characteristics (e.g., age, gender, concomitant medications or illness) or disease characteristics (e.g., duration or severity of disease, prior treatments).

For some indications, there will be a pharmacodynamic endpoint that correlates, with some degree of assurance, the product’s bioactivity with clinical benefit. In these cases, the Phase 2 study could assess efficacy using the pharmacodynamic endpoint at an earlier timepoint than the timepoint used to assess clinical benefit in Phase 3. For example, the primary endpoint in a Phase 2 study evaluating an investigational therapy for multiple sclerosis might be the number of new enhancing brain lesions detectable on MRI at 6 months, while the primary assessment of clinical benefit in Phase 3 will be based on the change in Kurtzke Expanded Disability Status Scale at 12 or 24 months. For diseases in which appropriate clinical endpoints are not well defined, Phase 2 studies can evaluate potential clinical endpoints, provide insights on measuring the endpoints, and establish their reliability in demonstrating clinically meaningful effect.

Phase 3 The goal of Phase 3 studies is to generate definitive evidence of the product’s safety and efficacy to support market authorization. During the Phase 3 studies, the sponsor must also collect sufficient clinical data to support statements within the package insert.

Design Issues

Phase 3 clinical studies are generally larger, lengthier, and more complex in design than studies conducted in the earlier phases of development. The studies are generally randomized, double blind, and placebo controlled whenever possible. When placebo controls are not feasible or are deemed unethical, an active control with known clinical benefit can be used as the comparator. The ICH’s *E10: Choice of Control Group and Related Issues in Clinical Trials* (2001)¹³ outlines general principles involved in choosing a control group in clinical efficacy studies, as well as other related study design issues, such as the utility of superiority and non-inferiority designs.

Study participants in Phase 3 studies are patients representative of the intended patient population and are defined by the study’s eligibility criteria. Although the study population should be sufficiently homogeneous to demonstrate the biological product’s effect, it must also be sufficiently representative to allow generalization of the results to the larger patient population.

The efficacy endpoint studied in Phase 3 trials must be one that demonstrates clinical benefit in the intended patient population. Generally, the endpoint is a clinical outcome measure that has been accepted by regulators and physicians as having clinical meaning to patients. The ideal efficacy endpoint is an objective and reliable measure of clinical outcome that is clinically interpretable and sensitive to changes in disease states. Whenever possible, the method of measuring the clinical endpoint should be well established and validated. If a product’s clinical endpoints are poorly defined, the Phase 3 study design may have to provide for the formal assessment of a combination of efficacy outcomes to provide a convincing demonstration of efficacy.

In Phase 3 studies, surrogate endpoints are often used as secondary endpoints to confirm the findings related to a primary efficacy endpoint and to further strengthen the evidence of a product’s efficacy. Although surrogate endpoints do not measure clinical benefit directly, they are considered predictive of

efficacy. For investigational products developed under the FDA's accelerated approval regulations, approval may be based upon a surrogate endpoint considered reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. For other products, a surrogate endpoint can be used as a primary endpoint in a Phase 3 study only if that endpoint is validated. Validation requires the testing of both the surrogate and the clinical endpoint in the same trial as well as a prospectively defined analysis that establishes a link between the two.

The statistical analytical plan is an important component of the Phase 3 clinical study design. A prospective plan defines the study's hypothesis, identifies the type of data to be collected, and describes how the data are to be analyzed. The analytical plan should include a definition of the endpoint(s), calculations for statistical power, statistical methods used in the analyses, procedures to optimally address and minimize the frequency of missing data, and a definition of the study participants to be included in different analyses. The study design and statistical plan should include analyses of populations based on demographic differences (e.g., race/ethnicity,¹⁴ sex, age¹⁵), which are required for market authorization.

The statistical analytical plan must be written prior to unblinding of the Phase 3 study and preferably prior to study initiation. *Post hoc* analyses of clinical data conducted after unblinding may provide information, but generally will lack the validity to support market authorization by themselves. The ICH's guidance document entitled, *E9: Statistical Principles in Clinical Trials*¹⁶ (1998) addresses the statistical monitoring of trials, describes available statistical approaches, and presents the principles involved in their implementation.

