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Docket 2005N-0285
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA's direct final rule/proposed rule to exempt phase 1 investigational drugs and biologics from the current, good manufacturing practice (CGMP) regulation

Dear Members of the U.S. Food and Drug Administration,

Thank you for the opportunity to comment on the agency's direct final rule/proposed rule to exempt phase 1 investigational drugs and biologics from the CGMP regulation. I am opposed to this rule, and believe that a guidance document, which is not legally binding, should not be used to replace an existing regulation that provides the minimum requirements for the safe manufacture of drugs or biologics for human beings. I believe that this rule may place patients in phase 1 in jeopardy.

Puts patients at risk, and is not legally binding

Guidance documents are not legally binding, and no one is required to follow them. They also cannot be enforced. Drugs or biologics made for use in human beings should be made per CGMP regulation, which provides the minimum, legal requirements to make them safely. In addition to putting patients at risk, this approach will make it very difficult to investigate or prosecute serious cases, and to prove what "current good manufacturing practice" is. This approach assumes that new sponsors would keep proper records, perform necessary testing, or keep retention samples for later investigations, or that they would take the time to learn and follow CGMP if there were no regulation requiring them to do so (why would they incriminate themselves?). FDA had always considered proposing CGMPs for investigational drugs (Preamble, Final Rule, *Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding*, 1978). Comments received on the direct final rule/proposed rule and draft guidance may be incorporated instead into a proposed rule on CGMPs for investigational drugs and biologics.

Unethical

In the proposed rule, FDA states that phase 1 material being made for the first time and for which an Investigational New Drug application (IND) has been submitted to FDA may be made using the guidance document (rather than the CGMP regulation), but if the material is already available in phase 2 or 3 clinical trials, or commercially available, the phase 1 material would have to be made per CGMP regulation. This would mean that some Phase 1 material would be made per CGMP regulation, and some may not. Patients or healthy volunteers in phase 1 are already shouldering the biggest burden of any participants because they are the first humans to receive the compound. Of the patients who participate, many of them are chronically ill, terminally ill, or immunocompromised. Introducing the possibility that the material they receive may be contaminated or superpotent, and not manufactured per the same standard as material

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used in other phase 1 trials, is unethical. This is a clear violation of the ethical principles governing the conduct of human research. The Belmont Report states that "an injustice occurs when some benefit to which a person 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." And the Declaration of Helsinki states that "in research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject."

As you know, FDA has a detailed regulation governing preclinical (or animal) testing (21 CFR 58), which requires a Quality Assurance Unit. With this proposal, FDA is continuing to require CGMP regulation be followed to manufacture material for phases 2 and 3. Questions: Are patients and volunteers in phase 1 less valuable than an animal? Are patients in phase 1 less valuable than patients in phases 2 and 3? Why drop the protection of the CGMP regulation in phase 1?

Ignores recent experience

The history of regulation in the United States is a response to tragedies that have occurred, and an attempt to prevent future tragedies from occurring. In the press release announcing the proposals, Janet Woodcock, MD, FDA Deputy Commissioner for Operations, states "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. 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."

In the recent past, we have had two patient deaths in phase 1 trials conducted at leading medical research institutions, Johns Hopkins and the University of Pennsylvania. In the Johns Hopkins case, clinical material was made using an unapproved drug, chemical grade, labeled "do not breathe dust... may be harmful if inhaled" yet it was administered by inhalation, resulting in the death of a healthy patient. In the University of Pennsylvania case, an experimental gene therapy compound shown to have caused the deaths of monkeys in preclinical testing was infused into Jesse Gelsinger, an 18 year old boy. Jesse subsequently died.

And in March 2006, six formerly healthy young males, all under the age of 40, were made seriously ill and suffered major organ failure, due to an experimental monoclonal antibody they received by injection in a phase 1 clinical trial in England. As you know, the Hippocratic Oath which physicians must follow states, "Do no harm."

Lacks common sense

In the recent past, there have also been both pharmacy compounding and medical device experiences that are directly applicable to this discussion.

Pharmacy Compounding Experience. We have had several deadly recalls, three infant deaths, one adult death, and blindness associated with drugs compounded by pharmacists. If trained pharmacists are not always able to safely make these products, particularly sterile or aseptic products, why would anyone assume that a medical researcher or other employee would be able to make them safely by reading a 17-page guidance document?

The infant deaths were associated with intravenous solutions compounded by a pharmacy which were not sterile. There have been several deadly, recent class I recalls due to drugs compounded by pharmacists which have been contaminated, such as the methylprednisolone injection contaminated with a rare fungus (*wangiella*) which caused meningitis in six patients and

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the death of one. Other deadly recalls of pharmacy-compounded products have included an albuterol inhaler for asthmatics that was contaminated with *Serratia liquefaciens*, which as you know may cause respiratory infections, sepsis, or death. One patient was also recently blinded in one eye due to using eyedrops prepared by a pharmacy that were not sterile.

Medical Device Experience. In the medical device industry, the number of deadly recalls has increased more than 300% since 1998. The single largest group of FDA warning letters for noncompliance are currently being issued to medical device firms, including a large percentage going to sponsors, clinical investigators, and institutional review boards involved in device human clinical trials. The only part of CGMP that must be followed when manufacturing investigational devices is that portion of device CGMP concerning design controls (which requires formal, documented reviews at the end of each design phase during product development, having an uninterested party present and actively contributing during those reviews, etc.)

Questions: Has the agency yet done a root cause analysis to determine what is causing the deadly product recalls, warning letters, and compliance problems in the device sector? Why would the agency want to emulate this sector (in reducing CGMP requirements for investigational drugs or biologics) without first understanding what is causing the problems in the device sector?

