

Chipping Away at the GMPs:

Understanding FDA's Proposal to Exempt Material for Phase 1 Clinical Trials from CGMP Regulations, and new Draft Guidance

Prepared for Participants of the
30th Annual International GMP Conference, University of Georgia, March 2006
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What FDA is Proposing

Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>, Proposed Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs, <http://www.fda.gov/ohrms/dockets/98fr/06-350.htm>

- On January 17, 2006, FDA published a proposed rule and a direct final rule in the Federal Register to amend current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most investigational "Phase 1" drugs from complying with the CGMP regulation (21 CFR 210/211).

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What FDA is Proposing

Source: Draft Guidance for Industry on Investigational New Drugs: Approaches to Complying with Current Good Manufacturing Practice During Phase 1; Availability, <http://www.fda.gov/ohrms/dockets/98fr/06-352.htm>, and INDs – Approaches to Complying with CGMP During Phase 1 Draft Guidance, January 2006,

<http://www.fda.gov/ohrms/dockets/98fr/05d-0286-gdl0001.pdf>

- At the same time, FDA published a draft guidance entitled *"INDs – Approaches to Complying with CGMP During Phase 1"* to provide guidance (to replace the existing regulation) to provide "recommendations on approaches to statutory compliance" to manufacture Phase 1 material.

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FDA's Phase 1 Proposals

- Written comments on the rule(s) are due by April 3, 2006, and for the draft guidance by March 20, 2006.
- If timely significant adverse comments are received, the agency will publish a notice of significant adverse comment in the Federal Register withdrawing the direct final rule.
- If FDA receives no significant adverse comments within the specified comment period, the agency will confirm the effective date of the final rule in the Federal Register, and the final rule will go into place on June 1, 2006.

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Significant Adverse Comment

Source: Guidance for FDA and Industry, Direct Final Rule Procedures, Nov. 21, 1997, <http://www.fda.gov/cber/gdins/drcftnrl.pdf>

- Explains why rule would be inappropriate
- Includes challenges to rule's underlying premise or approach
- Explains why rule would be ineffective or unacceptable without the change
- Is serious enough to warrant a substantive response in notice and comment process
- A comment recommending a rule change in addition to the rule is not a significant adverse comment unless the comment also states why this rule would be ineffective without the additional change
- Comments that are frivolous, insubstantial or outside the scope of the rule will not be considered significant

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Rationale

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs, Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- "This action is intended to streamline and promote the drug development process while ensuring the safety and quality of the earliest stage investigational drug products, those intended for use in Phase 1 clinical trials."

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Rationale

Source: FDA Press Release, FDA Issues Advice to Make Earliest Stages Of Clinical Drug Development More Efficient, January 12, 2006, <http://www.fda.gov/bbs/topics/news/2006/NEW01296.html>

- "The Food and Drug Administration (has) announced steps to

advance the earliest phases of clinical research in the development of innovative medical treatments. FDA's goal is to improve the process for bringing safe and effective drugs for potentially serious and life-threatening diseases, such as cancer, heart disease and neurological disorders, to the market."

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Rationale

Source: FDA Press Release, FDA Issues Advice to Make Earliest Stages Of Clinical Drug Development More Efficient, January 12, 2006, <http://www.fda.gov/bbs/topics/news/2006/NEW01296.html>

- "The problem is that researchers conducting very early studies were required to follow the same manufacturing procedures as those companies that mass produce products for broad scale distribution," said Janet Woodcock, MD, FDA Deputy Commissioner for Operations. "These requirements are so burdensome for early phase 1 studies that many leading medical research institutions have not been able to conduct these studies of discoveries made in their laboratories. Today, for the first time, medical researchers are getting specific advice from the FDA about how to safely prepare products for exploratory studies."

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Rationale

Source: FDA Press Release, FDA Issues Advice to Make Earliest Stages Of Clinical Drug Development More Efficient, January 12, 2006, <http://www.fda.gov/bbs/topics/news/2006/NEW01296.html>

- "The documents released .. are part of FDA's commitment to modernize existing CGMP regulations to streamline clinical development. These efforts are part of the Agency's Critical Path Initiative, launched in March 2004. The goal of the Critical Path Initiative is to reduce the time and resources expended on candidate products that are unlikely to succeed, by creating new tools to distinguish earlier in the process those candidates that hold promise."

