Legal and Scientific Considerations in Nonclinical Assessment of Biotechnology Products

Nonclinical evaluation of biotechnology-derived products is no longer an academic pursuit in product development. The conduct of relevant nonclinical studies serves the purposes of regulatory compliance and managing potential risks that may be associated with the product or the process. While the legal framework for the regulation of biotechnology/biological products is administratively different between the United States and the European Union, the scientific principles underpinning the safety, quality, and efficacy of biotechnology-derived products are not markedly different. Technical guidelines already developed at the International Conference on Harmonisation have been helpful in addressing global development of biotechnology-derived products. At each stage of any drug development program, product liability risks arising from poor product design as well as regulatory requirements must be considered. This article also briefly addresses the European product liability law as it relates to nonclinical evaluation of biotechnology-derived products.

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INTRODUCTION

Biological or biotechnological products are structurally complex and involve manufacturing processes which require tight control in order to ensure their safety, quality, and efficacy. Biological and biotechnological products cover a wide array of product types with diverse product characteristics (see Table 1). Therefore, there are philosophical and technical differences in the conduct of nonclinical studies between conventional chemically-synthesized products and those derived from a biological process. Such differences have resulted in the development of separate regulatory guidance.

Nonclinical testing of biological products includes nonclinical animal testing, long-term toxicity testing, and in some cases, testing performed when manufacturing processes are modified. The principal objectives of the conduct of nonclinical safety evaluation of biotechnology-derived pharmaceuticals are to address the following issues:

- To determine whether the pharmaceutical may be administered to human test subjects without unjustified risk,
- To identify an initial safe dose and subsequent dose escalation schemes in humans,
- To identify potential target organs for toxicity and for the study of whether such toxicity is reversible, and
- To identify safety parameters for clinical monitoring.

In designing the nonclinical animal testing, consideration should be given to the quality aspects of a given product, including its product characteristics, purity, and stability.

Long-term (chronic) animal testing includes tests that are intended to predict effects in humans that cannot be readily identified in preapproval clinical trials, principally, carcinogenicity and reproductive effects. Chronic animal tests will often be performed concurrently with clinical testing. In rare instances, such as the testing of antidotes of bio-weapons, appropriate nonclinical testing may be substituted for clinical testing that is not permissible because of ethical concerns. Testing performed to assess the safety of changes in manufacturing processes may include, for example, immunogenicity testing.

This article addresses legal issues relating to the design and performance of nonclinical testing of biotechnology products, in particular:

- The regulatory and legal framework governing biologicals and biotechnology products,

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TABLE 1

Products that are Considered "Biologicals"
Classical Biologicals
• Blood-derived products
• Vaccines
Recombinant Proteins
• Cytokines
• Hormones
• Monoclonal antibodies
Nucleic Acid Based Products
• Gene transfer medicinal products
• DNA vaccines
Cell-based products
• Autologous, allogeneic, and xenogeneic cell therapy products
Tissue-based Products
• Allogeneic grafts

- The regulatory requirements for nonclinical testing,
- Use of nonclinical testing to show product comparability when manufacturing processes change,
- Communication of information derived from nonclinical testing in the Summary of Product Characteristics, and
- Product liability exposure as related to nonclinical testing.

While this article primarily focuses on the European Union law governing the grant of marketing authorization, references are also made, where relevant and appropriate, to the United States requirements for the purpose of comparison.

REGULATORY FRAMEWORK

LEGAL DEFINITION OF A BIOTECHNOLOGY PRODUCT AND A BIOLOGICAL PRODUCT

European Union. In the European Union, Part A of Annex 1 to Council Regulation 2309/93/EC (1) provides a legal definition of a biotechnology medicinal product based on the manufacturing process employed: "Medicinal products developed by means of one of the following biotechnological processes: recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma and monoclonal antibody methods." The definition is sufficiently broad to capture recombinant proteins but also gene-based therapeutics and prophylactics such as gene transfer medicinal products and DNA vaccines. Products that are produced using the processes as defined in this annex must be authorized under the European Union Centralised Procedure pursuant to article 3 of the regulation. Between 1995 and November 2002, a total of 67 biotechnology or biological human medicinal products were authorized through the European Union Centralised Procedure. A breakdown of these authorizations by product-types is depicted in Figure 1.