Violates U.S. and European Union CGMPs, and lacks understanding of QC unit role

The draft guidance published with the proposed rule allows the same person who manufactured the material to release it to the clinic, and allows a non-QC unit employee to release material. This is a clear violation of U.S. current good manufacturing practice, which requires that a member of the Quality Control unit (QC unit) release product. It is also a clear violation of the European Union CGMPs, which require that a Qualified Person (qualified by training and experience) release investigational and commercial material. Even pharmacists learn that that when compounding sterile or aseptic product, they must incorporate necessary checks and balances.

This approach does not appear to recognize the importance of having an experienced and knowledgeable QC unit (or person) to manufacture the materials safely. The agency is undermining the QC unit, the one group inside organizations that is responsible for ensuring patient safety and enforcing CGMP requirements. If a quality assurance unit is required for animal testing, why would the agency propose that one is not needed to release investigational material being used in human beings for the first time?

Off mission

The mission of the U.S. Food and Drug Administration, mandated by Congress in The Food, Drug and Cosmetic Act (Sect. 903, U.S.C. 393) states that the Food and Drug Administration shall "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" and "with respect to such products, protect the public health by ensuring that ...human and veterinary drugs are safe and effective." The direct final rule states that the agency is making this proposal "to streamline and promote the drug development process." If my understanding is correct, this is outside the scope of the agency's mission. The FDA was established to serve as a consumer protection agency, and a check and a balance on regulated industry. The Congressional mandate includes promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner, not becoming a drug development organization.

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Insufficient testing requirements

The guidance document issued with the proposed rule *strongly recommends* performing confirmatory identity testing on active pharmaceutical ingredients, but it does not require it. This is a violation of current, good manufacturing practice. As you recall, in the sulfanilamide tragedy that occurred in the 1930s in the United States, diethylene glycol (the equivalent of antifreeze) was used in manufacturing an "elixir" of sulfanilamide, without sufficient testing or controls, and resulting in the death of more than 100 patients, many of them children. The guidance document *recommends* but does not require that testing of biological/biotechnology products be done for safety-related purposes such as viral loads, bioburden, detoxification of bacterial toxins, viral clearance or inactivation, and clearance of antibiotics. The guidance document *recommends* but does not require that laboratory testing of the investigational product be performed "as appropriate to evaluate identity, strength, potency, purity, and quality attributes." This is clearly insufficient.

Insufficient aseptic or sterile information

The guidance, which if under the current proposal, would be used to replace the existing CGMP regulation for the manufacture of some phase 1 materials, contains little more than one page on manufacturing sterile or aseptic products, and makes no reference to media fills. Manufacturing sterile or aseptic dosage forms requires a higher level of skill and judgment. The agency's guidance on *Sterile Drug Products Produced by Aseptic Processing* is very detailed and contains 63 pages. Even though the current CGMP regulation does not contain detailed information on manufacturing sterile or aseptic product, it is illogical to assume that a drug manufacturer, chemical manufacturer or (medical research) laboratory making clinical material for the first time would be able to follow this guidance and make sterile or aseptic material safely. It is illogical to assume that they would read or become familiar with other FDA guidance documents or take the time to learn or follow CGMP without having to do so per a CGMP regulation.

Insufficient employee training requirements

The direct final rule states that even though the agency does not know how many entities would be affected by the rule, that they believe that "all of the entities affected by this rule have personnel with skills necessary to comply with requirements." This is illogical. The amount of training required for aseptic technique alone is substantial, and not yet well described in the guidance.

Based on assumptions; no data provided

The FDA acknowledges that they do not know how many entities may be affected by this rule, and that they do not keep a database of firms affected by this rule. Since FDA only performs limited inspections of phase 1 material manufacturers (such as "for cause" or during treatment INDs), what data do FDA have to support their position? What are the results of the agency's "for cause" inspections, treatment IND inspections, or adverse drug events reported during phase 1? What do the data show? Does the agency have enough information to be making this proposal? What data are FDA using to support their position?

Proponents of this approach state that ICH Q7A, *Good Manufacturing Practice for Active Pharmaceutical Ingredients*, an internationally harmonized guidance, has been successfully used

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without the need for a regulation. ICH Q7A also has 57 detailed pages, and is used to manufacture material that will be further processed before being delivered to patients. The draft phase 1 guidance is currently 17 pages long and provides *recommendations* for drugs and biologics that may be delivered by injection or inhalation, resulting in patient injury or death if the material is improperly prepared or contaminated. FDA also at least inspects API manufacturers, although again, the agency does not routinely inspect in phase 1 unless for cause (or in certain specified circumstances, such as for Treatment INDs).

Too risky for estimated benefits

The proposed savings of \$1,440 per IND in documentation, training, and other "reduced" requirements (or the equivalent of paying tuition to send one person to an industry two-day seminar) is not justified by the additional risk to patients in phase 1. In addition, the potential costs (estimated at an additional \$810 per IND for chemical manufacturers and laboratories which have never made these materials before) is a gross underestimation of how much it will cost to manufacture sterile or aseptic product for the first time. The draft guidance does not yet discuss required equipment or facilities for these types of products, such as biosafety cabinets, isolators and other equipment. Nor does it limit movement from an animal colony to the human manufacturing environment (which is required in the European Union CGMPs; not limiting this movement has caused contamination in facilities manufacturing material for humans.)

As far as how many people may be affected by the proposed rule each year, using the agency's estimate of 255 INDs per year, and estimating up to 80 patients per trial, would mean that approximately 20,400 patients and volunteers would be affected. This is a substantial number of people who would be exposed to more risk.

Confusing

When the agency takes an existing regulation, and attempts to negate portions of the regulation using guidance documents, or issuing a rule that affects part of the rule (but not all), the agency causes a great deal of confusion in industry. I have already received one email message from a regulatory affairs executive who stated that from now on, when they plan to use non-GMP material in a phase 1 trial, they will provide more data for FDA in their chemistry, manufacturing and controls (CMC) section of the IND.

