R&D 101
Legal Issues During Research and Development

by Areta L. Kupchyk, Esq.; Reed Smith LLP
and
Josephine M. Torrente, JD; Hyman, Phelps & McNamara, P.C.

Developing a new drug or biological product is challenging and costly. Even minor missteps can significantly delay a product coming to market. Major missteps can add legal costs to the already mounting research and development costs that are required to prepare a new drug application ("NDA") or a biologics license application ("BLA"). Preparing for the submission of an investigational new drug application is the first and most important step in the development of a new drug product. Understanding human subject protection requirements both in and outside of the United States is necessary, particularly if you intend to rely on foreign clinical trial results to demonstrate the safety and efficacy of your product. This includes knowing how to recruit subjects and whether you can charge volunteers for the drug product. Finally, knowing the legal and regulatory consequences of wrongful conduct will help ensure that you protect the integrity of your data and ensure ultimate market success. These and other important issues are discussed here and will be addressed during the R&D 101 session.

A. Before Beginning Clinical Trials

FDA approves drug products for human use when the clinical data submitted in a NDA or BLA demonstrate the safety and efficacy of the drug product for its intended use. Before beginning clinical trials to support a marketing application, a sponsor must submit data in an investigational new drug application ("IND") showing that the drug is reasonably safe for use in initial, small-scale human studies. An IND should include nonclinical data from *in vitro* laboratory or animal studies, if available. In addition, the IND should include any data from clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population, if available. If such clinical testing is not available, the IND should include new preclinical studies designed to support the safety of human use.

Preclinical studies should identify a drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing. The FDA generally expects sponsors to: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals; and, (3) conduct short-term toxicity studies ranging from two weeks to three months, depending on the planned duration of use in the proposed clinical studies. FDA will review this data in the IND submission and determine whether there is any reason why a clinical trial using the new drug cannot proceed. Even if FDA has no objections to clinical trials beginning, the agency may expect that some animal testing continue after clinical trials begin to learn whether long-term use of a drug may cause cancer or birth defects.

(1) Investigational New Drug Applications

Before beginning a clinical trial, a sponsor must submit an IND to FDA. The IND is not an application for marketing approval. Rather, it is a request for an exemption from the Federal

law, which prohibits an unapproved drug from being shipped in interstate commerce.[1] This exemption must be granted before a sponsor ships the investigational drug to clinical investigators to any state.[2] To obtain the exemption, a sponsor submits to FDA an IND containing sufficient information and data to document that the drug is reasonably safe to begin human testing.

An IND generally includes: 1) animal pharmacology and toxicology studies to permit an assessment as to whether the product is reasonably safe for initial testing in humans; 2) information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and the drug product to ensure the company can adequately produce and supply consistent batches of the drug; and, 3) clinical protocol and investigator information to assess the potential risks to which subjects will be exposed and to assess whether the investigators are qualified to conduct the trials.

(a) Institutional Review Boards

Institutional Review Boards ("IRB") are responsible by law for protecting the rights and welfare of human subjects participating in clinical trials. IRBs at hospitals and research institutions throughout the country must ensure that trial volunteers are fully informed about the risks of participation and have given their written consent before studies begin.

IRBs are subject to FDA regulations and are monitored by FDA through inspections.[3] FDA regulations require that an IRB be composed of no less than five experts and lay people with varying backgrounds to ensure a complete and adequate review of research activities. In addition to professional competence, IRB members must have the experience and expertise to evaluate the acceptability of applications and proposals with respect to institutional commitments, applicable laws and regulations, and standards of professional conduct and practice, as well as community attitudes.[4]

(b) No FDA Approvals, Only Clinical Holds

FDA has 30 calendar days after an IND submission to evaluate the submission to determine whether there is any reason to prevent the study from going forward. Technically, FDA does not "approve" an IND. However, if it has concerns at any time about an IND, it may stop the study from beginning or from continuing.

---

[1] The Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 et seq., requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines.

[2] Even if a clinical trial is conducted in one state and the investigational drug is not shipped across state lines, virtually every drug is made up of one or more components that have crossed state lines. Therefore, FDA considers any use of such drug, even if only in one state, to require approval before it can be used. Use of such a drug in an investigational trial may proceed without approval *only if* the sponsor submits an IND to obtain an exemption from the requirement.

[3] 21 C.F.R. Part 56.

[4] 21 C.F.R. § 56.107.

If FDA has any concerns that volunteers may be exposed to an unacceptable risk, FDA has the authority to prohibit the trial from beginning and generally will inform the sponsor within the initial 30 day review period. If there are no concerns about unacceptable risk, FDA is not obligated to contact the sponsor or formally issue any type of approval. If the sponsor hears nothing from FDA, then on day 31 after submission of the IND, the study "legally" may proceed as submitted. More typically, however, a sponsor will make contact with the FDA division responsible for reviewing the IND and obtain verbal affirmation that FDA has no safety concerns that would impede the initiation of a trial. If an unacceptable risk exists or if there is insufficient data to make such a risk determination, FDA will notify the sponsor to obtain more information. Sponsors should not begin a trial until all issues raised by FDA have been resolved. If a sponsor initiates a trial, or does not adequately address FDA's concerns, FDA has the authority to issue a "clinical hold," which prohibits the trial from beginning or stops a trial that has already begun.