A biological medicinal product is now defined in the recently adopted Annex I to Directive 2001/83 (as amended by Directive 2003/63/EC) to mean a product, the active substance of which is a biological substance (2). A biological substance encapsulates two important aspects: that it is produced by or extracted from a biological source, and that there is a need to use a combination of physico-chemical-biological testing, together with the process control, to define its quality and characteristics. According to the annex, the following are considered biological medicinal products:

- Biotechnology-derived medicinal products,
- Blood and plasma-derived medicinal products, and
- Immunological medicinal products.

Indeed, articles 109 to 110 and articles 113 to 115 of Directive 2001/83/EC (2) set out specific legal provisions for the regulation of derivatives from human blood and plasma, and immunological medicinal products.

Directive 2001/20/EC (3), which is currently being transposed into domestic law of the Member States, creates a new category of medicinal products for the purpose of approval of clinical trials in the European Union. Article 9 defines

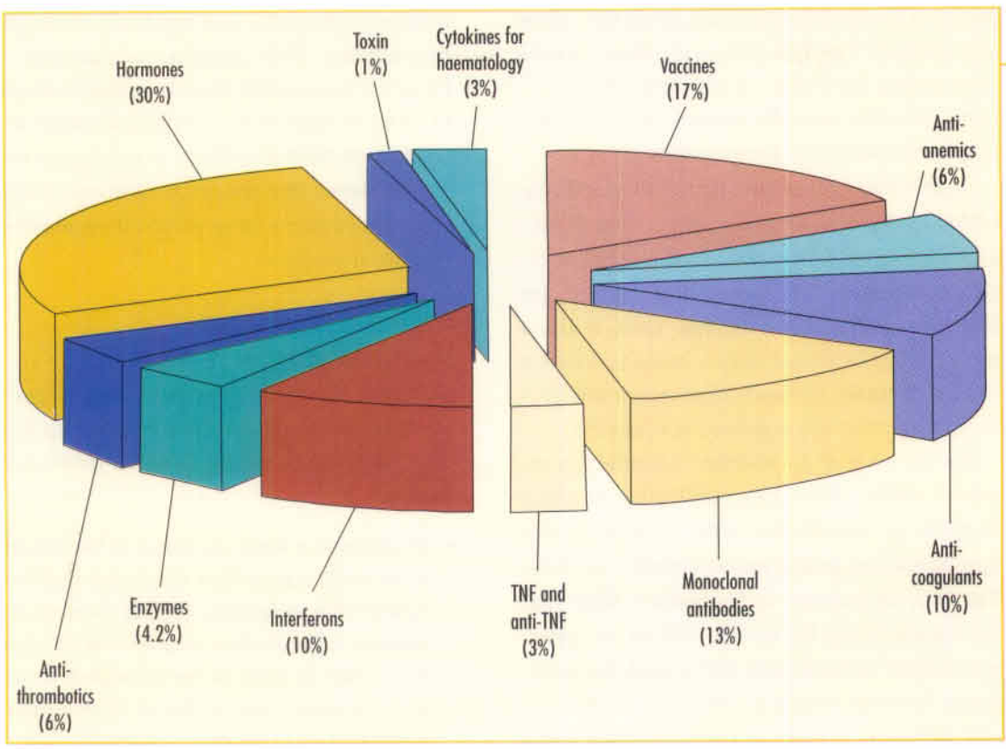

FIGURE 1

Distribution (%) of Biotechnology or Biological Human Medicinal Products Authorized through the European Centralised Procedure between 1995 and November 2002.