Surprising

Even though the agency has the authority to issue a direct final rule, it is surprising that the agency would choose to handle any rule concerning current good manufacturing practice in this way – in which "significant adverse comment" would be required to prevent the rule from becoming final. It is also surprising that some members of the agency believed that "the action taken should be noncontroversial, and the agency does not anticipate receiving any significant adverse comments on this rule," as stated in the direct final rule.

Illogical

The agency states in the direct final rule that they would regulate phase 1 material by means other than the CGMP regulation, namely by using the Federal Food, Drug, and Cosmetic Act (FD&C Act), which states that all drugs must be made per CGMPs or they are adulterated, but does not

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give specifics) and the information submitted by sponsors in an IND. The agency states that it can place an IND on clinical hold if study subjects are exposed to unreasonable and significant risk, or if the IND does not contain sufficient information to assess risks to patients. FDA also states in the direct final rule that it may terminate an IND if it discovers that the manufacturing of the investigational material is inadequate. Obviously, however, many of these actions may be after the fact, and well after patients have been injured in the trial.

The agency was given inspectional authority for a reason, and that is because paper reviews are insufficient. Questions: Is the agency throwing in the towel? (since the agency lacks the resources to routinely perform inspections during clinical trials?) Are some members of the agency seeking to indemnify medical researchers from accountability for their actions? Does the agency want to issue warning letters to institutions that do not meet basic CGMPs, or send restricted agreements to clinical investigators for failure to comply with existing regulations, after patients are injured? Is someone in the agency attempting to make CGMP regulation the scapegoat for the slowdown in new molecular entities? Common sense dictates that you drive quality as early as possible into the process, not reduce the basic quality required up front.

May delay products to market

Proponents of this proposal believe that it will speed products to market. In our experience, it may *delay* products to market. Phase 1 material is the foundation of the trials, and would be used to prove the safety of the compound in humans. For sterile or aseptic drugs or biologics, you must validate any sterilization or aseptic process used before manufacturing phase 1 clinical material, and for biologic products, must also ensure the necessary viral inactivation or clearance, detoxification of bacterial toxins, and so on.

If phase 1 material is not reproducible, not well-documented, or not well-controlled, the results of the trial will be meaningless. Typically phase 2 is the "big push" inside a small start-up, working to get its first product on the market. Why? Not only because of the criticality of the trial results, but also because the organization is working very hard to get all of their GMP systems in place, such that the material that they manufacture for the phase 3 and largest trials is bioequivalent to the material that they would be making for commercial production. If for any reason, an organization were to interpret the agency's current proposal as loosening the basic requirements needed for phase 1, it could jeopardize not only patients and the results of the trial but also any later stage trials.

Obviously if the material injures patients, it will delay the further development of the compound, and rightfully so. If more patients are seriously injured or die in phase 1 studies, or if patients or volunteers feel that pharmaceutical companies and medical researchers are not looking after their self interests, who then will volunteer to participate in clinical trials?

Conclusion

Is it possible for our society to learn from the mistakes of the past? Or are we doomed to repeat them? The CGMP regulation was established in 1963 in response to the thalidomide tragedy, in which an estimated 10,000 babies were born deformed due to a compound (that turned out to be teratogenic) that was prescribed to pregnant women for the treatment of morning sickness or insomnia. The CGMPs were substantially revised in 1978, in the wake of the large volume parenteral tragedies in the 1970s, in which patients died of sepsis due to improperly prepared, sterile injectable products. In the preamble to the 1978 regulation, the FDA Commissioner made

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clear that the CGMP regulation applied to both clinical and commercial material, and that the agency was considering publishing CGMPs for investigational materials.

In the aftermath of the death of the formerly healthy 24 year old Ellen Roche, as a direct result of her participating in the flawed phase I trial at Johns Hopkins, Edward Miller, CEO of Johns Hopkins Medicine, stated in *Johns Hopkins Magazine* that:

"There has got to be a cultural change here.... We're going to have to raise the bar higher. There can't be any slippage. None....

"In some ways, I'd say there's an antibody response by our faculty to following those rules and regulations, because it's thought to stifle creativity....

"There has to be some consequence of non-compliance. There will be some people who always believe that they are above the rules. The institution cannot take the risk of having one [person] bring the institution down."

The key, says Miller, lies in having everyone at the institution embrace the idea that federal regulations are in place for good reason: patient safety. "If we only call it compliance, we're not going to get anywhere," Miller says. There's got to be a buy-in that there's really value added to this. If we follow the rules, will it be safer for patients to come to us and trust their care to us, whether it's in clinical investigation, or clinical treatment? I don't really think we can separate these two, to tell you the truth. We have to have a culture in which everybody is trying to do the right thing, the right thing all the time."

I hope that the agency will consider withdrawing the direct final rule, and issuing proposed CGMPs for investigational drugs, as the agency had always considered doing. Options include finalizing the draft guidance, to provide further clarification or recommended approaches during phase I, but keeping phase I material within the protection of the CGMP regulation.

Sincerely,



Barbara Immel
President, Immel Resources LLC
Editor, *Immel Report*TM

Attachments:

- 1) A Brief History of the GMPs: The Power of Storytelling Article
- 2) Chipping Away at the GMPs Tutorial (Powerpoint Slides), 30th Annual GMP Conference, University of Georgia, earlier delivered as an audioconference for *BioPharm Magazine*

Compliance Leadership™ Series

A Brief History of the GMPs

The Power of Storytelling

"If you have an important point to make, don't try to be subtle or clever. Use a pile driver. Hit the point once. Then come back and hit it again. Then hit it a third time with a tremendous whack!" - Winston Churchill

Friedrich Nietzsche once said, "If you know the *why* for living, you can endure any *how*." Everyone in our industry should know the story of how the good manufacturing practices (GMPs) have come to be.

To obtain and maintain GMP compliance, every manager and supervisor should provide frequent, meaningful GMP reminders, train and develop all employees, and fully participate in formal, ongoing training programs. Senior management must state publicly and make it clear through their actions that following GMPs is the only way their company does business.