A "clinical hold" is an administrative order that FDA issues when it believes a study cannot be conducted without unreasonable risk to the participants in the trial. A clinical hold may be applied to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. As applied to ongoing studies, a hold prohibits the recruitment of new subjects. In addition, FDA will require that patients already in the study be taken off the investigational drug unless FDA specifically allows continuation in the interest of patient safety.[5]

The sponsor must submit to FDA a response addressing the issues raised in the clinical hold order. FDA will review the sponsor's response and within 30 days notify the sponsor whether the hold will be lifted.[6] The hold will be lifted only after a sponsor adequately resolves the pertinent issues.

If other deficiencies are found in an IND that the review division determines are not serious enough to justify delaying clinical studies, FDA generally allows the sponsor to proceed with the planned clinical trials, but may require additional information be submitted to the IND file, or identify issues that should be addressed in the future submission of a new drug application (NDA).[7]

(2) Types of INDs

INDs are applications typically submitted by companies whose ultimate goal is to obtain marketing approval for a new product. However, many INDs are filed for reasons other than to obtain marketing approval. These INDs include "Investigator INDs," "Emergency Use INDs," and "Treatment INDs," which are subject to specific regulatory requirements.[8] Treatment INDs are intended to make potentially effective new treatments available to seriously ill patients as

---

[5] 21 C.F.R. § 312.42(a).

[6] 21 C.F.R. § 312.42(d) and (e).

[7] *See* MAPP 6030.1, *"IND Process and Review Procedures."*

[8] *See* 21 C.F.R. §§ 312.34, 312.35, and 312.36.

early in the drug development process as possible. FDA generally permits an investigational drug to be used under a Treatment IND if (1) there is preliminary evidence of efficacy for the treatment of a serious or life-threatening disease, or (2) there is no comparable alternative drug or therapy available to treat the disease.[9]

(3) Phases of Clinical Trials

There are three basic phases for clinical research conducted under an IND. The phases start with small studies to establish initial safety data and then proceed to involve more and more patients to establish efficacy data. The ultimate goal is to seek sufficient clinical data of efficacy to meet the legal requirement for marketing approval.

Phase 1 is when an investigational new drug is first introduced into humans. These studies, conducted in healthy or patient volunteers, are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, where possible, to gain early insight into effectiveness. The data intended to be gathered in Phase 1 should provide adequate information for the design of well-controlled, scientifically valid, Phase 2 studies. In addition, Phase 1 studies evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. The total number of subjects included in Phase 1 studies varies with the drug, but is generally small, in the range of 20 to 80.[10]

Phase 2 clinical studies are conducted to obtain preliminary data on the effectiveness of the drug for an intended use. This phase helps identify common short-term side effects and risks associated with the drug. FDA expects Phase 2 studies to be well-controlled and closely monitored. These trials are typically conducted in trials with several hundred people.[11]

Phase 3 studies are usually pivotal and intended to gather the additional information about effectiveness and safety needed to evaluate the overall risk-benefit of the drug. This evaluation will determine whether there is sufficient evidence of efficacy needed for approval. FDA looks at the results of Phase 3 studies to support applicability of the drug usage to the general population and to determine what information is necessary for physician labeling. Phase 3 study results should be statistically significant and may include several hundred to several thousand people to ensure that they are adequately powered.[12]

B. Charging for Investigational Products

There are times, under certain circumstances, when FDA will allow a sponsor to charge clinical trial subjects for the investigational drug product. Any decision concerning charging for investigational products is subject to FDA regulations and IRB policies. The FDA informed

---

[9] 21 C.F.R. § 312.34.

[10] 21 C.F.R. § 312.21(a).

[11] 21 C.F.R. § 312.21(b).

[12] 21 C.F.R. § 312.21(c).

consent regulations require the consent document to include a description of any additional costs to the subject that may result from participation in the research.[13] IRBs should ensure that the informed consent documents outline any additional costs that will be billed to study subjects or their insurance company as a result of participation in the study. IRBs should also ensure that any such charges are appropriate and equitable. FDA does not prohibit charging the subjects for related treatment or for services.

The IND regulations permit a sponsor to charge for an investigational drug or biologic that has not been approved for marketing, only under specific conditions.[14] In both a clinical trial and a treatment IND, the charge should not exceed an amount that is necessary to recover the costs associated with "the manufacture, research, development, and handling" of the investigational drug or biologic.[15] FDA may withdraw authorization to charge if the Agency finds that the conditions underlying the authorization are no longer satisfied.

A sponsor may not charge for an investigational drug or biologic in a clinical trial under an IND without the Agency's prior written approval. In requesting such approval, the sponsor must explain why a charge is necessary, i.e., why providing the product without charge should not be considered part of the normal cost of conducting a clinical trial.[16] A sponsor may also be permitted to charge for an investigational drug or biologic in a Treatment IND provided:

> (1) there is adequate enrollment in the ongoing clinical investigations under the authorized IND;
>
> (2) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved;
>
> (3) the drug or biologic is not being commercially promoted or advertised; and
>
> (4) the sponsor is actively pursuing marketing approval with due diligence.[17]

FDA must be notified in writing prior to commencing any such charges. Authorization for charging goes into effect automatically 30 days after receipt of the information by FDA, unless FDA notifies the sponsor to the contrary.[18]

C. Acceptance of Foreign Clinical Studies

---

[13] 21 C.F.R. § 50.25(b)(3).