Proposed Change

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs, Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- An investigational drug for use in a Phase 1 study, as defined in Sec. 312.21(a) of this chapter, is subject to the statutory requirements set forth at 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a Phase 1 study once the investigational drug has been made available for use by or for the sponsor in a Phase 2 or Phase 3 study, as defined in Sec. 312.21(b) and (c)

of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a Phase 2 or 3 study or the drug has been lawfully marketed, the drug for use in the Phase 1 study must comply with part 211.

Background

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- Phase 1 studies are the first introduction of an investigational new drug into humans.
- Phase 1 studies are designed to establish basic safety of the compound, and to determine the metabolism and pharmacologic actions of the drug in humans.
- Number of subjects is limited to no more than 80 patients per phase 1 trial.
- Phases 2 and 3 enroll larger numbers of subjects, with the aim to test the effectiveness of the product.

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- FDA is proposing regulating phase 1 material by means other than CGMP regulations. How?
 - 1) By Federal Food Drug & Cosmetic Act that deems a drug adulterated if its manufacturing does not conform to CGMPs (statutory requirement).
 - 2) By investigational new drug (IND) submissions of sponsors, which include a chemistry, manufacturing, and controls (CMC) section.
- FDA states that it may place an IND on clinical hold if study subjects are exposed to unreasonable and significant risk, or if IND does not contain sufficient information to assess risks to subjects.
- FDA states that it may also terminate an IND if it discovers that the manufacturing of the investigational material is inadequate.

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- Although unstated, FDA currently does not commonly inspect during phase 1 studies unless for cause.
- FDA says that it believes the change is appropriate because many issues presented by production of investigational drugs intended for use in relatively small phase 1 clinical trials are different from issues presented by production of drug products for use in larger Phase 2 and Phase 3 clinical trials or for commercial marketing.
- FDA is considering additional guidance and regulations to clarify agency's expectations re: CGMP requirements for phase 2 and 3 studies.

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs.

Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- FDA adds many requirements in 21 CFR 211 do not apply to limited production of investigational drugs for phase 1; for example, fully validated manufacturing processes, rotation of stock for drug product containers, repackaging and relabeling of drug products, and separate packaging and production areas.
- This rule, if approved, would apply to investigational biological products that are subject to CGMP requirements, including recombinant and non-recombinant therapeutic products, vaccine products, allergenic products, in vivo diagnostics, plasma derivative products, blood and blood products, gene therapy products, and somatic cellular therapy products (including xenotransplantation products).

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs.

Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- So, Agency is proposing that production of an investigational new drug for use in a phase 1 study conducted under an IND when drug has not yet been, or is not being, manufactured for use in phase 2 or 3 studies or for an already approved use, is not subject to requirements in 21 CFR 211.
- Once an investigational drug product has already been manufactured and is available for use in phase 2 or 3 studies or for an already approved use, investigational drug product used in any subsequent phase 1 study must comply with 21 CFR 211.
- "The action taken should be noncontroversial, and the agency does not anticipate receiving any significant adverse comment on this rule."

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs.

Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- Rule would affect drug manufacturers, chemical manufacturers, and laboratories that manufacture drugs on a small scale for use in phase 1 clinical trials.
- The agency states that they believe that for drug manufacturers that product Phase 1 material in house and approved drug products, this rule will *reduce the amount of documentation* they produce and maintain when they manufacture a phase 1 drug. In some cases, it should also *reduce the amount of component and product testing*.

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs.

Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- FDA states that it lacks data to estimate the extent of cost savings. Some examples where substantial savings may be realized are the *level of testing and analyzing components and in-process materials*. These costs typically range from \$50 to \$1,200 per component tested.

- The extent of the need for *SOPs and methods validation* may also be greatly reduced. FDA estimates that large drug manufacturers that produce phase 1 drugs in-house could potentially save 24-40 hours per IND (or lead some large firms to product phase 1 material in house, rather than contracting the work out).

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- For chemical manufacturers and labs, requirement may increase time required for developing SOPs for quality, process, and procedural controls. May be in incremental increase in training costs to educate employees on the CGMPs. We estimate additional 12 to 24 hours may be required depending on experience of firm and its employees on CGMPs.

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- Agency notes that they do not keep a database of facilities manufacturing phase 1 materials, so do not have a number affected by rule.
- In 2003, FDA received 350 research and 500 commercial INDs. Not all affected by this rule, since the majority are for drug products that already have approvals. Since about 30% of INDs are for new molecular entities each year, agency estimates that the rule would affect about 255 INDs per year.
- Since companies produce multiple drug products for phase 1 trials in given year, and use different companies to produce them, FDA does not know how many entities would be affected each year.
- Estimated patient impact: 255 INDs per year X 80 patients = 20,400 patients affected.