THE 1900s

Early in this country's history, traveling medicine shows sold bottles of ointment or "miracle elixir" from the backs of wagons. Such medication was said to be good for aches and pains; for catarrh, rheumatism, and gout — of course it completely cured cancer — and it worked on horses too. Luckily, those days are long gone.

In 1905, a book called *The Jungle* helped catalyze public opinion for change. "Muckraker" social reformer Upton Sinclair wrote about the Chicago meat packing industry — the unsanitary conditions in which animals were slaughtered and processed and the practice of selling rotten or diseased meat to the public. He also reported that ground meat sometimes contained remains of poisoned rats and even unfortunate workers who fell into the machinery. Sinclair's main interest was in bringing attention to the miserable working conditions and the plight of the impoverished factory workers, many of whom were immigrants (1).

The Pure Food and Drug Act. *The Jungle* had a major impact on the American public. Congress passed the Pure Food and Drug Act in 1906, and for the first time it became illegal to sell contaminated (*adulterated*) food or meat. Also for the first time, labeling had to be truthful — no longer could anyone promise on a label "the moon and the stars."

Syrup to calm "colicky" babies and "tonics" for adults often contained alcohol, opium, or morphine, which addicted many people who used them. So the 1906 Act also required selected dangerous ingredients to be labeled on all drugs. Inaccurate or false labeling was called misbranding, and that became illegal. "Misbranded" applies to statements, designs, or pictures in labeling that

are false or misleading as well as to the failure to provide required information in labeling (2). Over the years, the word "adulterated" has been expanded to include products manufactured without following GMPs.

Before the publication of *The Jungle*, Harvey Wiley and others had been pressing for such a law for 25 years. The Act created one of the first government regulatory agencies, now known as FDA, and it also allowed for the seizure of illegal foods and drugs (3). Wiley later became chief chemist of the bureau given authority to enforce that act (the Bureau of Chemistry, U.S. Department of Agriculture), a forerunner of FDA (4).

Biologic products were first regulated a few years before *The Jungle*, when at least 12 children died from a diphtheria antitoxin that was contaminated with live tetanus bacilli (3). Congress responded to that tragedy by passing the Biologics Control Act of 1902, which required inspections of manufacturers and sellers of biological products and testing of such products for purity and strength (5).

THE 1930s

A 1933 FDA exhibit of dangerous food, medicines, medical devices, and cosmetics illustrated the shortcomings of the 1906 law. "America's Chamber of Horrors," included a womb supporter (also used as a contraceptive) that could puncture the uterus if inserted incorrectly; a weight-loss

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The Power of Storytelling

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drug that caused death; a hair remover that caused baldness, even if not used on the head; lotions and creams that could cause mercury poisoning; hair dyes that could cause lead poisoning; and an eyelash dye that blinded women (3). Eleanor Roosevelt took that exhibit to the White House, asking Americans to campaign for stronger consumer protections. A tragedy was waiting around the corner that would make her case for her.

Sulfa drugs were introduced in 1935. Many manufacturers began making the new anti-infectives. One company used diethylene glycol, a poisonous solvent and chemical analog of anti-freeze, in an oral "elixir of sulfanilamide." Before the problem was discovered, 107 people died, many of them children (3).

In response, Congress passed the Federal Food, Drug and Cosmetic (FD&C) Act of 1938. For the first time companies were required to prove that their products were safe before marketing them (3). Still the major act covering our subject matter on the books, it extended FDA oversight to cosmetics and therapeutic devices, explicitly authorized factory inspections, required standards for foods, and added injunctions to previous penalties of seizures and criminal prosecutions (6).

THE 1940s AND 1950s

In 1941 nearly 300 people were killed or injured by one company's sulfathiazole tablets, a sulfa drug tainted with the sedative, phenobarbital. That incident caused FDA to revise manufacturing and quality control requirements, leading to what would later be called GMPs (6). The Public Health Services (PHS) Act passed in 1944 covered a broad spectrum of concerns, including regulation of biological products and control of communicable diseases (7).

Also during the WWII era, batch certification by FDA became a requirement for certain drugs. It required companies to submit samples from each lot to FDA for testing, and the agency would give permission for their release. That practice, begun in 1941 for insulin and 1945 for penicillin, was later expanded to include all antibiotics. By 1983, the requirement for batch certification of drugs was dropped (7).

In 1955, Jonas Salk discovered a way to vaccinate against polio (8). Many manufacturers began making his polio vaccine. One company failed to inactivate the virus completely in a single lot. About 60 individuals inoculated developed polio, and another 89 of their family members (mothers, fathers, brothers, sisters, and grandparents) contracted polio from them (9). We vaccinate our children to prevent them from getting a disease and also as a public health measure to protect society from the spread of disease.

THE 1960s

Thalidomide was marketed in Europe as a sleeping pill and to treat morning sickness. When regulatory agencies gave permission to sell the drug for that indication, they had no knowledge of its serious side effects. It turned out to be

teratogenic. It caused serious deformities in developing fetuses. Children whose mothers took thalidomide in the first trimester were born with severely deformed arms and legs. An estimated 10,000 cases of infant deformities in Europe were linked to thalidomide use (3).

The product was not allowed on the market in the United States. The drug reviewer responsible for the thalidomide application in the United States was Frances Kelsey. In 1962 President Kennedy awarded her the President's Distinguished Federal Civilian Service Award, the highest honor a government employee may earn as a civilian (3).

Thalidomide galvanized public opinion. Two legislators, Kefauver and Harris, pushed more stringent legislation through Congress that required companies to test not only to ensure that products were safe, but that they were efficacious for their intended uses. Regulating clinical trials, the amendments required drugs to be tested in animals before people. They made investigators responsible for supervising drugs under study. Manufacturers were expected to inform participants if a drug was being used for investigational purposes and to obtain their consent before testing it on them. Drugs had to be shown to work before going on the market. Manufacturers were required to report unexpected harm (adverse events). FDA was given authority to regulate advertising of prescription drugs (3). And in 1963, the first GMPs for finished pharmaceuticals were made final (10).