"medicinal products with special characteristics," which may include: human somatic cell therapy, xenogeneic cell therapy, gene therapy, and products containing a biological active ingredient of human or animal origin or products containing biological components of human or animal origin or the manufacturing of which requires such component.

Distinguishable from its chemical counterparts, this category of products requires a written authorization according to article 9 of the directive. For xenogeneic cell therapy products, there is no time-limit for the approval process. In the case of gene therapy products, there is a statutory bar for germ-line modification (see below).

Further, in the revised Annex 1 to Directive 2001/83/EC (2), a separate class of product called "advanced therapy medicinal products" is defined. This includes gene therapy, human, and xenogeneic somatic cell therapy products. The revision sets out additional legal requirements specific to the regulation of this class of products.

United States. In the United States, the Food and Drug Administration (FDA) approves biological products by review of biologics licence applications (BLAs) pursuant to Section 351 of the Public Health Service (PHS) Act, 42 USC 262(a) (4). For purposes other than approval, biological products are regulated under the Federal Food, Drug and Cosmetic Act. "Biological product" is defined in § 351(i) (PHS) act as: "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood and blood component or derviative allergenic product or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."

Using this definition, products such as therapeutic and prophylactic vaccines, clotting factors and immunological products derived from blood are regulated as biological products. The FDA utilizes PHS provisions to enable it to regulate gene therapy and tissues for xenotransplantation. The statutory criteria for assessment of

products licensed through BLA are purity, safety, and potency. The FDA interprets these criteria as requiring (with rare exceptions) clinical evidence of safety and effectiveness as well as appropriate nonclinical investigations.

Certain naturally occurring products are regulated by the FDA as drugs rather than as biologics, for example, hormones, which include insulins, fertility hormones, and drugs for hormone replacement therapy. Even if those products are extracted from a biological milieu or manufactured by means of recombinant DNA technology, they are regulated as drugs (5).

The decision as to whether a product is reviewed under a New Drug Application or a BLA is made in accordance with an Inter-Center Agreement first published on October 31, 1991. The FDA announced in September 2002 that the responsibility for review of BLAs for "pharmaceutical" biological products would be transferred from the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). However, the review of products derived from blood, vaccines, toxoids, allergens, anti-toxins, and products derived from cutting-edge technologies such as gene therapy and cell therapy will remain in CBER. The process of transferring certain biotechnology products from the CBER to the CDER for regulatory reviews entered its final phase in January 2003. The FDA announced that the CDER would have jurisdiction over the regulatory oversight of: monoclonal antibodies; cytokines, growth factors, enzymes, and interferons; and proteins extracted from animals and micro-organisms.

The CBER will retain its responsibility to oversee monoclonal antibodies, cytokines, growth factors, and other proteins used solely for an ex vivo constituent in a manufacturing process or as a reagent in production of a CBER-regulated product. While the CBER retains the lead responsibility for therapeutic vaccines and cellular products and this policy decision fits well with its current research interests, the FDA indicates that the reviews will be fully coordinated with the CDER (6).

The impact of the reorganization of the FDA in relation to the policy and regulatory oversight of recombinant DNA proteins is currently unknown. It seems likely that there will be changes in terms of approaches to the evaluation of recombinant proteins. There is no reason to expect, however, that the reorganization will affect FDA requirements for nonclinical testing of new biological products.

LEGAL REQUIREMENTS FOR NONCLINICAL TESTING

European Union regulatory requirements for nonclinical animal studies are set out in Annex 1 to 2001/83/EC (2). The salient points are as follows:

- All information which is relevant to the evaluation of the medicinal product concerned shall be included in the application, whether favorable or unfavorable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmacotoxicological or clinical data test or trial relating to the medicinal product, and
- All safety tests should be carried out according to Good Laboratory Practice as laid down in Council Directive 87/18/EEC (7) and 88/320/EEC (8). An equivalent provision can be found in US 21 CFR §58.1 (9).