[14] 21 C.F.R. § 312.7(d).

[15] *Id.*

[16] 21 C.F.R. § 312.7(d)(1).

[17] 21 C.F.R. §§ 312.34 and 312.35.

[18] 21 C.F.R. § 312.7(d)(2).

Results of clinical studies conducted outside the United States and outside the scope of an IND may still be accepted by FDA in support of safety and efficacy claims for drugs, biological products and medical devices. FDA will accept a foreign clinical study involving a drug or biological product not conducted under an IND only if the study conforms to whichever of the following provides greater protection of the human subjects:

- The ethical principles contained in the **1989 version** of the Declaration of Helsinki, or
- The laws and regulations of the country in which the research was conducted.[19]

A slightly different version of the Declaration of Helsinki is applicable to medical device clinical trials conducted outside the U.S. FDA issued its device foreign study regulation in 1986, when the 1983 version of the Declaration was in effect.[20] The 1983 and 1989 versions differ in one respect. Both versions state that the design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol, which should be transmitted for consideration, comment, and guidance to a specially appointed committee. However, the 1989 version qualifies the principle by stating that the specially appointed committee should be "independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed." Therefore, FDA will accept a foreign clinical study involving a medical device that is not subject to an IDE only if the study conforms to the ethical principles contained in the **1983 version** of the Declaration or with the laws and regulations of the country in which the research was conducted, whichever provides greater protection of the human subjects.

In October 2000, the World Medical Association revised the Declaration of Helsinki for the fifth time since the Declaration was first adopted in 1964. Although FDA had amended the regulations to incorporate past amendments to the Declaration,[21] FDA has not taken any action to incorporate the October 2000 revisions into its regulations. Moreover, FDA issued a guidance document to state explicitly that "the [October 2000] action of the World Medical Association did not change FDA regulations."[22]

D. Recruiting Study Subjects

FDA expects IRB's to review and approve methods and material that investigators propose to use to recruit subjects. Direct advertising for research subjects, i.e., advertising that is

---

[19] 21 C.F.R. § 312.120(c)(1).

[20] 21 C.F.R. § 814.15(a) and (b).

[21] FDA incorporated the 1964 Declaration in its regulation governing foreign investigational drug trials originally in 1975. In 1981, FDA revised the regulation to replace the 1964 Declaration with the 1975 revision of the Declaration. In 1991, it replaced the 1975 Declaration with the 1989 version. 46 Fed Reg. 8942 (January 27, 1981); 56 Fed. Reg. 22113 (May 14, 1991).

[22] FDA Guidance for Industry: Acceptance of Foreign Clinical Studies (March 2001), http://www.fda.gov/cber/gdlns/clinical031301.pdf

intended to be seen or heard by prospective subjects to solicit their participation in a study may includes newspaper, radio, TV, bulletin boards, posters, flyers, and even Internet advertising.[23] **Not included** are: (1) communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), (2) news stories and (3) publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. IRBs are expected to review advertisements as part of the package for initial review and ensure that the advertisements are not unduly coercive and do not promise a certainty of cure beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence.[24] For example, advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the product is investigational, because "[a] phrase such as 'receive new treatments' leads study subjects to believe they will be receiving newly improved products of proven worth."[25] Similarly, advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of all of the listed items.

1. The name and address of the clinical investigator and/or research facility;
2. The condition under study and/or the purpose of the research;
3. In summary form, the criteria that will be used to determine eligibility for the study;
4. A brief list of participation benefits, if any (e.g., a no-cost health examination);
5. The time or other commitment required of the subjects; and

---

[23] IRB review and approval of listings of clinical trials on the Internet is not required when such review provide no additional safeguard (e.g., when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information.) Clinical trial listing services that do not require prospective IRB approval include, for example, the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

[24] 21 C.F.R. §§ 50.20, 50.25, 56.111(a)(3), 56.111(b) and 812.20(b)(11).

[25] *See* FDA Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update, http://www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting.

6. The location of the research and the person or office to contact for further information.[26]

E. Special Populations

Since the mid-1980s, FDA has increasingly sought to address the specific therapeutic needs of special populations. The agency's initiatives, often implemented through the issuance or adoption of regulatory guidance (but in one instance through notice and comment rulemaking), have focused primarily on three special population groupings: pediatric patients, geriatric patients, and racial or gender differences.[27] FDA's guidelines for each of these special populations outline the design and conduct of clinical studies in general, or product labeling, and are directed primarily to new or currently-marketed products that are likely to have a significant use in a special population either because the disease or condition intended to be treated is characteristically a disease or condition experienced by that special population, or because the population to be treated is generally known to include substantial numbers of patients from a particular special population.