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- FDA estimates that 65% of entities submitting NDAs and BLAs to FDA are small entities. The Small Business Administration defines biologic product manufacturers as small if they employ fewer than 500 people, and drug manufacturers as small if they employ fewer than 750 people.
- FDA believes that all of the entities affected by this rule have personnel with skills necessary to comply with requirements.

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- Agency adds that does not know experience levels of affected entities.
- Estimate savings to large manufacturers from *reduced SOP and validation requirements* for phase 1 drug production in-house, assuming time savings of 32 hours per application, fully loaded wage rate of \$45 and 90 INDs per year (35% of 255) would be \$1,440 per IND.
- For chemical manufacturers and laboratories, assuming all would incur costs and assuming average of 18 hours per application for writing SOPs and training, a fully loaded wage rate of \$45, and 165 INDs (65% of 255) would be \$810 per IND.

Specifics

Source: Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs, Direct Final Rule: <http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>

- FDA states that they do not know the number and size distribution of entities affected by this rule, they believe the impact on them will be negligible and should “actually reduce the compliance burden for some.” “To clarify the requirements for the manufacture of drugs for phase 1 trials, we have prepared a draft guidance document with recommendations for compliance.”

Guidance

Source: *INDs – Approaches to Complying with CGMP During Phase 1*, Draft Guidance, U.S. Food and Drug Administration, January 2006, <http://www.fda.gov/cber/gdlns/indcgmp.pdf>

- Draft guidance applies to investigational new human drug and biological products (including finished dosage forms used as placebos) intended for human use during phase 1 development. Examples of investigational biological products covered by this guidance include investigational recombinant and nonrecombinant therapeutic products, vaccine products, allergenic products, in vivo diagnostics, plasma derivative products, blood and blood components, gene therapy products, and somatic cellular therapy products (including xenotransplantation products) that are subject to the CGMP requirements of 501(a)(2)(b) of the FD&C Act.
- The guidance applies to investigational products whether they are produced in small- or large-scale environments because such studies are typically designed to assess tolerability or feasibility for further development of a specific drug or biological product.
- Guidance does not apply to human cell or tissue products; clinical trials for products regulated as devices, or already approved products that are being used during phase 1 studies (e.g.. for a new indication).

Rationale

Source: FDA Press Release, FDA Issues Advice to Make Earliest Stages Of Clinical Drug Development More Efficient, January 12, 2006, <http://www.fda.gov/bbs/topics/news/2006/NEW01296.html>

- In its draft guidance, “FDA outlines a suggested approach to complying with current good manufacturing practice (CGMP) requirements for drugs intended for use solely in phase 1 studies. With this new guidance and an accompanying regulation, FDA formally recognizes specific standards for the manufacture of small amounts of drug product for phase 1 studies and formulating an approach to CGMP compliance that is appropriate for the particular

stage of drug development.”

Guidance

Source: *INDs – Approaches to Complying with CGMP During Phase 1*, Draft Guidance, U.S. Food and Drug Administration, January 2006, <http://www.fda.gov/cber/gdlns/indcgmp.pdf>

- The draft guidance describes FDA’s current thinking regarding controls for special production situations (e.g., a laboratory setting, exploratory studies, multi-product and multi-batch testing) and specific product types (e.g., biological/biotechnology, aseptically processed products) of IND products manufactured for use during phase 1 clinical trials as described in the scope section of the guidance. As the new rule will specify if finalized, the particular requirements in part 211 need not be met for most exploratory products manufactured for use during phase 1 clinical trials.
- When finalized, this guidance will replace the 1991 “Guideline on the Preparation of Investigational New Drug Products (Human and Animal)” for the production of IND products for phase 1 clinical trials described in the scope section of the guidance. Phase 2 and 3 trials will continue to be subject to those portions of parts 210 and 211 that are applicable.

Concerns re: Draft Guidance

Source: *INDs – Approaches to Complying with CGMP During Phase 1*, Draft Guidance, U.S. Food and Drug Administration, January 2006, <http://www.fda.gov/cber/gdlns/indcgmp.pdf>

- Provides recommendations; not legally binding
- Would be used (per current proposals) to replace an existing regulation for phase 1 material
- As currently written, appears insufficient to protect patients
- As currently written, appears insufficient to manufacture material safely
- Does not harmonize with EU requirements that Qualified Person release investigational material
- Assumption that sponsors or others would read or follow it (or learn enough about CGMPs, aseptic processing, etc.) without a regulation requiring them to do so
- Assumption that a reader would be able to review a 17-page document and manufacture material safely per basic GMP principles, particularly for biologic products, or aseptic/sterile dosage forms