The preamble to Annex I specifically states that all tests on animals are conducted in accordance with Council Directive 86/609/EEC regarding the protection of animals for experimental and other scientific purposes (10).

These legal requirements oblige the marketing authorization applicants to submit full data in order that a full risk/benefit evaluation can be conducted by the competent authority. The current Annex I provides for a case-by-case approach to the conduct of nonclinical testing, taking into account the following:

- All tests requiring repeated administration of the product "shall be designed to take account of possible induction of and interference by antibodies," and
- Examination of reproductive function of embryofetal and perinatal toxicity of mutagenic potential and of carcinogenic potential "shall be considered. Where components other than the active substance(s) are incriminated, validation of their removal may replace the study."

The legal provisions above-mentioned appear to reinforce the importance of product and process characterization in addressing certain safety concerns.

The introduction of the revised Annex I to Directive 2001/83 (2) states, among other things, the following: "In assembling the dossier for application for marketing authorization, applicants shall take into account the scientific guidelines relating to the quality, safety, and efficacy of medicinal products adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and other pharmaceutical Community guidelines published by the Commission in different volumes of *The Rules Governing Medicinal Products in the European Community*."

The guideline itself is not legally binding, but the express reference to it in law renders it an important tool for interpreting the legal requirements and several decisions of the European Court of Justice have relied upon it as persuasive for these purposes.

REGULATORY GUIDANCE

There are already several useful regulatory guidelines promulgated under the auspices of the International Conference on Harmonisation (ICH) pertaining to nonclinical pharmacotoxicological testing of biotechnology or biological products:

- *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (ICH S6) (11),
- *Guideline on Safety Pharmacology Studies for Human Pharmaceuticals* (ICH S7A) (12), and
- *Guideline on Specification: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (Q6B) (13).

These guidelines have been in operation for some time following their adoption by the European Committee for Proprietary Medicinal Products (CPMP) and incorporation into the United States *Federal Register*. There are also regional product-specific regulatory guidelines, which have been or are currently being developed by the FDA or the CPMP pertaining to gene transfer, human and xenogeneic cell therapy, and vaccines.

Nonclinical testing of biological and biotechnological products defines pharmacological and toxicological effects not only prior to initiation of human studies but throughout clinical development. To this end, there is a need to characterize the relevant nonclinical endpoints that form the basis of clinical patient monitoring (see introduction). As already stated above, an understanding of the product and process characterization is also pivotal to the rational design and conduct of the nonclinical pharmacotoxicology studies that form a part of the overall risk/benefit assessment (see below also). The ICH S6 guidance addresses the following key factors in the design of nonclinical studies:

- The quality of the testing material including its control,
- The biological activity and pharmacodynamics of the drug substance,
- The animal species and model selection for the conduct of the studies,
- The administration and dose selection in order to provide information on a dose response relationship including a toxic dose and a no observed adverse effect level, and
- The assessment of immunogenicity and its impact on the interpretation of nonclinical findings.

The guidance also recommends that "conventional approaches to toxicity testing of pharmaceuticals may not be appropriate for biopharmaceuticals due to the unique and diverse structural and biological properties of the latter that may include species specificity, immunogenicity, and unpredicted pleiotropic activities." Indeed, in most cases, the adverse effects are due to exaggerated primary pharmacological response or secondary pharmacological properties of the product under examination. There are also documented examples of unexpected clinical findings which may be associated with the mode of action of the product, for example:

1. Thromboembolic events and hypertension associated with certain anti-angiogenesis monoclonal antibodies,

2. T cell mediated allergy associated with abciximab, or
3. Trastuzumab and potential cardiomyopathy.

RELEVANCE OF NONCLINICAL TESTING TO HUMANS WHERE CLINICAL EFFICACY TESTING IS IMPOSSIBLE

There are circumstances under which nonclinical testing results may be helpful in predicting or assessing the potential clinical efficacy and safety of certain products where conventional clinical testing is deemed to be impossible. An example of this is the development of vaccinia virus-based vaccines against smallpox to combat possible bioterrorist threats. Since the World Health Organisation declared its complete eradication of smallpox in 1980, there has been no active development for the prophylactic use of smallpox vaccine. The vaccines in use at the time when the disease was still prevalent were associated with a significant level of adverse reactions of varying severity, including deaths (see, for example, 14), and were never subjected to a controlled clinical trial to determine their field efficacy accurately.