Phase 3 studies are generally large, multicenter studies that include multinational sites. Given the complexity of Phase 3 trials, sponsors will often establish a data monitoring committee (DMC) to assist in monitoring a Phase 3 study. In addition to providing an objective assessment of safety events, DMCs can be chartered to monitor the conduct of the clinical study (e.g., rates of recruitment, accrual of important subsets), assess the impact of new data on the study (e.g., results of a related study, introduction of a new therapy), or conduct an interim analysis of unblinded data in an effort to address specific efficacy-related questions. Based upon its review, the DMC can make recommendations regarding the study conduct (e.g., early termination, increasing the sample size, modifications to the informed consent, discontinuation of a treatment arm). In a 2001 draft guidance entitled, *The Establishment and Operation of Clinical Trial Data Monitoring Committees*,¹⁷ the FDA recommends situations in which DMCs should be used, and discusses related issues (e.g., independence) regarding their use in clinical trials.

Postmarketing Studies Postmarketing, or Phase 4, clinical studies often evaluate an approved biological therapeutic product in the approved or a closely related patient population to address certain safety or efficacy questions that arose during the BLA review, that were not completely answered during clinical development, or that remain of clinical interest to the sponsor and/or the FDA. A Phase 4 study, for example, could be conducted to further characterize a product's safety profile, evaluate a new indication, or assess a different delivery system.

Some Phase 4 clinical studies are required by the FDA (see Chapter 11). For products approved under the accelerated approval provisions, the FDA requires Phase 4 studies designed to confirm a product's clinical benefit. These Phase 4 studies may be designed to evaluate a similar or different patient population, to assess a different stage of the disease, or to utilize a clinical endpoint to demonstrate benefit. As noted below, a company's failure to demonstrate clinical benefit in such cases could lead to the FDA's withdrawal of market authorization. Sponsors discuss the design of these postmarketing studies with the FDA and, under the accelerated approval provisions, initiate such studies prior to market authorization. Phase 4 clin-

ical studies are also required when the FDA grants a deferral of pediatric studies/data at the time of market authorization.

Other Phase 4 studies are conducted when, following discussion with the FDA at the time of approval, the sponsor commits to further evaluate remaining issues or questions regarding a drug's safety, efficacy or clinical use. Phase 4 studies may be a component of a risk management program that a sponsor implements in an effort to assess the effectiveness of programs designed to reduce risks to patients. Frequently, Phase 4 studies for biological products include a further evaluation of immunogenicity, the evaluation of long-term safety using a patient registry, or the establishment and evaluation of clinical data from a pregnancy registry.¹⁸ Such postmarketing studies, including those involving registries, are based on a written protocol that describes the study design, patient population, and data collection and analysis.¹⁹

Special Topics in the Clinical Development of Biologically Derived Therapeutics

While a single chapter cannot address all aspects of clinical trial programs for therapeutic biological products, the following section discusses cell and gene therapies, which comprise a special category of biological therapeutics. This section also addresses a number of scientific and regulatory issues that can affect the clinical testing of biologically derived therapeutics.

Cell Therapy and Gene Therapy Relative to other biologically derived therapeutics, industry and the FDA have significantly less experience in the clinical development of cell therapies and gene therapies. At the same time, clinical programs assessing the value of cellular and gene therapies for numerous indications, ranging from chronic, non-life-threatening diseases to acute, life-threatening diseases remain extremely active.

Cell Therapy Over the past decade, the FDA has issued several notices or rules regarding the regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps). HCT/Ps include cellular therapies, human tissues and cells intended for transplantation, and reproductive tissue. The exhibit below identifies several types of HCT/Ps and specifies how they are regulated.

In most cases, the amount of *ex vivo* manipulation to which a product is subjected determines how the specific HCT/P is regulated. Human cells or tissues that are minimally manipulated (e.g., skin, cadaveric cornea) are regulated under section 361 of the PHS Act and 21 CFR 1271. The FDA is in the process of formulating regulations regarding the type of data that will be necessary to support the marketing of minimally manipulated human cell and tissues. The "tissue rules"—21 CFR 1271 and a pair of proposed rules (see discussion below)—are intended to minimize the risk of transmitting disease to recipients, to prevent contamination, and to preserve the integrity of the cells and tissues. Currently, clinical data from adequate and well-controlled studies are not required for such cells and tissues. FDA regulations (21 CFR 207, 807, and 1271) require establishments that process, test, or store human tissue for transplantation to register with the FDA. The FDA's proposed donor eligibility rule—*Suitability Determination for Donors of Human Cellular & Tissue-Based Products* (64 FR 52696)—would require that donors be properly screened and tested for communicable diseases. In its January 2001 Good Tissue Practices proposed rule, the FDA describes the proper handling and processing of cells and tissues as well as appropriate facility controls (Current Good Tissue Practice (cGTP) for Manufacture of Human Cellular and Tissue-Based Products; Inspection and Enforcement, proposed rule, 66 FR 1508).