Concerns Re: Draft Guidance

Source: *INDs – Approaches to Complying with CGMP During Phase 1*, Draft Guidance, U.S. Food and Drug Administration, January 2006, <http://www.fda.gov/cber/gdlns/indcgmp.pdf>

- Allows non QC unit (non QA) personnel to release product; allows same individual who performed production to also release or reject batch
- Insufficient facilities, equipment, and environmental controls for aseptic, sterile or biological products (particularly injectable or inhaled products.) Allows GMP work and research to be done in same area; *recommends* that equipment used for sterilization be qualified
- Insufficient training requirements (very difficult to train or learn aseptic technique, even for experienced laboratory employees)
- Appears to allow reduced testing (for example, strongly recommends performing confirmatory ID testing for APIs)
- Does not require approval of proposed changes (but record and give rationale)
- Does not appear to require method validation (recommends tests be done under controlled conditions, follow written SOPs)
- *Recommends* the use of aseptic techniques to prevent microbial and endotoxin contamination if you are manufacturing aseptically
- *Recommends* that testing of biological/biotechnological products for safety-related purposes such as viral loads, bioburden, detoxification of bacterial toxins, viral clearance or inactivation, and clearance of antibiotics be done

Concerns Re: Draft Guidance

Source: *INDs – Approaches to Complying with CGMP During Phase 1*, Draft Guidance, U.S. Food and Drug Administration, January 2006, <http://www.fda.gov/cber/gdlns/indcgmp.pdf>

- Does not yet appear to discuss or limit movement from animal colony to human production area
- Does not yet discuss routine, periodic auditing (one of most important quality systems) and require careful selection of contractors
- Does not seem to acknowledge the skills and experience needed of primary QA individual
- *Recommends* keeping a record (such as a log book) containing relevant information concerning all components; *recommends* establishing acceptance criteria for specified attributes of each component.
- *Recommends* that lab testing of the investigational product be performed as appropriate to evaluate identity, strength, potency, purity, and quality attributes.
- *Recommends* that for known safety-related concerns, specifications should be established and met.
- Does not seem to acknowledge the years of hard work and effort in getting R&D groups, new companies, universities to comply (or that organizations with “shared space” usually have conflicting priorities, difficulty following requirements)

Exploratory Studies Guidance

Source: *Exploratory IND Studies*, January 2006, <http://www.fda.gov/cder/guidance/7086fnl.pdf>

- This guidance clarifies what preclinical and clinical issues (including chemistry, manufacturing, and controls issues) should be considered when planning exploratory studies. Once finalized, it will represent FDA’s thinking on this topic.
- The phrase exploratory IND study is intended to describe a clinical trial that is conducted early in phase 1, involves very limited human exposure, and has no therapeutic or diagnostic intent (such as screening studies, microdose studies).
- Such exploratory IND studies are conducted prior to the traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program. The duration of dosing in an exploratory IND study is expected to be limited (e.g., 7 days).

Exploratory Studies Guidance

Source: *Exploratory IND Studies*, January 2006, <http://www.fda.gov/cder/guidance/7086fnl.pdf>

- “Existing regulations allow a great deal of flexibility in terms of the amount of data that need to be submitted with any IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility. As a result, limited, early phase 1 studies, such as those described in this guidance, are often supported by a more extensive preclinical database than is required by the regulations.”
- *“Because exploratory IND studies present fewer potential risks than do traditional phase 1 studies that look for dose-limiting toxicities, such limited exploratory IND investigations in humans can be initiated with less, or different, preclinical support than is required for traditional IND studies.”*

Concerns re: Guidance

Source: *Exploratory IND Studies*, January 2006, <http://www.fda.gov/cder/guidance/7086fnl.pdf>

- “It is expected that all preclinical safety studies supporting the safety of an exploratory IND application will be performed in a manner consistent with good laboratory practices (GLPs)... GLP provisions apply to a broad variety of studies, test articles, and test systems. Sponsors are encouraged to discuss any need for an exemption from GLP provisions with the FDA prior to conducting safety related studies, for example, during a pre-IND meeting. Sponsors must justify any nonconformance with GLP provisions (21 CFR 312.23 (a)(8)(iii).”
- “The common theme throughout this guidance is that, depending on the study, the preclinical testing programs for exploratory IND studies can be less extensive than for traditional IND studies. This is because the approaches discussed in this guidance, which involve administering sub-pharmacologic doses of a candidate product or products, the potential risks to human subjects are less than for a traditional phase 1 study.”
- “This guidance describes some exploratory approaches...that will enable sponsors to move ahead more efficiently with the development of promising candidate products while maintaining needed human subject protections.”