THE 1970s

The 1970s were a watershed for product regulation. In 1978, good manufacturing practices for drugs (21 CFR Parts 210 and 211) were greatly expanded and medical devices (21 CFR 820) and GMPs were, for the first time, made final. They were intended to help ensure the safety and efficacy of all products:

The regulations . . . contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. (11)

GMP requirements for devices were intended "to govern the methods used in and the facilities and controls used for the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished medical devices intended for human use," as described in the most recent revision (12).

Good Laboratory Practices (GLPs) were made final in 1979. They define:

good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug

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Important Definitions: Drugs, Biologics, and Devices

The following definitions describing the major differences between drugs, biologicals, and devices, are abstracted from the Requirements of Laws and Regulations Enforced by the U.S. Food and Drug Administration (2).

Drugs

The Food, Drug & Cosmetic (FD&C) Act defines drugs as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." It is the intended use that determines whether something is a drug. Thus, foods and cosmetics may be subject to the drug requirements of the law if therapeutic claims are made for them. The FD&C Act prohibits adulteration or misbranding of any drug and requires that "new drugs" be reviewed and approved by FDA before they go to market. Drug applications typically fall into three categories: a New Drug Application (NDA), a New Animal Drug Application (NADA), or an Abbreviated New Drug Application (ANDA) for generic products.

Biologicals

The Public Health Services Act defines a biological product as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of diseases or injuries of man . . ." Biologicals include such vitally important products as polio and measles vaccines, diphtheria and tetanus toxoids, and skin test substances as well as whole blood and blood components for transfusions. Biological products are subject to all the adulteration, misbranding, and registrations provisions of the FD&C Act. Because most biological products are derived from living organisms, they are

Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed. (12)

A few years earlier, the Medical Device Amendments (signed as law in 1976) strengthened FDA's authority to oversee medical devices. The law was precipitated by incidents involving a contraceptive intrauterine device (IUD) that about two million women were using. Many users were seriously injured (3). The product was taken off the market in 1975 because it was associated with a high incidence of pelvic infections, infertility, and some deaths (13).

The Medical Device Amendments required manufacturers of most medical devices (particularly moderate- or high-risk devices) to provide FDA with safety and effectiveness data before marketing them. Furthermore, the law provided for a system of pre- and postmarket oversight including FDA inspections to ensure that companies follow GMPs, keep appropriate records on the design and manufacture of their products, and maintain systems for handling complaints (14).

by their nature potentially dangerous if improperly prepared or tested. Under the PHS Act, manufacturers wishing to ship biological products in interstate commerce or for import or export must obtain the appropriate U.S. license(s). Previous licensing requirements called for both an Establishment and a Product License Application (ELA and PLA) to be filed. That has recently been streamlined into the single Biologics Licensing Application (BLA).

Devices

Medical devices include several thousand health products, from simple items such as thermometers, tongue depressors, and heating pads to IUDs, heart pacemakers, and kidney dialysis machines. Under the FD&C Act, a device is defined as "any health care product that does not achieve its principal intended purposes by chemical action in or on the body or by being metabolized." Products that work by chemical or metabolic action are regulated as drugs. The term "devices" also includes components, parts, or accessories of medical devices, diagnostic aids such as reagents, antibiotic sensitivity disks, and test kits for in vitro (outside the body) diagnosis of diseases and other conditions. Three classes of medical device exist:

- Class I, General Controls (registration of manufacturers, record keeping and labeling requirements, compliance with GMPs)
- Class II, Special Controls (including performance standards, post market surveillance, and patient registries)
- Class III, Pre market Approval (implanted and life-supporting or life-sustaining devices). Devices "substantially equivalent" to others may be filed using a 510(K) application; all others, and all Class III devices, require filing a pre market approval application (PMA).

THE 1980s AND 1990s

In 1980, Congress passed the Infant Formula Act giving FDA authority to create and enforce standards and specify nutritional requirements for commercial infant formulas. That followed 1979 reports that more than 100 infants were made seriously ill by a lack of chloride in two soy-based formulas (15). Manufacturers are now required to analyze each batch of formula for nutrient levels and make safety checks, conduct stability tests, code each container with a lot number, keep detailed records of production and analysis, and so on (16). The food GMPs (21 CFR Part 110), which include special provisions for infant formulas, were finalized in the 1980s.

In 1982, 12-year-old Mary Kellerman told her parents that she felt like she had a cold. They gave her an extra-strength Tylenol acetaminophen capsule, and within a few hours she died. Six other people died in this tragic incident, including three members from one family (two brothers and one of their wives) and a woman who had just given birth to her fourth child (17).

Johnson & Johnson announced a nationwide recall of 31 million bottles of Tylenol. Their investigation revealed that a criminal tamperer (who has never been found or prosecuted) had opened up and laced some capsules with cyanide. The company destroyed all 31 million bottles of the largest-selling over-the-counter medicine in the country.

A GMP Timeline

1902 Biologics Control Act

Tragedy: At least 12 children die of tetanus contracted from contaminated diphtheria vaccine. Result: Requires inspections and testing of biologics manufacturers' facilities and products

1906 Pure Food and Drug Act

Creates one of the first government regulatory agencies (now known as FDA); the culmination of 25 years of lobbying, this act makes it illegal to sell "adulterated" or "misbranded" food or drugs.

1938 Federal Food, Drug and Cosmetic (FD&C) Act

Tragedy: Sulfanilamide made with poisonous solvent causes 107 deaths. Result: Requires manufacturers to prove the safety of products before marketing.

1941 Two Unrelated Events

Insulin Amendment requires FDA to test and certify purity and potency of insulin. Tragedy: nearly 300 deaths and injuries from distribution of sulfathiazole tablets tainted with phenobarbital. Result: FDA revises manufacturing and quality controls drastically, the beginning of what will later be called GMPs.