In contrast, products comprising more-than-minimally manipulated cells and tissues are regulated under 351 of the PHS Act and 21 CFR 312 and 600. When finalized, elements of the proposed regulations cited above revising CFR 1271 will apply to these products as well. Sponsors for these investigational therapies must demonstrate safety and efficacy in adequate and well-controlled clinical trials to support market authorization. As described in 21 CFR 312, the FDA reviews proposed clinical investigations through investigational new drug applications (see Chapter 3) and/or through investigational device exemption applications (IDE).

By definition, most somatic cell therapies are considered “more than minimally manipulated,” and therefore clinical safety and efficacy data from adequate and well-controlled investigations are required to market these products. Somatic cell therapies involve the *ex vivo* propagation, expansion, selection, and/or pharmacological treatment of cells (or other modification of the cell’s biological characteristics) intended to treat or cure disease. Given that the cell therapy field is evolving rapidly and that the clinical data requirements differ dramatically among various HCT/Ps, developers should seek FDA advice regarding the regulation of a particular cellular product early in the product development process.

In June 2002, the FDA requested that holders of cell therapy INDs and IDEs submit information regarding product manufacturing quality control procedures and clinical oversight (see Chapter 7). Issued in

Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/P)

Regulated under Section 351 of the PHS Act and 21 CFR 312 and 600

Cell therapies (e.g., isolation and expansion of peripheral CD34⁺ hematopoietic cells, activation and *ex vivo* expansion of lymphocytes, *ex vivo* expansion of bone marrow cells)

Genetically modified cells (e.g., autologous tumor cells genetically modified to express a cytokine, introduction of multi-drug resistance gene into stem cells, infusion of cells modified *ex vivo* with the Factor VIII gene for the treatment of patients with hemophilia A)

Non-homologous use of cells or tissues. Non-homologous cells are cells isolated from one tissue and used for a cellular function other than their normal *in vivo* function (e.g., the implantation of stem cells directed to differentiate into specific cell types, such as dopaminergic neuronal cells, for the treatment of Parkinson’s disease, or insulin-secreting cells for the treatment of diabetes)

Cells whose clinical effect depends upon their systemic effect or metabolic activity (e.g., implantation of human pancreatic islet cells for the treatment of diabetes, neural cells for treatment of Parkinson’s or spinal cord injury)

Any cells or tissues that are combined with a drug, biological product, or device (Note: Depending upon the cell product, materials such as matrices, other biological products, or drugs may be considered excipients, active components, or medical devices and be made subject to additional regulation.)

Regulated under Section 361 of the PHS Act and 21 CFR 1271

Human cells or tissues for transplantation (e.g., musculoskeletal tissue, dura mater, cadaveric cornea, human stem cells that are “minimally manipulated” and for homologous use)

Reproductive tissue

response to safety-related concerns, this agency request harmonized the type of data that sponsors of cell and gene therapies must submit to the FDA. The FDA will continue to request that new INDs and IDEs for cell therapies include a comprehensive description of the clinical monitoring plan as well as the quality control procedures for the cellular product manufacture.

Gene Therapy Gene therapy involves the modification of a living cell's genetic material in an effort to treat or cure a disease. As discussed above, gene therapy can involve the administration of *ex vivo* genetically modified cells through infusion, implantation, or other means. Alternatively, a gene therapy can be administered directly *in vivo* (e.g., inhalation, injection into a tumor, intramuscular injection).

Currently, gene therapies are being evaluated for their ability to replace missing or defective genes, and to deliver genes that destroy cancer cells, promote growth or new tissue, or stimulate regeneration of damaged tissue. Numerous genes have been evaluated, including CFTR for cystic fibrosis, VEGF for coronary artery disease and peripheral vascular disease, and p53, E1A, and IL-2 for cancer.