FDA Mission

Source: Food, Drug and Cosmetic Act (FD&C Act, Sec. 903, U.S.C. 393), <http://www.fda.gov/opacom/laws/fdcaact/fdcaact9.htm>

- (a) IN GENERAL. – There is established in the Department of Health and Human Services the Food and Drug Administration (hereinafter in this Section referred to as the “Administration”).
- (b) MISSION. – The Administration shall –
 - (1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner
 - (2) with respect to such products, protect the public health by ensuring that –
 - (A) foods are safe, wholesome, sanitary, and properly labeled;
 - (B) human and veterinary drugs are safe and effective;

FDA Mission

Source: Food, Drug and Cosmetic Act (FD&C Act, Sec. 903, U.S.C. 393), <http://www.fda.gov/opacom/laws/fdcaact/fdcaact9.htm>

- (C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;
- (D) cosmetics are safe and properly labeled; and
- (E) public health and safety are protected from electronic product radiation;
- (3) participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and
- (4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

Tragedy and Response:

A Brief History of Regulation in the U.S.

Source: *A Brief History of the GMPs: The Power of Storytelling*, Immel Resources LLC, earlier published as *The BioPharm Guide to GMP History*, by B. Immel, November 2002

- 1902 Biologics Control Act

- (diphtheria vaccine) (requires inspections and testing of biologic products for purity and strength)
- 1906 Pure Food and Drug Act (Upton Sinclair's *The Jungle*) (illegal to manufacture/sell adulterated or misbranded food or drug products; accurate labeling required)
- 1938 Food, Drug, and Cosmetic Act (sulfanilamide) (safety; authorized inspections)
- 1962 Drug Amendments of 1962 (thalidomide) (efficacy; required drugs to be tested in animals before people; informed consent, ADEs)
- 1963 First GMPs published
- 1978 Current GMPs published

Tragedy and Response:

A Brief History of Regulation in the U.S.

Source: *A Brief History of the GMPs: The Power of Storytelling*, Immel Resources LLC, earlier published as *The BioPharm Guide to GMP History*, by B. Immel, November 2002

- 1980 Infant Formula Act (sodium chloride)
- 1982 Tamper-Resistant Packaging (acetaminophen)
- 1983 "Guide to Inspection of Computerized Systems"
- 1987 "Guide to Inspection of Bulk Drug Manufacture (L-Tryptophan)
- 1990 Safe Medical Devices Act (heart valve)
- 1990s on Updated, Revised Regulations

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research, April 18, 1979, <http://www.fda.gov/oc/ohrt/irbs/belmont.html>

- Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.
- Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethic of research involving human subjects: the principles of respect for persons, beneficence, and justice...
- Respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.... Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do no harm and (2) maximize possible benefits and minimize possible harms...

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research, April 18, 1979, <http://www.fda.gov/oc/ohrt/irbs/belmont.html>

- An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally.
- For informed consent, "there (should be) no undisclosed risks to subjects that are more than minimal...."
- "In balancing these different elements, the risks and benefits affecting the immediate research

subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against the risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research."

The Declaration of Helsinki

World Medical Associations, Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, 1983 and 1989, <http://www.fda.gov/oc/health/helsinki83.html> and <http://www.fda.gov/oc/health/helsinki89.html>

- "Concern for the interests of the subject must always prevail over the interests of science and society..."
- "Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable...."
- "In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail...."
- "The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods...."
- "In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject."

Recent, pertinent events

- Patient deaths in phase 1 trials
 - Johns Hopkins
 - University of Pennsylvania
- Pharmacy compounding experience
- Medical device experience
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Johns Hopkins

Sources: FDA Warning Letter, http://www.fda.gov/foi/warning_letters/g3936d.pdf, FDA Enforcement Story 2003, http://www.fda.gov/ora/about/enf_story/ch3/cder1.htm, Johns Hopkins Magazine, February 2002, Trials & Tribulations, <http://www.jhu.edu/~jhumag/0202web/trials.html>, FDA Disqualified/Restricted/Assurances Lists for Clinical Investigators, http://www.fda.gov/ora/compliance_ref/bimo/restlist.htm