1944 Public Health Services Act

Regulates biological products and control of communicable diseases.

1962 Kefauver-Harris Drug Amendments

Tragedy: Thalidomide causes birth defects in thousands of European babies. Result: Manufacturers must prove efficacy of products before marketing them and ensure stricter control over drug testing.

FDA issued tamper-resistant packaging regulations for all over-the-counter human drug products and incorporated them into the GMPs. Congress passed the Federal Anti-Tampering Act in 1983, making it a crime to tamper with packaged consumer products (18). The acetaminophen tragedy had a major impact on the industry. Not only do we need to provide ongoing GMP training to all of our employees, making sure they are adequately and thoroughly trained and supervised, but now we worry about how murderers could use our products to harm the public.

Guidance documents. In the 1980s, FDA began publishing a series of guidance documents that have had a major effect on our interpretation of current good manufacturing practice. One such document was the "Guide to Inspection of Computerized Systems in Drug Processing" published in 1983, which gave early expectations for the functioning of computer systems and perhaps signaled the beginning of computer validation (19). Of course, the very famous "Guideline on General Principles of Process Validation" in 1987 outlined current thinking or expectations of process validation for drugs and devices (20). Such documents, including the *Points to Consider*, provide guidance only on principles and practices that are not legal requirements. However, typically they reflect current agency thinking and expectations.

L-tryptophan. Active pharmaceutical ingredients (APIs) used to be called bulk pharmaceutical chemicals (BPCs).

1963 GMPs for Drugs (28 FR 6385)

Good manufacturing practices for manufacturing, processing, packing, or holding finished pharmaceuticals were first published.

1975 CGMPs for Blood and Blood Components Final Rule

Establishes minimum current good manufacturing practices for blood establishments in the collecting, processing, compatibility testing, storing, and distributing of blood and blood components.

1976 Medical Device Amendments

Tragedy: the Dalkon Shield IUD seriously injures many patients. Response: New law strengthens FDA authority to oversee medical devices.

1978 CGMPs for Drugs and Devices (21 CFR 210-211 and 820)

A major rewrite for the drug GMPs and GMPs for medical devices were published. These regulations establish minimum current good manufacturing practices for manufacturing, processing, packing, or holding drug products and medical devices.

1979 GLPs (21 CFR 58) Final Rule

Establishes good laboratory practices for conducting nonclinical laboratory studies that support applications for research or marketing permits for human and animal drugs, medical devices for human use, and biological products.

1980 Infant Formula Act

Tragedy: 100 children reported seriously ill linked to lack of chloride in soy-based formulas. Result: Congress gives FDA authority to set and enforce nutritional and quality standards.

The terminology recently changed to reflect the fact that some active ingredients are made using biological rather than chemical processes. The term "new chemical entity" (NCE) is also now often referred to as a "new molecular entity" (NME) for the same reason.

The naturally occurring amino acid, L-tryptophan, used to be widely promoted as a dietary supplement and was used as an aid for insomnia, depression, obesity, and for children with attention deficit disorder. In 1989, an epidemic of eosinophilia-myalgia syndrome (EMS) was linked to dietary supplements containing L-tryptophan. The Centers for Disease Control (CDC) identified more than 1,500 cases of EMS, including at least 38 deaths, that were associated with L-tryptophan. In tests run by both FDA and the Mayo Clinic, impurities were confirmed in some L-tryptophan products on the market. One impurity was called Peak X. Although its significance remains unknown, Peak X was found in one case of EMS associated with L-tryptophan in 1991. Unfortunately, the exact cause of the 1989 epidemic and of the EMS associated with 5HTP continue to be unclear, in part because 5HTP is synthesized from L-tryptophan in the body. Research has not yet conclusively resolved whether EMS was caused by L-tryptophan, by 5HTP, by one or more impurities, or by some other factors (21).

Some 70-80% or more of the APIs used to

A GMP Timeline (continued)

1982 Tamper-Resistant Packaging Regulations Issued for OTC Products

Tragedy: Acetaminophen-capsule poisoning by cyanide causes 7 deaths. Result: Revision of GMPs to require tamper-resistant packaging.

1983 Two Unrelated Regulatory Events

The "Guide to the Inspection of Computerized Systems in Drug Processing" initiates tighter controls on computers and computer validation. Federal Anti-Tampering Act makes it a federal crime to tamper with packaged consumer products.

1987 Guideline on General Principles of Process Validation

Agency expectations regarding the need for process validation are outlined.

1990 Safe Medical Devices Act

Tragedy: Shiley heart valves and other incidents. Result: FDA given authority to add preproduction design controls and tracking of critical or implantable devices to CGMPs; requires notification of serious device problems by user facilities to FDA. The agency gains ability to order device recalls.

1992 Generic Drug Enforcement Act

Precipitated by illegal acts involving abbreviated new drug applications. Result: Creates debarment penalty.

1996 Two Unrelated Events

Proposed revision to *U.S. CGMPs for Drugs and Biologics* (21 CFR 210-211) adds detail for validation, blend uniformity, prevention of cross-contamination, and handling out-of-specification results.

"ICH Guidance for Industry: E6, Good Clinical Practice: Consolidated Guidance" becomes the de facto standard for conducting human clinical trials.

manufacture products for the United States come from sources outside the country, where manufacturing standards may not be as stringent. For this reason, both the European Union and the United States recently published draft guidance documents for the manufacture of APIs. Recently, the International Conference on Harmonization (ICH), a consortium of individuals from Europe, North America, and Japan, published "ICH Q7A on Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients." (22) This document has been published and accepted in Europe, Japan, and the United States, and it is considered the de facto standard for manufacturing active pharmaceutical ingredients.

Illegal catheters. Most of the cases in this representative history were mistakes and/or mysteries, meaning that the individuals or companies involved had no intention or desire of harming anyone. The acetaminophen poisoning case was clearly criminal. Let's look at a different kind of criminal case.