Gene transfer vectors are designed to transfer the gene of interest into the target cell and regulate gene expression. To this point, a number of vectors derived from viral and non-viral components have been employed. Viral vectors take advantage of a virus' ability to infect different cell types and deliver the gene to the cell's nucleus. Due to the concern about the potential risks of cancer or viral infection, most vectors under active clinical investigation are replication incompetent or require a helper virus to replicate. Based on the target cell or therapeutic goal, components from poxviruses, adenovirus, herpes virus, and retroviruses have been used. Non-viral vectors consisting of plasmid DNA with the inserted gene are often packaged in liposomes to facilitate cell entry.

To regulate gene expression, the vector design will incorporate a promoter to control gene expression. Numerous promoters are being investigated, including those with cell-specific, inducible, and constitutive expression.

Needless to say, because of limited experience with different vector types and genetic insertions, both regulators and investigators recognize the need to exercise significant caution when investigating gene therapies. Therefore, proposals for clinical investigations involving new gene therapy products must be submitted to the National Institute of Health's (NIH) Recombinant DNA Advisory Committee (RAC). This additional level of review (i.e., in addition to the FDA's review of the IND) is unique to gene therapy. The RAC is responsible for conducting a public scientific and ethical review, and for discussing the novel application of the gene therapy and related public policy issues.

Given emerging safety-related concerns regarding gene therapy trials, the FDA used a November 1999 letter to outline the processes through which gene therapy investigators must submit documentation to the RAC and the FDA.²⁰ Following its initial review of a gene therapy proposal, the RAC may decide to publicly discuss the reviewed protocol. Factors that may influence the RAC's decision to hold a public hearing include the use of new vectors or new gene delivery systems, the use of gene therapy in a new disease, or the unique application of gene transfer. It is important to note that any adverse event reported to the FDA during the protocol study period should also be reported to the NIH's Office of Recombinant DNA Activities (ORDA), as required by the NIH Guidelines for Research Involving Recombinant DNA Molecules.²¹

Following the report of a patient death after the administration of an experimental gene therapy product in the United States, the FDA issued a March 2000 letter requesting that all sponsors/investigators involved

in gene therapy trials submit a detailed plan describing the monitoring and oversight for the clinical study as well as information on the quality control procedures for the product's manufacture. In addition, sponsors were also required to submit an organizational chart identifying the units responsible for clinical study oversight as well as the individuals responsible for clinical study oversight (including their training and qualifications). Under this March 2000 Gene Therapy Monitoring Plan, CBER continues to require that gene therapy study sponsors routinely submit their monitoring plans, certain manufacturing-related information, and other information to the agency.

As part of the March 2000 initiative, the FDA discussed appropriate monitoring procedures for gene therapy trials with its Biological Response Modifiers Advisory Committee (BRMAC) in October 2001. Much of the discussion focused on the need for long-term monitoring of study participants exposed to gene therapies. Based upon the committee's recommendations, the FDA is requesting that sponsors of all new gene therapies, regardless of vector type, continue to monitor study participants for at least 15 years post-study. The advisory committee recommended that the principal investigator physically examine study participants for the first five years following study participation. Subsequent monitoring need not include physical examination, but may involve telephone calls, questionnaires, postcards, or other vehicles. Throughout the 15 year follow-up period, information on the occurrence of new malignancies or autoimmune, neurological, or hematological diseases should be collected annually. Study participants should also be asked about any changes in medication or the need for hospitalization. These recommendations may be modified in the future as clinicians, researchers, industry, and regulators meet to discuss this topic.

Studies involving gene therapies that employ retroviral vectors to transduce CD34⁺ hematopoietic stem cells require special consideration. These types of studies were placed on clinical hold in January 2003 following a second report of leukemia in a France-based clinical trial involving children with X-linked severe combined immunodeficiency syndrome (X-SCID). Following a discussion at a February 2003 BRMAC meeting, the FDA allowed these studies to continue on a case-by-case basis after sponsors notified IRBs, investigators, and study participants of the potential risk of hematopoietic malignancy associated with the vector use.