- Healthy volunteer Ellen Roche, 24 years old, died as result of participating in a phase 1 safety trial in 2001
- Physician conducting trial, Dr. Alkis Togias, restricted by FDA for 3 years
- FDA issued warning letter 21 months after Ellen's death, and offered restricted agreement
- Within five days of inhaling experimental compound, Ellen was admitted to intensive care with respiratory distress. She died within a month of lung failure.
- Dr. Togias had submitted an IND to FDA years earlier (1997) to study capsaicin in lungs; FDA prohibited him from initiating that study

Johns Hopkins

Sources: FDA Warning Letter, http://www.fda.gov/foi/warning_letters/g3936d.pdf, FDA Enforcement Story 2003, http://www.fda.gov/ora/about/enf_story/ch3/cder1.htm, Johns Hopkins Magazine, February 2002, Trials & Tribulations, <http://www.jhu.edu/~jhumag/0202web/trials.html>, FDA Disqualified/Restricted/Assurances Lists for Clinical Investigators, http://www.fda.gov/ora/compliance_ref/bimo/restlist.htm

- Violations

- Did not submit IND application for use of unapproved new drug
- Informed consent failed to disclose inhalation of hexamethonium bromide experimental use of drug
- Informed consent failed to disclose material chemical grade, labeled for laboratory use only, with labeling stating: "Do not breathe dust; may be harmful if inhaled"
- Consent form not updated to include unexpected adverse events experienced by first two subjects in trial (persistent cough/shortness of breath)

University of Pennsylvania

Sources: U.S. Department of Justice Press Release, <http://66.98.181.12/newsources/uofp.pdf/>, FDA warning letters, http://www.fda.gov/foi/warning_letters/m3897n.pdf, http://www.fda.gov/foi/warning_letters/m3435n.pdf, Washington Post, February 10, 2005, <http://www.washingtonpost.com/wp-dyn/articles/A121306-2005Feb9.html> and FDA Restricted List, http://www.fda.gov/ora/compliance_ref/bimo/restlist.htm, Online News Hour, Feb. 2, 2000, http://www.pbs.org/newshour/bb/health/jan-june00/gene_therapy_2-2.html, and Dec. 8, 1999, http://www.pbs.org/newshour/bb/health/july-dec99/gene_therapy.htm

- Jesse Gelsinger, an 18-year-old teenager, died in 1999 during a phase 1 gene therapy trial.
- Clinical investigators: James Wilson, Mark Batshaw, and Steven Raper, have all been restricted, with restrictions more severe for principal investigator
- Trial investigating use of genetically engineered adenovirus to ameliorate an enzyme deficiency, ornithine transcarbamylase deficiency (OTCD)
- Some individuals are born with OTCD, which is a deficiency in an essential enzyme needed to form urea; coma and death can occur with OTCD

University of Pennsylvania

Sources: U.S. Department of Justice Press Release, <http://66.98.181.12/newsources/uofp.pdf/>, FDA warning letters, http://www.fda.gov/foi/warning_letters/m3897n.pdf, http://www.fda.gov/foi/warning_letters/m3435n.pdf, Washington Post, February 10, 2005, <http://www.washingtonpost.com/wp-dyn/articles/A121306-2005Feb9.html> and FDA Restricted List, http://www.fda.gov/ora/compliance_ref/bimo/restlist.htm, Online News Hour, Feb. 2, 2000, http://www.pbs.org/newshour/bb/health/jan-june00/gene_therapy_2-2.html, and Dec. 8, 1999, http://www.pbs.org/newshour/bb/health/july-dec99/gene_therapy.htm

- Deaths in monkeys during preclinical testing
- Jesse's disease was being well controlled by medication
- Jesse died within a few days of having compound infused into his liver
- U.S. government prosecuted investigators and their organizations, alleging:
 - Trial produced toxicities in humans that should have resulted in its termination, but study continued
 - Reports misrepresented actual clinical findings submitted to FDA, NIH, and IRBs
 - Informed consent process did not disclose all anticipated toxicities
 - Violations of Civil False Claims Act in submitting false statements to FDA and IRBs
- Physicians contend conduct at all times lawful and appropriate
- Their employers paid fines of \$517,496 and \$514,622 to settle the case

Pharmacy Compounding Experience

Sources: Pharmacy Compounding, FDA Consumer Magazine, July-August 2000, http://www.fda.gov/fdac/features/2000/400_compound.html, FDA Compliance Policy Guide, Sec. 460.200, Pharmacy Compounding, http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html, FDAMA, <http://www.fda.gov/cder/guidance/105-115.htm#SEC.%20127>, Steven Galson, Congressional Testimony, October 23, 2003, <http://www.fda.gov/ola/2003/pharmacycompounding1023.html>