Since smallpox does not exist in the population, assessment of the protective effect of smallpox vaccines is not possible in man either in formal efficacy trials or in challenge testing in vaccinated individuals with pox viruses for ethical reasons. Therefore, the likely protective effect in humans will have to be assessed in relevant animal species and inferred from clinically-relevant parameters in animals and/or in human subjects. On July 1, 2002, the CPMP adopted its multidisciplinary *Note for Guidance on the Development of Vaccinia Virus Vaccines against Smallpox* (CPMP/1100/02) (15). This guidance sets out scientific principles in the evaluation of the pharmacodynamics and toxicity of second-generation smallpox vaccines in animals. It also provides guidance on the endpoints, including histopathological, biochemical, and cellular markers relevant to the evaluation of efficacy and safety. As stated in the guidance, however, "pre-clinical testing of second-generation smallpox vaccines, even in relevant animal models, can only partly replace clinical studies in man."

In the United States, the FDA has amended its regulations to permit the use of animal testing to demonstrate the effectiveness of drugs and biologics when human efficacy studies are not feasible. The final regulation and a preamble explanatory FDA position may be found in the *Federal Register* (16).

There has been interest in employing gene-based or cell-based technology platforms for the development of therapeutic or prophylactic products. Appropriately designed, relevant animal studies are pivotal to their development (17). For example, one area of particular importance in the evaluation of the safety of gene-based products is the potential for insertional mutagenesis and germ line integration. Article 9(6) of Directive 2001/20/EC (the Clinical Trials Directive) (3) specifically stipulates that "*no gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.*" Studies of this kind in man are not possible in practice or ethical. The CPMP *Note for Guidance on Quality, Pre-clinical and Clinical Aspects of Gene Transfer Medicinal Products* sets out special recommendations to address issues concerning insertional mutagenesis and germ line integration in a nonclinical setting (18). The FDA has made similar recommendations in its *Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy* (19).

In contrast, according to the CPMP *Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* (20), a change in the virus strain to the trivalent vaccines already authorized in the European Union, produced in eggs, does not require nonclinical animal testing for investigating the pharmacotoxicology. The new trivalent vaccine is considered a variation to the marketing authorization under the amended rules for variation applications. For the support of such a marketing authorization variation, the biological activity is determined by means of appropriate quality testing and serological data based on a cohort of subjects with a defined age range against the requirements as set out in the guidance note. However, a change to the cell substrate, for example, using a cell culture, for the production of the influenza vaccine, will, ac-

cording to the annex, require appropriate assessment of the safety and efficacy of the vaccine. This illustrates the point that a substantial and fundamental change to the process, for example, a change to the cell substrate, in regulatory terms, will require a more robust data-set to assure safety, quality, and efficacy of a given product. This is a fundamental point regarding the issue of product comparability as indicated below.

PRODUCT COMPARABILITY WHEN MANUFACTURING PROCESSES CHANGE

In July 2002, the Committee for Proprietary Medicinal Products released a draft regulatory guidance which will be annexed (21), as soon as it is adopted, to the *Note for Guidance on Comparability of Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance* (22). This guidance builds on the ICH S6 guideline to set out the general principles for the conduct of nonclinical and clinical studies for the demonstration of product comparability, for example, in the case of a change in the manufacturing process during product development. The data requirements and timing of submission of these data as elaborated in this draft guidance will be guided by:

- The extent to which the product may be characterized,
- The nature of changes in the '*new*' product compared to the '*original*' product,
- Observed/potential differences between the two products, and
- Clinical experience pertaining to the particular class of products