In addition, the FDA requested additional analyses that will most likely apply to future investigations of gene therapy using retroviral vectors, particularly for the transduction of hematopoietic stem cells. Specifically, the FDA requested that sponsors analyze patients' peripheral blood mononuclear cells (PBMCs) for the clonality of vector integration sites at least every six months for the first five years after administration, and then annually for the next ten years. If a predominant clone is detected, then the researchers should assess the presence of a predominant integration site, something that would necessitate repeat analysis within three months to determine if the clone is persistent. If clonality is persistent, the integration site should be sequenced to determine any association with known human cancers, and the study participant should be closely monitored for malignancy. Needless to say, the design of all future investigations involving retroviral vectors, particularly those involving transduced hematopoietic stem cells, must take these known risks into account.

Immunogenicity Immunogenicity, or the stimulation of antibody formation to an investigational biological product (or some portion of the biological product), has become a major clinical and regulatory safety concern for biologically derived therapeutics in general. The exhibit below identifies possible causes of immunogenicity for biologically derived therapeutics.

The impact of an antibody response to a biological product on safety and efficacy is variable and unpredictable. Antibody development can result in no apparent clinical effect, an altered pharmacokinetic profile, neutralization of the product's activity, or local or life-threatening systemic allergic reactions.

Due to species specificity, the utility of preclinical models to predict immunogenicity or its effects may be limited. Some therapeutic proteins are "human" or "humanized" and, therefore, naturally trigger an immune response in animals. Also, the biological product may not demonstrate the same activity in animals (e.g., differences in clearance or target protein, cell, or receptor). This variability in effect and the difficulty of assessing potential clinical effects of antibody formation from preclinical toxicology studies for some products make careful study monitoring even more important, particularly for adverse events in early human studies. Thus, an assessment of antibody formation and the effect of immunogenicity on safety and efficacy should be incorporated into the design of early clinical studies and should continue throughout clinical development. Obviously, the development and validation of sensitive assays are necessary for evaluating immunogenicity.

The degree of immunogenicity can vary depending upon the patient population, the route of administration, and the frequency of administration. The risk of antibody formation may be lower in immunocompromised study participants than study participants with an intact immune response. The risk may be also higher when biological products are administered intradermally as opposed to intravenously or intramuscularly, and when administered repeatedly or intermittently on a chronic basis. Although the proportion of

Possible Causes of Immunogenicity

- Non-self immunogenic epitopes
 - Presence of non-human proteins (e.g., bacterial, bovine, porcine products)
 - Alteration in protein sequences (e.g., fusion proteins, chimeras)
 - Impurities
- Exposure of "hidden" epitopes
 - Glycosylation
 - Dissociation of multimeric proteins
 - Denaturation
- Breaking tolerance
 - Exposure to high levels of "natural" sequences
 - Exposure to altered "self" proteins
 - Stimulation of "clonally ignorant" B-cells
- Aggregation
 - Caused by non-glycosylation, oxidation, deamidation, shearing, heating, etc.
- Unknown factors

patients who develop antibodies may be higher with some types of biological products, there may be no correlation between the frequency or degree of antibody response and its effect on safety and efficacy. All of these factors must be taken into account when designing clinical studies, and will ultimately determine the quantity of immunogenicity data that should be collected.

Safety with Chronic Administration Most, if not all, of the early clinical investigations of biologically derived therapeutics were conducted in study populations with severe or life-threatening diseases (e.g., patients with solid tumors or hematological malignancies). Over the last 10 to 15 years, however, increasing numbers of biological products have been developed to treat patients with moderate to severe stages of chronic diseases, such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, and asthma. The underlying pathology for these and other chronic diseases under investigation is a dysfunction in the body's immune response.

Currently, approved and investigational biologically derived therapeutics are intended to treat these diseases by modifying the body's response to either an auto- or exogenous antigen. The biological products differ in their primary target for the immune response, and in the degree of inhibition of the immune response. It is unknown what effect chronic administration of such immunomodulatory agents will have on long-term safety. Potential concerns for patients include an increased risk for infectious diseases, new onset autoimmune diseases, and cancer, particularly lymphoma.

Therefore, the long-term effects of chronically administered biologically derived products must be monitored carefully following approval. Given these concerns, the FDA has frequently requested that sponsors agree to monitor the long-term safety of these products in postmarketing studies or patient registries. Often, these registries are large (5,000 to 10,000 patients) and are conducted over five to ten years.

Regulatory Processes Because biologically derived therapeutics are commonly developed to treat patients with serious or life-threatening diseases, sponsors increasingly employ special regulatory processes designed to expedite the development and approval of these products. The so-called fast-track program and accelerated approval process are among the most commonly used for such products.