(1) Pediatrics

Although pediatric patients have historically been treated as "therapeutic orphans," over the past several years, FDA and Congress have taken action to address this concern. Those actions are summarized below.

In a final rule published in the Federal Register on December 13, 1994, FDA revised its prescription drug labeling regulations to provide for the inclusion of more complete information about the use of a drug (or biological product) in the pediatric population.[28] Prior to the issuance of FDA's final rule, the "Pediatric Use" labeling subsection, adopted in 1979, required that pediatric indications (if any) be described in the "Indications and Usage" labeling section, and that pediatric dosing information be provided in the "Dosing and Administration" labeling section. FDA's 1994 regulations encouraged (but did not require) sponsors to provide as much information as possible about pediatric use in labeling so that practitioners would have reliable pediatric use information.[29]

---

[26] *Id.*

[27] In addition to increased requirements to address the needs of these special subgroups in the clinical development of drug products, FDA amended its NDA format and content regulations to require safety and effectiveness data for important subgroups, including age subgroups. *See* 63 Fed. Reg. 6854 (Feb. 11, 1998) ("Since the early 1980s, FDA has been concerned about possible differences in response to drugs among subsets of the overall population, such as age, gender, or racial subsets. . . . Evaluation of potential differences among demographic subsets requires that individuals from these subsets be included in studies and that analyses to seek differences be included in studies and that analysis to seek differences in response be carried out.") (emphasis added); 21 C.F.R. § 314.50(d)(5)(v). In addition to these requirements, the regulation also amended FDA's IND regulations to require sponsors to tabulate in their annual reports the number of subjects enrolled in clinical trials according to certain subgroups, including age. *See* 21 C.F.R. § 312.33(a)(2).

[28] See 59 Fed. Reg. 64,240 (Dec. 13, 1994).

[29] See 21 C.F.R. § 201.57(c)(9)(iv).

Section 111 of FDAMA, "Pediatric Studies of Drugs," amended the FDC Act to add section 505A.[30] Section 505A was subsequently reauthorized and amended by the "Best Pharmaceuticals for Children Act."[31] Section 505A, as amended, provides an additional six months of market exclusivity to sponsors that conduct acceptable pediatric studies of new and currently-marketed drug products identified by FDA for which pediatric information would be beneficial.

Pediatric exclusivity extends all other types of patent and non-patent market exclusivity an NDA holder may have under the FDC Act. An important aspect of pediatric exclusivity is that it provides additional market exclusivity not just for the pediatric indications or formulations, but for all protected indications and formulations of that drug. That is, pediatric exclusivity attaches to the patent and non-patent market exclusivity for a drug product that contains the active moiety for which pediatric exclusivity was granted, and not to a specific drug product.[32]

Pediatric studies conducted pursuant to § 505A of the FDC Act do not have to result in new labeling or show safety and effectiveness in pediatric patients in order for a drug to obtain pediatric exclusivity. Rather, pediatric exclusivity depends on whether an applicant meets the requirements contained in a Written Request issued by FDA. The reports of pediatric studies should be submitted to FDA in an NDA supplement to support a change in an approved product's labeling. If FDA approves the NDA supplement, and the application meets the requirements of 21 C.F.R. § 314.108(b)(5), the sponsor may obtain three years of exclusivity plus six months of pediatric exclusivity.

On December 3, 2003, the Pediatric Research Equity Act ("PREA") was signed into law. PREA amended the FDC Act to create § 505B. PREA is the most recent of more than a decade of legislative and regulatory attempts to address the lack of pediatric use information in drug product labeling. In PREA, Congress codified many of the elements of a final rule issued by FDA on December 2, 1998, but that was suspended by a court order in October 2002.[33]

PREA authorizes FDA to require pediatric studies for drugs to ensure the drugs' safety and efficacy in children. PREA requires that marketing applications "for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration" contain data assessing the safety and effectiveness for the claimed indication in all relevant pediatric subpopulations.[34] Dosing and administration must be supported for each pediatric subpopulation for which the drug is safe and effective. FDA requires these data in a marketing application for a drug that is used in pediatric patients for the labeled indication, unless the Agency has granted a deferral for the submission of such data, or unless the Agency has granted a full or partial waivers from PREA. PREA does not apply to any drug for an indication with orphan designation.

(2) Geriatrics

---

30 See Pub. L. No. 105-115, 111 Stat. 2296 (1997).

31 See Pub. L. No. 107-109, 115 Stat. 1408 (2002).

32 See National Pharm. Alliance v. Henney, 47 F. Supp. 2d 37 (D.D.C. 1999).

33 See Association of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002); 21 C.F.R. § 314.55.

34 See FDC Act § 505B(a)(1).

In 1989 and 1994, FDA issued two guidance documents to encourage drug sponsors to include more elderly subjects (especially those over 75 years of age) in clinical trials, and provide scientific principles for testing drugs in geriatric populations.