In relation to nonclinical studies, the draft guidance indicates that data obtained from pertinent studies can provide useful pointers to potential therapeutic differences in the biological properties of the product following a process change while acknowledging the limitations of nonclinical studies in addressing certain clinical safety concerns such as immunogenicity. It has, however, recommended the following approach to addressing nonclinical testing: "In vitro studies: a battery of receptor-binding studies, many of which may already be available from quality-related bioassays, should normally be undertaken in order to assess if any alterations in reactivity have occurred and to determine the likely causative factor(s). In vivo animal studies: if there are specific uncertainties or concerns regarding safety, in vivo studies in one or more suitable animal models may be considered. Greater reliance would be placed on results from studies in a species shown for the 'original' product to be a good model for man. Animal studies should be designed to maximize the information obtained and to compare 'original' and 'varied' products in the final formulation."

In relation to in vivo testing, the monitoring of a number of relevant endpoints is recommended:

- Changes in pharmacokinetic parameters, for example, clearance,
- The immune response, for example, antibody titres, neutralizing capacity, and cross-reactivity,
- Areas of specific concern, for example, respiratory, renal, or cardiovascular parameters, and
- Other toxicological observations (in-life and post-mortem).

The draft guidance also encourages the application of emerging technologies and techniques in addressing subtle changes in the biological properties which may hitherto be undetectable by the conventional methods.

United States law also recognizes the potential need for nonclinical (and clinical) studies to support changes in manufacturing processes for biological products. The FDA may require such testing to be completed prior to approval of any manufacturing change (23). In addition, plans for such tests, referred to as "comparability protocols" may be submitted to the FDA for prior approval (24); and generally (25).

RISK COMMUNICATION: RELATING PHARMACOTOXICOLOGICAL DATA TO THE DRAFTING OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Nonclinical testing data are important in formulating a risk management strategy for a given

medicinal product and they form the scientific basis for patient monitoring and risk communication with the prescribers and patients. Therefore, there is a need to relate the relevant pharmacotoxicological findings to the drafting of the Summary of Product Characteristics (SmPC).

Article 8 of 2001/83/EC (2) and its annex define the data package for regulatory submissions. Article 11 defines the information, that is, the SmPC, to be provided about the product upon authorization and is based on the data submitted by the marketing authorization applicant. The European Commission *Guideline on Summary of Product Characteristics* which has been incorporated into the *Rules Governing Medicinal Products in the European Community Volume 2A and 2B Notice to Applicants* (26) provides the following salient points about the SmPC:

- It sets out the agreed position of the medicinal product regarding the grant of a marketing authorization, and
- It forms the basis of the information, such as package leaflets, to be provided for health professionals on how to use the medicinal product safely and effectively.

Section 5.3 of a European SmPC concerns nonclinical (preclinical) safety data. The guideline contains the following salient points:

- Information should be given on any findings in the nonclinical (preclinical) testing which could be of relevance for the prescriber in recognizing the safety profile of the medicinal product for the authorized indication(s), and
- The information should be presented in a way that enables the prescribing physician to make use of any relevant findings that might apply to the use of the product in patients.

The guideline advises that the findings of the nonclinical testing should be described in brief, and qualitative statements will need to indicate whether, for example:

- The data reveal any special hazard for humans based on conventional nonclinical studies,
- Nonclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use, and
- Adverse reactions seen in animals at exposure levels, but not in humans, similar to clinical exposure levels are relevant to clinical use.