Fast Track Under the FDA Modernization Act of 1997 (FDAMA), Congress established the fast track process to facilitate the development, and expedite the review, of products that demonstrate the potential to address unmet medical needs in the treatment of serious or life-threatening conditions (Section 506 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 356). To become eligible for the benefits offered under the fast track program, a drug sponsor must first apply for, and obtain, a fast track designation for its drug product. The sponsor can seek an FDA fast track designation for a product at any point in the product's development, although most fast track designations have been granted during the clinical development process. CBER and CDER outline the fast track application and designation process in a 1998 guidance entitled, *Fast Track Drug Development Programs—Designation, Development, and Application Review*.²²

The fast track program offers several benefits, although many are available under other FDA regulations and programs. Under the program, the FDA can approve a designated biological product after the sponsor demonstrates either the product's clinical benefit or its effect on a clinical or surrogate endpoint that is reasonably likely to predict clinical benefit (see discussion on accelerated approval below). Although most sponsors have found CBER reviewers to be open to meetings, the FDA's designation of a product as a fast track product can facilitate the agency/applicant meetings process. Further, fast track products generally are granted priority review status (i.e., six month review target).

In addition, sponsors of designated fast track products can request, by submitting clinical data indicating that the product may be effective, that the agency accept for formal review completed portions of a BLA before the other sections of the application are submitted. If the agency permits this submission—sometimes called a rolling submission—the sponsor is required to provide a schedule for submitting the information necessary to make the BLA submission complete. The rolling NDA/BLA was the model for the “reviewable unit” concept that will be studied formally under PDUFA III’s continuous marketing application (CMA) pilot program (see Chapter 8).^{23,24} Sponsors intending to employ the rolling submission approach for their BLA must discuss the logistics and requirements with the FDA prior to its implementation.

Biologics sponsors have been active in pursuing fast track designations. Between March 1, 1998, and September 30, 2003, industry had submitted 114 designation requests to CBER, of which 66 have been granted. CBER had denied 44 of the requests (four additional requests were pending).

Accelerated Approval The FDA’s accelerated approval program was implemented under a December 1992 regulation (21 CFR 601, Subpart E-biologics and 21 CFR 314, Subpart H-drugs) in an effort to expedite the review and approval process for significant new products that are intended to treat serious or life-threatening diseases and that provide meaningful therapeutic benefit over currently available therapies. A unique feature of the program is that it permits the FDA to approve products based upon either: (1) an effect on a surrogate endpoint considered reasonably likely to predict a clinical benefit (survival or the prevention of irreversible morbidity); or (2) an effect on a clinical endpoint other than survival or irreversible morbidity.

Generally, market authorization under the accelerated approval program is contingent upon an applicant’s commitment to conduct new evaluations or complete ongoing studies to verify and describe the clinical benefit. In most cases, the Phase 4 studies are initiated prior to market authorization. If these trials fail to demonstrate clinical benefit (i.e., the surrogate did not correlate with clinical response), the FDA could withdraw its approval for the product. Thus far, no product approved under the accelerated approval program has had its market authorization withdrawn.

Special Protocol Assessment Under PDUFA II, the FDA introduced the “special protocol question assessment and agreement” process. As part of this process, the FDA agreed to evaluate Phase 3 clinical trial protocols (as well as carcinogenicity and stability protocols) to determine whether a trial’s design and size are adequate to meet scientific and regulatory requirements identified by the sponsor. A review division may also consider other clinical protocols under the special protocol assessment process, provided that the division agrees and is aware of the clinical study’s role within the overall clinical development plan. Within 45 days of receiving such a protocol and specific sponsor questions, the agency provides a written response that includes “a succinct assessment of the protocol and answers to the sponsor’s questions.”

In part, this process is designed to produce formal FDA commitments on study design issues. According to text that accompanied the FDA’s PDUFA II commitments, “the fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues...unless public health concerns unrecognized at the time of protocol assessment under this process are evident.” Language in the FDA Modernization Act of 1997 adds that, “any agreement regarding the parameters of the design and size of clinical trials of a new drug...that is reached between the [FDA] and a sponsor or applicant shall be reduced to writing and made part of the administrative records...[and] shall not be changed after the testing begins, except (i) with the written agreement of the sponsor or applicant; or (ii) pursuant to a decision...by the director of the review-

ing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified....”