The 1989 guidance document, titled "Guideline for the Study of Drugs Likely to be Used in the Elderly," recommends that drug sponsors enroll a sufficient number of geriatric patients in their clinical studies and study the pharmacokinetic and pharmacodynamic differences between geriatric and younger volunteers. Specifically, the guidance document recommends that pharmacokinetic evaluations should include the effects of the study drug on renal and hepatic impairment.[35]

The 1994 guidance document, issued in conjunction with the ICH and titled "Studies in Support of Special Populations: Geriatrics,"[36] provides specific guidance and expectations regarding the enrollment of geriatric patients in clinical trials. The guidance document states:

> Geriatric patients should be included in the Phase 3 database (and in Phase 2, at the sponsor's option) in meaningful numbers. The geriatric subpopulation should be represented sufficiently to permit the comparison of drug response in them to that of younger patients. For drugs used in diseases not unique to, but present in, the elderly, a minimum of 100 patients would usually allow detection of clinically important differences. For drugs to treat relatively uncommon diseases, smaller numbers of the elderly would be expected.[37]

In addition to this clinical trial enrollment expectation, the guidance document also specifies what types of studies should ordinarily be conducted. These studies include formal pharmacokinetic studies or pharmacokinetic screening in renally or hepatically impaired patients, pharmacodynamic/dose-response studies, and drug-drug interaction studies.[38]

In 1997, FDA issued a final regulation establishing, in the "Precautions" section of prescription drug labeling, a subsection ("Geriatric use") on the use of drugs in elderly or geriatric patients (aged 65 years or over).[39] The regulation applies to all products with an approved NDA, BLA, or ANDA. Although the labeling change did not require manufacturers to

---

[35] *See* FDA, "Guideline for the Study of Drugs Likely to be Used in the Elderly," (Nov. 1989) at 8-9 ("Information should be developed to support dosing instructions that provide appropriate adjustments for varying degrees of renal impairment;" "Special pharmacokinetic studies should be carried out [for drugs that are metabolized by oxidative mechanisms or that have active metabolites] to explore the effects of decreased liver function and to look for possible genetic variability in metabolism of drug-drug interactions.").

[36] *See* FDA, ICH, "E7: Studies in Support of Special Populations: Geriatrics," (Aug. 1994).

[37] *I*d. at 2-3.

[38] *Id.* at 3-6.

[39] *See* 62 Fed. Reg. 45313 (Aug. 27, 1997); 21 C.F.R. § 201.57(f)(10).

conduct additional clinical studies, it does require that if special pharmacokinetic or pharmacodynamic studies of a drug's action were carried out in the elderly, those results must be described briefly in the "geriatric use" subsection, and in detail in the "Clinical Pharmacology" section of the drug's labeling. In instances in which there are not sufficient numbers of geriatric subjects enrolled in clinical studies to determine whether the drug product acts differently in geriatric patients than in younger patients, and when other reported clinical experience does not identify any differences between geriatric and younger patients, a drug's labeling must include a statement to this effect and instruct geriatric patients to take the product with caution.[40]

In 2001, FDA finalized a guidance document regarding the content and format for geriatric labeling supplements.[41] The guidance document states in detail the types of data necessary to support geriatric use labeling, including: the source of the data, what methods were used to collect and analyze the data, and necessary safety data (including extent of exposure, duration of exposure, and adverse events).[42]

(3) Race/Gender

Similar to the agency's initiatives regarding the pediatric and geriatric subpopulations, FDA's attempt to encourage the analysis of racial and gender differences in the evaluation of drugs extends back to the mid-1980s. In 1985, the agency revised 21 C.F.R. § 314.50, which called for evidence to support modifications of dosage for specific subgroups. FDA's 1988 guidance document, "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications," explained aspects of the 1985 CFR revision, and discussed the importance of analyzing data from population subsets. In 1993, a General Accounting Office ("GAO") report on gender differences in prescription drug testing concluded that clinical trial data are infrequently analyzed to determine gender-specific responses, and that the study of drugs in women usually occurs only during the later stages of drug development.[43] In response to the GAO report, FDA published a guidance document titled "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs."[44] The guidance document provided guidance to industry on FDA's expectations regarding "inclusion of patients of both genders in drug development, analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and where appropriate, assessment of pharmacodynamic differences and the conduct of specific additional studies in women."[45]

By 1998, FDA determined that sponsor analysis of gender and racial-specific safety and effectiveness data was inconsistent, and promulgated a regulation to "make[] the need for these

---

[40] *See* 62 Fed. Reg. 45313, 45314 (Aug. 27, 1997).

[41] *See* FDA, "Guidance for Industry: Content and Format for Geriatric Labeling" (Oct. 2001).

[42] *See id.* at 8-9.

[43] GAO Report, "FDA Needs to Ensure More Study of Gender Differences in Prescription Drug Testing" (1993).

[44] *See* 58 Fed. Reg. 39406 (July 22, 1993).

[45] *Id.* at 39407.

subgroup analyses completely clear."[46] The regulation revised the IND annual reporting regulations (21 C.F.R. § 312.33(a)(2)) to require that the number of subjects entered into a clinical study be tabulated by age group, gender, and race. Further, the regulation allows FDA to refuse to file any NDA that failed analyze safety and efficacy information appropriately by the specified demographic subgroups.