The published and approved SmPC for a therapeutic monoclonal antibody is used as an example to illustrate these points. MabCampath is a genetically engineered humanized IgG1 kappa monoclonal antibody specific for a 21–28 kD lymphocyte cell surface glycoprotein (CD52). The monoclonal antibody has been authorized for the treatment of patients with chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed to achieve a complete or partial response or achieved only a short remission (less than 6 months) following fluadarabine phosphate therapy. Sections 5.1 and 5.2 of the SmPC set out the pharmacodynamic and pharmacokinetic properties of the drug substance. In section 5.3 (nonclinical or preclinical safety data), the SmPC addresses the nonclinical findings in animals, recognizing the limitation of an appropriate animal model:

- The nonclinical studies were limited to cynomolgus monkey because of the lack of expression of the antigen on nonprimate species,
- The most common treatment-related effect in nonhuman primate was lymphocytopenia, which was cumulative in repeated dose studies as compared with single dose studies.

However, the observed lymphocyte depletion was reversible on cessation of dosing, The SmPC also characterizes histopathological results from relevant tissue samples, such as bone marrow, and characterizes cross-reactivity with various relevant tissue types.

In the United States, the rules on data that must be submitted for approval of a BLA may be found in 21 CFR Part 61 (27). Generally, product labeling for biological drugs, such as that for nonbiological drugs, conforms to the requirements set out in 21 CFR 201.57 (28). While labeling generally needs not contain a separate section detailing nonclinical trials, the data derived from such trials will be expected to be included as appropriate in sections of the product labeling, 21 CFR 201.57(1) (29). Thus, animal

data may be described under headings of carcinogenicity, mutagenicity, and pregnancy (21 CFR 201.57(f)(5), (6) (30).

PRODUCT LIABILITY

In addition to regulatory requirements, in the planning of implementation of nonclinical testing, consideration should be given to issues pertaining to liability. Article 14 of Council Regulation 2309/93/EC states (1): "The granting of authorisation shall not diminish the general civil and criminal liability in the member states of the manufacturer or, where applicable, of the person responsible for placing the medicinal product on the market."

A similar provision is also incorporated into Article 25 of Directive 2001/83/EC (2). Similarly, in the United States, FDA approval generally does not provide a defense to product liability claims. The one exception is in the state of Michigan, where a challenge to a tort reform provision giving limited protection based on FDA approval was endorsed by the State Supreme Court (31). The court's decision is expected to significantly reduce litigation involving pharmaceutical products in Michigan in the future. This decision also creates a favorable precedent that may pave the way for consideration of similar statues in other jurisdictions of allowing compliance with the regulatory agency as a defense in a lawsuit concerning product liability.

It is outside the scope of this article to provide a detailed analysis of the applicable laws. Suffice it to say that liability may arise from product defects with inadequate characterization and safety evaluation. Liability under common law is fault based. In addition, in the European Union, Council Directive 85/374/EEC (as amended) (32) establishes the principle of objective liability or liability without fault of the product in cases of damage caused by a defective product. Article 7 of the directive sets out the exemptions of producers from liability. Among them, paragraph (e) sets out specifically the so-called "development risk defense," which is of particular importance in the context of the product design and development. This provision states, in effect, that the producer is not liable as a result of the directive if he proves: "the state of scientific and technical knowledge at the time when he put the product into circulation was not such as to enable the existence of the defect to be discovered."

In analyzing the legal provision as set out in Article 7(e), the European Court of Justice states in the case of *Commission vs. UK* (33) the following: "The producer of a defective product must prove that the objective state of scientific and technical knowledge, including the most advanced level of such knowledge, at the time when the product was put into circulation, was not such as to enable the existence of a defect to be discovered."

CONCLUSION

This article sets out the legal and regulatory requirements for the conduct of nonclinical pharmacotoxicology studies principally in the European Union. However, references have been made to the United States regulatory and legal framework for the purpose of comparison. These requirements have practical implications not only from a regulatory compliance perspective but also from a perspective of risk management to minimize liability exposure. Adverse events associated with certain gene therapy trials, which include dose-related toxicity associated with an adenoviral delivery vector and possible induction of leukemia by a murine leukemic viral vector, have been reported recently. There is, therefore, a further need to examine the relevance and importance of nonclinical studies for products derived from novel technologies, including those that are gene-based or cell-based in order to assess the potential clinical safety concerns.

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