The special protocol assessment process is particularly valuable when a study involves an indication or disease for which there is no previously approved therapy or when the study's design or endpoints are unique. CDER and CBER released a 2002 industry guidance entitled, *Special Protocol Assessment* to outline the process under which such assessments will be conducted and agreements will be reached.²⁶

Manufacturing Changes During Clinical Development During the clinical development program, manufacturing processes for the biologically derived therapeutic will undergo changes designed to reduce impurities, increase yield, or improve efficiency. Manufacturing process changes for biologically derived therapeutics have been known to affect a product's clinical safety or efficacy. Following the selection of a different cell line, for example, some biological products have shown a decline in efficacy in clinical studies. Changes in immunogenicity have been attributed to variation in the amount or types of aggregates, the structural presentation of the product, or the degree of denaturation that occurred following a manufacturing change.

Among the complexities associated with implementing biological product manufacturing changes is our inability to predict precisely what effect, if any, a given manufacturing change will have on a biological product's safety or efficacy. Many times, problems encountered in the clinic cannot be fully or logically explained, and may reflect our inexperience with certain classes of biological products or the inability of available assays to characterize the biological product fully.

Given these realities, it is critical that manufacturers analyze the product on a pre- and post-change basis to demonstrate comparability (i.e., a side-by-side analysis). The demonstration of comparability provides the FDA with assurance that the manufacturing change did not result in a significant change in the product's characteristics (i.e., identity, strength, quality, purity, and potency (efficacy)). It is important to note that the FDA decides whether the data are sufficient to demonstrate comparability. The agency has extensive scientific and regulatory experience with manufacturing changes across a number of different types of biological products and can often provide invaluable guidance. Therefore, manufacturers should consult with the FDA before implementing manufacturing changes during clinical development.

The demonstration of a product's comparability is based upon extensive chemical, physical, and biological assays and, when necessary, preclinical or clinical evaluation. Biological assays should be valid and, whenever feasible, reflect *in vivo* biological activity. Rather than detecting the presence of an expressed gene product or binding to the target, the *in vitro* and/or *in vivo* biological assay(s) should demonstrate the cellular or enzymatic response.

The need for additional preclinical (e.g., pharmacokinetics, immunogenicity, specific toxicology) or clinical (e.g., pharmacokinetic, immunogenicity, safety/efficacy) data will depend on the adequacy of the analytical and biological assays as well as the results of these tests. While a well-designed comparability program should circumvent the need for clinical evaluation, clinical data regarding pharmacokinetics or immunogenicity may sometimes be needed during clinical development (e.g., when animal specificity necessitates evaluation of pharmacokinetics in humans).

The FDA's 1999 guidance entitled, *Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products* outlines the types of data necessary to demonstrate comparability.²⁷ The ICH guidance entitled, *Q6B: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*²⁸ is

another useful document in this area. The ICH parties have selected the demonstration of comparability of biologically derived therapeutics as a future topic for harmonization.

The timing of major manufacturing changes implemented during the later stages of clinical development could affect the acceptability of Phase 3 clinical data designed to support marketing approval. Ideally, the product used throughout Phase 3 studies should be manufactured using a process as close as possible to the process to be used following a product's commercialization. There are, however, cases in which significant manufacturing changes (e.g., scale-up of process, change in working cell bank, changes in fermentation processes, moving to a commercial manufacturing plant, etc.) are introduced during or after Phase 3. When these occur, the sponsor must discuss the type of manufacturing change and the anticipated impact on the Phase 3 clinical with the FDA.

When significant manufacturing changes are introduced during Phase 3, the FDA can analyze the clinical data for differences in safety and efficacy between pre- and post-change material. The absence of significant differences or trends in differences will support the comparability testing, and the results of the Phase 3 study will not be compromised. When differences are detected or the commercialization of the manufacturing process occurs following the clinical development program's completion, the FDA may require additional preclinical or clinical data (e.g., pharmacokinetic data, immunogenicity, or even safety/efficacy) to support comparability.

In summary, although process changes are routinely implemented during the clinical development program, the comparability of the biological product must be demonstrated. The quantity and type of data necessary to demonstrate the comparability of biologically derived therapeutics both during clinical development and after market authorization continue to evolve as the analytical tests used to characterize the product improve and as experience with post-change clinical effects for different biological products grows.

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