Finally, in addition to FDA's regulatory initiatives, section 115 of FDAMA ("Clinical Investigations. (b) Women and Minorities") amended § 505(b)(1) of the FDC Act to require FDA to "review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials." Subsequent to the implementation of this provision, FDA developed the "FDAMA Women and Minorities Working Group." Since its inception, the Working Group has held several meeting, and has determined that "additional guidance is not needed at this time."[47]

F. Orphan Drugs

The Orphan Drug Act permits a manufacturer or sponsor to request that the FDA designate a drug, biological, or antibiotic, whether patentable or not, as a drug for a rare disease or condition. A "rare disease or condition" is one that: (1) affects less than 200,000 persons in the United States; or (2) affects more than 200,000 persons and for which the sponsor can show that it will be unable to recover its development and marketing costs from sales of the product in the United States.[48] Upon such a showing, FDA must designate the drug as a drug for a rare disease or condition — an orphan drug. The sponsor may submit a request for orphan drug designation any time before it submits a marketing application.[49]

A formal request for orphan drug designation must include a scientific rationale for the use of the drug and the prevalence of the disease.[50] Applicants are expected to "make every effort to survey the literature and obtain all information available on the prevalence of the indicated disease" counting only "diagnosed symptomatic patients."[51] FDA publishes orphan drug designations in its Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book").[52] More than one sponsor can receive orphan drug designation for the same drug for the same rare disease or condition.[53]

---

[46] 63 Fed. Reg. 6854, 6856 (Feb. 11, 1998).

[47] FDA, "FDAMA Women and Minorities Working Group Report" (July 20, 1998).

[48] 21 U.S.C. § 360bb(a)(2).

[49] *Id.* § 360bb(a)(1).

[50] 21 C.F.R. § 316.20.

[51] 57 Fed. Reg. 62076, 62081 (Dec. 29, 1992) (preamble to the Orphan Drug Regulations, final rule).

[52] *Id.* § 316.28.

[53] *Id.* § 316.20.

The sponsor must also conduct the studies necessary to support a marketing application for the drug. If FDA approves the marketing application, the sponsor is awarded seven-year exclusive United States marketing rights for the drug for the declared rare disease or condition.[54] Orphan drug exclusivity prevents FDA from approving other marketing applications for the same drug for the same disease or condition. However, FDA may approve a second marketing application: (1) for the same drug if it is intended to treat a different disease or condition; or (2) for a different drug intended for the same indication. For purposes of exclusivity, a second drug is "different" from an approved orphan drug if it is structurally distinct, or if it is demonstrated to be "clinically superior."[55] The second drug is clinically superior if it is more effective, safer, or makes "a major contribution to patient care."[56]

For each taxable year, a taxpayer may credit against its federal income tax 50 percent of the "qualified clinical testing expenses" related to orphan drug development. In general terms, to be eligible for the orphan drug tax credit, the sponsor's expenses must arise from clinical testing conducted in humans: (1) under an IND application, (2) after FDA designates such drug as an orphan drug and before FDA approves a marketing application "with respect to such drug," and (3) "by or on behalf of the taxpayer to whom the designation" for orphan drug status applies.[57]

The Internal Revenue Code (IRC) imposes a number of limitations on coverage. It excludes from coverage any clinical testing expenses "funded by any grant, contract, or otherwise by another person or any governmental entity."[58] Also excluded from coverage is any clinical testing conducted outside the United States unless there is an insufficient testing population in the United States for the subject drug and the testing is conducted by a party unrelated to the taxpayer whose product has been designated an orphan drug.[59] Finally, the "[h]uman clinical testing . . . [must be] related to the use of a drug for the rare disease or condition for which it was designated."[60]

The Taxpayer Relief Act of 1997[61] made the orphan drug tax credit permanent. In the Small Business Job Protection Act of 1996,[62] Congress permitted the taxpayer to carry back

---

[54] 21 U.S.C. § 360cc(a); 21 C.F.R. § 316.31(a). This period of exclusivity begins on the date that the marketing application is approved for the designated orphan drug. Exclusivity is voided if the orphan drug sponsor fails to provide sufficient quantities of the drug to meet the orphan use need, or the orphan drug sponsor consents to the approval of other applications. 21 U.S.C. § 360cc(b)(1)-(2).

[55] 21 C.F.R. § 316.3(b)(13).

[56] *Id.* § 316.3(b)(3).

[57] 26 U.S.C. § 45C(b)(2)(A).

[58] *Id.* § 45C(b)(1)(C).

[59] *Id.* § 45C(d)(A).

[60] *Id.* § 45C(b)(2)(B).

[61] Pub. L. No. 105-34, § 604, 111 Stat. 788, 863 (1997).

[62] Pub. L. No. 104-188, § 1205, 110 Stat. 1755, 1775 (1996).

unused orphan drug tax credits three years, and to carry forward unused credits for up to 15 years.

Congress provided the most recent stimulus for orphan drug research and development in the FDA Modernization Act of 1997.[63] This law amended 21 U.S.C. § 379h(a)(1) to specifically exclude drugs intended to treat rare diseases or conditions from application and supplement fees.