In 1996, three former executives of a company that made balloon heart catheters in the United States each were sentenced to 18 months in prison followed by two years

1997 CGMPs for Medical Devices (Quality System Regulation) Final Rule

Major revision to current good manufacturing practices for medical devices becomes effective, with design controls in R&D the major change (design controls effective June 1998, rest of rule June 1997).

1997 Electronic Records Final Rule (21 CFR 11)

Requires controls that ensure security and integrity of all electronic data.

1998 Draft Guidances

"Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients" and "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production."

1999 QSIT Inspection Handbook

New FDA technique for inspecting device companies focuses on four major subsystems: management controls, design controls, production and process controls, and corrective and preventive action.

2001 ICH Q7A API Guidance

ICH's "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (APIs)" is adopted by the United States, Europe, and Japan, and becomes the de facto manufacturing standard for APIs.

2002 Drug Manufacturing Inspections Compliance Manual

New FDA technique for routine drug manufacturing inspections focuses on two or more systems, with mandatory coverage of the quality system. Other systems are: facilities and equipment, materials, production, packaging and labeling, and laboratory controls.

of supervised release for conspiring to defraud FDA by selling illegal heart catheters. The company itself pled guilty to similar charges in 1993 and agreed to pay \$61 million for health fraud. (The U.S. government estimated that total sales of illegal catheters had amounted to \$77 million.) It had been the first company to obtain approval to market a balloon angioplasty catheter in this country, and from 1980 to 1985 it was the only distributor of heart catheters in the United States.

Heart catheters are used in angioplasty to clear clogged arteries. In 1987, the company began to redesign those already approved by FDA and sold the new version without obtaining approval. The redesigned catheters often malfunctioned, but the company failed to report those problems to FDA. The company learned during illegal human clinical trials that the catheter tips broke off in the arteries of two percent of patients, but it kept that information from FDA. The agency approved the redesigned device in January 1989, unaware of the tip breakage problem. Within three months, the company received 33 reports of tip breakage, so it redesigned the catheter again, again without informing FDA, and in

March began distributing the redesigned catheters.

Upon learning of the malfunctions, FDA informed the company that its catheters were illegal and subject to seizure. In June 1989, the company recalled previous versions or models. When FDA told the company that its latest model violated the law as well, it recalled that model, modified it, renamed it, and continued to distribute it. When FDA told the company it needed a premarket approval application for the model on the market, the company discontinued selling it and reintroduced the original model, which had major problems that had necessitated the redesign in the first place. Finally, FDA seized all the catheters and witnessed their destruction (23).

Those heart catheters were associated with at least one death and with emergency heart surgery for at least 20 patients (24). A grand jury handed down a 393-count indictment against the three former executives and others in 1995. In sentencing those former executives, the judge emphasized that "corporate entities do not commit crimes; people do," and that "executives running other companies who might engage in such conduct should bear in mind the prison terms imposed in this case" (23).

Defective heart valves. The Bjork-Shiley Convexo-Concave mechanical heart valve was manufactured and sold between 1979 and 1986. About 86,000 of those valves are believed to have been implanted in patients worldwide, including 30,000 in the United States. In a small number of cases, the valves experience a "strut fracture" failure that necessitates immediate cardiac surgery.

As of November 1998, about 620 fractures had been reported to Shiley worldwide. In roughly two-thirds of those cases, a patient died following the fracture. The company, which no longer makes heart valves, has entered into a settlement agreement with the government to pay for the costs of valve strut failures and replacement surgeries, including hospital care, medical supplies, and the usual fees of physicians, surgeons, and other health care professionals. Furthermore, Shiley and its parent company will pay the costs incurred by each patient from admission through discharge, including emergency services. They will also pay for any complications directly resulting from the treatment over a reasonable period thereafter (25).

Obviously, that is a very serious case. When we discuss the case in GMP classes, I often ask, "How many defects do you think that you can have in a heart valve?" (The answer, of course, is *none*.) Implantable devices are especially dangerous when something goes wrong. A difficult decision must be reached: whether it is better for the patient to continue with the device or whether the risks necessitate removal. Patients must be well enough to survive *explantation*, opening them up (literally and figuratively) to infection, possible additional complications, another recovery period, and so on.

Medical device safety. In response to the Shiley heart valve and other cases, Congress passed the Safe Medical Devices Act of 1990, for the first time giving FDA authority to go into R&D regularly. The act authorized addition of

preproduction design controls to the CGMP regulations; when FDA analyzed device recalls over a six-year period, it found that about 44 % of quality problems leading to recalls were attributed to errors or deficiencies designed into those devices. When the agency analyzed software-related recalls, it found that over 90 % of all software-related device failures were design related, particularly the failure to validate software before routine production (12).

In the 1990 Act, Congress authorized FDA to make its medical device regulations more thorough and consistent with other world standards, such as ISO 9000. The act required nursing homes, hospitals, and other facilities using medical devices to report to FDA all incidents in which a medical device probably caused or contributed to a death or serious injury. Manufacturers are required to conduct postmarket surveillance on permanently implanted devices whose failure might cause serious harm or death and to establish methods for tracing and locating patients having those devices. The Act also authorized FDA to order device product recalls (7). During the 1990s, the medical device regulations went through a major revision, with one major change being in design control, or the need to formally review and document product design at predetermined stages. The final rule became effective in June 1997; the design control portion of the regulations became effective a year later in June 1998.

In the late 1990s, FDA turned to a more directed inspectional approach to medical devices called the Quality System Inspection Technique (QSIT). That approach calls for focusing on several key systems, including management controls, design controls, production and process controls, and corrective and preventive actions (26).

Also in the 1990s, proposed revisions to the GMPs for drugs and biologics were issued. Although those revisions were not yet final when this article went to press, they do represent FDA's current thinking. The Electronic Records Final Rule (21 CFR Part 11), requires controls that ensure the security and accuracy of all data and computer systems used. Part 11 will have sweeping ramifications on the industry for years to come, and is perhaps the biggest change in our industry since CGMPs were first published.