- Pharmacy compounding law is part of 1997 Food, Drug and Modernization Act (FDAMA)
- Limited to Rx requests; may not compound large quantities of commercially available drugs
- List of acceptable ingredients, approved products, monographs or USP drugs
- Serious problems: 3 infants died of intravenous solution incorrectly prepared by pharmacy, 1 patient blind in one eye due to pharmacy-prepared eye drops

that were not sterile

Pharmacy Compounding Experience

Sources: FDA Enforcement Story 2003, http://www.fda.gov/ora/about/enf_story/ch3/cder1.htm#pc, FDA warning letters to Med-Mart Pulmonary Services, September 30, 2002, http://www.fda.gov/foi/warning_letters/g3527d.htm, FDA warning letter to Carneys Drug, May 27, 2003, http://www.fda.gov/foi/warning_letters/g4057d.htm, FDA press release, Nov. 15, 2002, Nationwide Alert on Injectable Drugs Prepared by Urgent Care Pharmacy, <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01171.html>, Steven Galson, Congressional Testimony, October 23, 2003, <http://www.fda.gov/oc/2003/pharmacycompound1023.html>.

- Carneys Drug, Rochester, NH – Fentanyl lollipops (narcotic analgesic) without required labeling (safety hazard for children)
- Urgent Care Pharmacy, Spartanburg, SC – contaminated methylprednisolone acetate injection – rare fungal (*wangiella*) meningitis, six patients affected, one died
- Med-Mart Pulmonary Services, Novato and Bakersfield, CA – Class I recalls of albuterol inhaler due to *Serratia liquefaciens*
- Since 1990, FDA has found at least 55 quality problems with compounded products
- In 2001, FDA survey of 29 programs (including hormonal products, antibiotics, anesthetics, steroids, sterile injectables, ophthalmics, and asthma medications) found 34% of tested products failed one or more tests. Many were subpotent (59% - 89% of labeled strength)
- In some operations, large quantities are being made in advance of receiving prescription, copying approved commercial drug, subpotent/superpotent issues

Medical Device Experience

Source: *Immel Report*, "Downregulating the FDA – Part I, Inspections," September-October 2005 Issue, Medical Devices Current Good Manufacturing Practice, <http://www.fda.gov/cdrh/fr1007ap.pdf>

- Deadly class I recalls have increased more than 300% since 1998
- Greatest number of warning letters from FDA are being issued to medical device firms, with a large number to sponsors, clinical investigators and IRBs
- For investigational devices, only part of CGMP (Quality System Regulation) which must be followed is Design Controls
- Question: Could there be a link between not following CGMPs for investigational devices, hasty or rushed clinical or product development, and the deadly recalls, warning letters, and compliance problems?

Why Logic May Be Flawed

- Patient safety concerns. If material is going into humans, it should be made under a minimum, CGMP regulation.
- Phase 1 is foundation of trial
- Guidance is not legally binding, nor easily enforceable
- Question: Does agency yet have enough experience with phase 1 or earlier (medical research, etc.) situations to be making proposal? What data do FDA have that supports this proposal? (ADEs in phase 1 and their root causes, common inspectional findings during phase 1 or treatment IND inspections, survey or analysis of phase 1 operations, etc.)
- Assumption that individuals will learn aseptic technique, CGMPs, without regulation requiring them to
- Assumption that individuals will be able to learn enough about GMP or especially aseptic processing to produce clinical material safely by reading a guidance document
- Guidance is currently 17 pages long; aseptic or sterile products very difficult to make
- While Immel Resources is not concerned about pioneer firms, we are very concerned about firms or medical research institutions which have never made clinical materials before.

Why Logic May Be Flawed

- Assumption that will speed products to market (our experience tells us that it may *delay* products to market: if not reproducible or sufficiently documented, or if patients injured. Phase 2 is typically "big push" in small companies in implementing all CGMP systems.)
- FDA has detailed regulation (21 CFR 58, Good Laboratory Practices) for preclinical or animal testing, also

- is still requiring GMPs for phase II and III – why drop protection during phase I?
- Question: Are members of the agency seeking to indemnify companies, physicians, or medical researchers from accountability in phase I?
- Are human beings who volunteer for phase 1 clinical trials less valuable than animals? Are patients in phase 1 trials less valuable than patients in phase 2 or phase 3 trials? Are human beings who volunteer for phase 1 trials expendable since there are fewer of them?
- It costs nothing for agency to keep CGMP regulations on books
- Question: Is the agency throwing in the towel? Recognizing that they do not have the staff to enforce or routinely inspect in human clinical trials?
- APIs currently regulated off FD&C Act statutory authority, *but* ICH Q7A for APIs contains 57 detailed pages.