F. Fraud, Bribery, and Illegal Gratuities: FDA's Application Integrity Policy

FDA's Fraud Policy emerged from what became known as the "Generic Drug Scandals" in the late 1980's. The House Subcommittee on Oversight and Investigations began an investigation of "wrongful acts" involving some manufacturers of generic drugs and some employees of FDA during July 1988. As a result of those investigations and investigations conducted by FDA, four FDA employees were found to have accepted illegal gratuities from generic drug companies. Eleven generic drug companies were found to have falsified data submitted in premarket applications to FDA.

FDA began its investigations when it suspected that FDA investigators had been offered and had accepted illegal gratuities and that applicants had made questionable data submissions in abbreviated new drug applications ("ANDAs"). FDA discovered broad patterns and practices of fraud in numerous ANDAs. The discovery of this extensive pattern of fraudulent data submissions prompted FDA to develop a program that would:

(1) Ensure the validity of data submissions called into question by fraud, untrue statements of material fact, bribery, and illegal gratuities, etc., and

(2) Ensure that approval was withdrawn, or that approval would be refused, for any applications containing fraudulent or unreliable data.

On September 10, 1991, FDA published a final policy on Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities, which became known as the Application Integrity Policy ("AIP").[64] Under this policy, FDA promised to suspend all substantive scientific review of any pending application before it if it had reason to question the integrity of any part of a submission to the agency. FDA explained that certain acts would be considered "wrongful acts" because they appeared to subvert the integrity of the FDA review process. Such wrongful acts included:

- submitting fraudulent applications,
- making untrue statements of material facts, or
- giving or promising bribes or illegal gratuities.

---

[63] Pub. L. No. 105-115, § 103, 111 Stat. 2296, 2300 (1997).

[64] 56 Fed. Reg. 46191 (Sept. 10, 1991).

If a wrongful act raises a significant question regarding reliability of data in some or all of the pending applications, FDA stated that "ordinarily" it would "defer substantive scientific review pending completion of 'validity assessments' of those applications." Once FDA invoked the AIP, the company's name would be placed on the "AIP List" on FDA's webpage and stay there until the AIP was revoked. Only when a company successfully validated the questionable data or, if it could not validate the data had withdrawn the application, would FDA revoke the AIP. Typically, an extensive corrective action plan would need to be developed and implemented to assure the agency that such wrongful acts would not recur. A listing of companies currently under the AIP can be found at http://www.fda.gov/ora/compliance_ref/aiplist.html.

G. Clinical Investigator Regulatory Sanctions

FDA has the authority to apply regulatory sanctions to clinical investigators who violate regulations applicable to clinical trials. Other than pursuing criminal prosecution, the most serious sanction in FDA's enforcement arsenal is disqualification. FDA may disqualify clinical investigators from receiving investigational drugs, biologics and devices only when the investigator has repeatedly or deliberately violated the Agency's regulations, or has submitted false information to the sponsor in a required report. To begin disqualification proceedings, FDA sends the investigator a written notice describing the noncompliance or false submission and offers the investigator an opportunity to respond to the notice at an informal conference or in writing. If the investigator offers a timely and satisfactory explanation for the noncompliance, and the Center accepts, the process is terminated and the investigator is so notified in writing. If, however, the investigator's explanation is not acceptable, or if the investigator fails to respond within the specified time period, the disqualification process continues with an opportunity for a hearing to determine whether the investigator should remain eligible to receive investigational test articles.

If FDA ultimately finds that the investigator has repeatedly or deliberately failed to comply with the regulatory requirements, or has deliberately or repeatedly submitted false information to the sponsor in any required report, the FDA will disqualify the investigator, which means that:

(1) The investigator is not entitled to receive investigational drugs, biologics or devices.

(2) FDA will not accept the investigator's work in support of claims of safety and efficacy without validating information establishing that the study results were unaffected by the investigator's misconduct.

(3) After the investigator's data are eliminated from consideration, FDA will determine whether the data remaining can support a conclusion that studies under the IND may continue.

(4) After the investigator's data are eliminated from consideration, FDA will determine whether any continued approval of related drug is justified. If it is not, FDA will move to withdraw approval of the drug.

H. Product Liability Concerns

An inherent danger in the use of every experimental drug is that unknown safety risks may exist for human research subjects. Of even greater concern is that an experimental drug may have a serious adverse effect on a developing fetus or on the reproductive health of the study participants. An essential mitigating factor against clinical trial liability risk is adequate informed consent. However, the protection afforded by informed consent varies from State to State and is, at best, uneven. For example, some States permit a child who has reached the age of majority or a spouse to sue for injuries caused by a parent's medical decision to use a drug. To succeed in such a lawsuit, the child or spouse must show, among other things, that warnings about the use of the drug were inadequate or that consent was not fully informed. In some States, a parent's informed consent based on FDA-approved warnings for marketed drugs might not preclude a child from filing a lawsuit. In States permitting such lawsuits, the courts have described FDA standards for such warnings as minimum requirements for disclosing risk information. Because manufacturers and sponsors have the ultimate responsibility to provide risk information to FDA as well as to consumers, in some States, FDA approval of warning statements for marketed drugs is evidence of the warning's adequacy but may not be dispositive. Thus, a warning might be inadequate when a sponsor or manufacturer obscures or withholds risk information from FDA, or delays submission of supplemental risk information obtained after the product was approved.

The sponsor or investigator, with IRB oversight, is responsible for providing risk information to subjects and obtaining informed consent from them.[65] Rather than rely solely on informed consent to mitigate liability risks, sponsors have tried to exclude participants who might be at risk of injury. For example, sponsors routinely have excluded women of childbearing potential from research studies.

Few liability cases have been reported involving injuries from experimental drugs and even fewer involving such injuries to offspring. In those cases involving injuries to the offspring of mothers who ingested experimental drugs, the inadequacy of warnings, or the lack of informed consent, was an essential element of the lawsuit.[66] Although these cases involved research subjects who were pregnant women, they do show that liability can be mitigated when patients are informed adequately about a study and its risks. The women who brought these lawsuits claimed that they were not told that research was being conducted, much less asked for informed consent. Indeed, to find any protection against liability, a sponsor and manufacture must ensure, at a minimum, that there is adequate informed consent identifying all foreseeable or scientifically knowable risks and a fully informed patient.

There are no reported cases in which a sponsor or manufacturer of a drug was held liable when warnings were found to be adequate or the consent to be informed. In determining the adequacy of a warning for prescription drug products, the standard generally applied is the drug

---

65 *See* 21 C.F.R. §§ 312.50 and 312.53(c)(1)(vi)(d); 21 C.F.R. parts 50 and 56.

66 *See Craft v. Vanderbilt University*, 940 F. Supp. 1185 (M.D. Tenn. 1996); *Wetherill v. University of Chicago*, 570 F. Supp. 1124 (N.D. Ill. 1983); *Mink v. University of Chicago,* 460 F. Supp. 713 (N.D. Ill. 1978); and *Diaz v. Hillsborough County Hospital Authority*, 165 F.R.D. 689 (M.D. Fla. 1996).

maker's actual or constructive knowledge of the risk at the time the product was sold or distributed. Considering reported cases involving experimental drugs, the risk of liability for injuries to offspring resulting from their mother's ingestion of an experimental drug appears remote where sponsors and manufacturers provide adequate warnings and obtain fully informed consent.

However, what is "adequate" and what constitutes being "fully informed" continues to be an unsettled and perplexing issue for researchers as well as for lawyers. How much risk information is enough? How far should a researcher speculate about potential risk? Is there appropriate language that will not effectively discourage participation in clinical trials yet still fully inform every study volunteer?

Despite such questions, based upon the belief that informed consent can indeed be effective for human subject protection, in June 2000 FDA required sponsors to provide women of childbearing potential an opportunity to participate in clinical trials involving life-threatening illnesses.[67] FDA amended its regulations to permit a clinical hold on one or more studies under an IND if men or women with reproductive potential, who have the disease or condition being treated and are otherwise eligible, are categorically excluded from participation "solely because of a perceived risk or potential risk of reproductive or developmental toxicity from use of the investigational drug."[68] In response to product liability fears expressed by sponsors, FDA reasoned that the rule reduces the exposure to liability lawsuits by applying to a very limited number of studies, *i.e.,* studies that seek subjects who are suffering from the life- threatening disease or condition at issue. FDA stated that the risk of liability is further minimized when the sponsor uses informed consent "with careful study design, pregnancy screening techniques, and counseling about contraception and abstinence."[69]

The purpose of informed consent is to provide research volunteers with sufficient information to determine for themselves whether the risks are justified. Informed consent regulations require a sponsor, when appropriate, to describe the reasonably foreseeable risks, and currently unforeseeable risks, to the participant or to an embryo or fetus in the event the participant should become pregnant during the study.[70] FDA emphatically rejected an argument that unqualified disclosure might discourage study participation. In the final rule, FDA stated,

> "That the disclosure of complete risk and benefit information might discourage participation is not a reason to withhold information or to preempt the opportunity to participate in a study. On the contrary, disclosure serves the interests of self-determination regarding a person's decision to participate in medical research and ensures

---

67 Investigational New Drug Applications; Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Diseases and Conditions; Final Rule, 65 Fed. Reg. 34963 (June 1, 2000).

68 *Id.* at 34964.

69 *Id*. at 34967.

70 21 C.F.R. § 50.26(b)(1).

informed decisionmaking as to whether the risks are indeed outweighed by the benefits."[71]

Nevertheless, informed consent alone may not be adequate to reduce either the risk of injury to a participant or the risk of liability to a sponsor. The full nature and extent of any potential reproductive toxicity may not be sufficiently characterized at the time of the desired access to a given investigational therapy to allow IRB's, investigators, or potential study subjects to make a complete determination of any potential risk. Such risks will continue for all sponsors until there is adequate Federal, uniform protections against liability.

Conclusion

Presented here are only some of the legal and regulatory issues that are important to consider for a drug research and development program. Interactions with FDA are often times informal. Become familiar not only with the written requirements, but with FDA's written guidance documents and FDA's informal practices. Every action a researcher or sponsor takes may have serious consequences, both for the individual as well as the success of the drug product. Fortunately, there are many resources available to sponsors and investigators.

[71] 65 Fed. Reg. at 34967.