Why Logic May Be Flawed

- Question: Is this a flawed use of risk management concept? Are the numbers involved more important than the species involved?
- Estimated savings are minimal (\$1,440 per IND – same cost to send 1 person to an industry two-day seminar) for risks involved
- Estimated additional cost of \$810 per IND for chemical producers and laboratories who have not yet made product does not yet appear to address costs involved in facility, equipment, or contracting work out, particularly for aseptic/sterile products (unless that is a given)
- Question: Is Agency becoming more of a research-enabling or product marketing agency rather than a consumer protection agency?
- Does agency want to write many warning letters for violative firms or organizations? Or issue restricted agreements to clinical investigators or take them to court if there are more patient deaths in phase 1?
- Agency's mission: where two standards apply, stricter should prevail.
- History has shown that paper reviews do not work (it's why FDA was granted inspectional authority), and that not performing necessary testing can be deadly (sulfanilamide, etc.)

Why Logic May Be Flawed

- Has Agency yet done a root cause analysis of what is causing dramatic increase in medical device deadly class I recalls, and increased number of warning letters? Why emulate device sector without understanding why there are compliance issues?
- Does not acknowledge the confusion that is already resulting in some individuals thinking that they may use non-GMP material in phase 1
- Informed consent will need to change to inform patients of change in standard, increased risk to patients
- Ethical considerations: Per Belmont Report, Declaration of Helsinki – individual patient's rights outweigh all other rights, and patients should be treated equally
- So what? Why should we care about this? Because all of us know (or will know) someone or a family member who will consider participating in clinical trial.
- From a QA perspective, cannot allow harm to come to patient if know it can be prevented. Protecting the patient is number one.

Questions

- Are CGMP requirements in phase 1 truly the impediment to scientific exploration or innovation?
- Are CGMPs truly that burdensome?
- Why does this new rule apply to phase 1 and not phases 2 and 3?
- Is the agency just seeking to deregulate something (anything) where it may affect the fewest people?

S.CFM

- Or send two copies of your written comments to:

■ Docket 2005N-0285
Dockets Management (HFA-305)
and Drug Administration
Rm. 1061

Division of
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5630 Fishers Lane,
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Recommended Reading

- Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
<http://www.fda.gov/ohrms/dockets/98fr/06-353.htm>
- Proposed Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs, <http://www.fda.gov/ohrms/dockets/98fr/06-350.htm>
- INDs – Approaches to Complying with CGMP During Phase 1 Draft Guidance, January 2006,
<http://www.fda.gov/ohrms/dockets/98fr/05d-0286-gdl0001.pdf>
- Exploratory IND Studies Guidance, January 2006,
<http://www.fda.gov/cder/guidance/7086fnl.pdf>

Review

- What FDA is proposing
 - Proposed rule and direct final rule
 - Draft guidance to replace CGMP regulation
- FDA's mission and history
- Recent events
 - Patient deaths in phase 1 trials
 - Pharmacy compounding experience
 - Medical device experience
- Draft guidance
- Why logic may be flawed
- What your organization can do
- Questions and answers

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Thank You

- Thank you all for participating
- Charlie Gammill, University of Georgia GMP Conference
- To all of my clients and subscribers, mentors, friends, and current and former members of the agency who have helped me to formulate my thoughts on this subject

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About Us

- Barbara Immel is president of Immel Resources LLC, where she helps pharmaceutical, biopharmaceutical, and medical device companies improve their quality systems and compliance track records. Since 1996, Immel Resources LLC has worked with more than 100 firms.
- Barbara is currently editor of the *Immel Report* newsletter, which provides advice and guidance for managers in FDA-regulated industry. She is also a member of *BioPharm Magazine's* Editorial Advisory Board, and served as their GMP columnist for 10 years. Before starting her company, Barbara gained more than 12 years of hands-on experience in quality assurance and regulatory compliance at Syva Co.,

Chiron Corp., and Syntex Corp. She is the author of the Quality Assurance chapter of Dekker's *Encyclopedia of Pharmaceutical Technology*. She has taught at UC Berkeley, Stanford University, and the University of Wisconsin at Madison.

- Please keep us in mind as you need assistance with quality assurance, regulatory compliance, or training projects. And please contact us with any comments on this presentation. Thank you very much.

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