International harmony. Besides producing the API guide, ICH has been working on a number of quality, safety, and effectiveness documents. As these documents are adopted or made final by ICH, they become "industry practice" in all participating countries. The 1996 ICH E6 guidance on good clinical practices has become the de facto standard on performing human clinical trials (27). A number of other FDA guidance documents, including a draft guidance on handling out-of-specification results, recently became available (28). Even though guidelines and draft guidances are not legally binding, they represent current thinking on their subject matter and tend to be adopted rapidly and/or viewed as "current industry practice."

Generic drug scandal. Congress passed the Generic Drug Enforcement Act of 1992 to impose debarment and other penalties for illegal acts involving abbreviated drug

applications (6). The 1992 Act resulted from a bribery and fraud case in which executives of one or more generic companies bribed FDA reviewers (one for as little as \$1,000 in gift certificates). Rather than testing its own generic version of a drug, the company tested the brand name version instead and sent those results with a generic application.

Although typically executives (presidents, vice presidents, chairmen, and so on) are indicted in fraud or other cases, the lowest-ranking employees successfully prosecuted in the generics companies falsified Certificates of Analysis, destroyed samples, directed others to change manufacturing procedures, and falsified records to hide or conceal manufacturing changes (29,30). Be sure to train all employees in your company to record data thoroughly and accurately. Teach them that making a false entry, falsifying dates or backdating, signing for someone else, making up data, and signing for something they did not do is fraud, and the consequences can be severe.

Individuals found guilty in the generic drug scandal were "debarred" from working in the industry. The names of all such individuals can be found along with many of their stories on the FDA web site. Check that potential job candidates are not on that list before you make a job offer. When you submit any marketing application to FDA (whether an NDA, ANDA, BLA, 510(K), or PMA) you must certify in writing that no one who has been debarred worked on the product.

Similarly, before hiring any clinical trial investigators, check their backgrounds to ensure that they are not "disqualified." Disqualification can occur if an investigator repeatedly or deliberately fails to comply with regulatory requirements, or if he or she has submitted false information to a study sponsor. Studies from individuals who become disqualified will be under great scrutiny and may be disallowed (31). With the recent death of a young man participating in a gene therapy trial, clinical trials undoubtedly will be under increased scrutiny (32).

Making better changes. The Scale-Up and Post-Approval Change (SUPAC) documents presented on the FDA web site provide guidance on what is needed before changes to approved drug applications can be made. The documents itemize the types of information or studies required based upon the magnitude or risk of proposed changes. For biological products, companies are now preparing "comparability protocols" to address proposed changes.

Abbreviated, routine drug inspections. In 2002, FDA went to a new, abbreviated inspection technique, focusing on two or more systems, including mandatory coverage of the quality system, in routine drug manufacturing inspections. The other systems? Facilities and equipment, materials, production, packaging and labeling, and laboratory controls. FDA has said publicly that they consider a company to be "out of control if any system is out of control." (33)

Brave New World? In a recent consent decree, one of the world's largest diagnostics companies agreed to stop manufacturing and distributing many of its in vitro diagnostic tests until it corrects manufacturing problems. The company immediately paid a \$100 million civil money penalty and agreed to pay the U.S. Treasury 16% of the gross sales of all medically necessary devices (the company's entire profit portion) until confirming that those products are produced by GMPs. In addition, it agreed to pay \$15,000 per day per process on medically necessary products until each process is validated and \$15,000 per day of operation until it is GMP compliant. (34)

In the most expensive consent decree to date, a major pharmaceutical and over-the-counter (OTC) company agreed to pay a record \$500 million dollars to the U.S. Treasury, to disgorge profits made by the company on drug products produced over the past three years that were made in violation of CGMPs. The company also agreed to future monetary payments of up to \$175 million dollars and to disgorge additional profits should it fail to meet the timelines of the decree. The action follows 13 inspections at four East Coast and Puerto Rico plants since 1998 in which FDA found significant violations of CGMP regulations. The decree affects 125 different prescription and OTC drugs produced at those facilities. As part of the consent decree, the company has agreed to suspend manufacturing of 73 other products. (35)

LOOKING TO THE FUTURE

As we enter the 21st century, let's remember that we are all responsible. We will see things in our day-to-day work that others will not, or we may reach a conclusion faster than someone else. In all the classes I teach, I always ask people to speak up — and continue to do so until important issues are addressed. Otherwise patients, companies, or employees may suffer.

Our industry exists to relieve suffering or pain, and to find cures for diseases. It also is highly regulated. Because of the tragedies that have occurred, most people see the regulations and world regulatory agencies as checks and balances on industry, believing as I do that we all have a similar goal in common -- to bring innovative, safe, and effective products to market.

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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
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 University of Georgia, March 2006
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Overview

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What FDA is Proposing

Direct Final Rule, Current Good Manufacturing Practice Regulations and Investigational New Drug: <http://www.fda.gov/cgmp/2006/01/2006-01-17-Proposed-Rule-Current-Good-Manufacturing-Practice-Regulation-and-Investigational-New-Drugs>

- 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

Review Draft Guidance for Industry on Investigational New Drug Applications to Complying with Current Good Manufacturing Practice During Phase 1 Development, <http://www.fda.gov/cgmp/2006/01/2006-01-17-Proposed-Rule-Current-Good-Manufacturing-Practice-Regulation-and-Investigational-New-Drugs>

- 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 Industry and OIG Policy, Draft Final Rule Proposals, Rev. 21, 1997, <http://www.fda.gov/oc/ohrt/ohrt21.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/oc/ohrt/ohrt21.pdf>

- "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 Public, Critical Stages of Clinical Drug Development Now Easier, January 13, 2006, <http://www.fda.gov/oc/ohrt/ohrt21.pdf>

- "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 Public, Critical Stages of Clinical Drug Development Now Easier, January 13, 2006, <http://www.fda.gov/oc/ohrt/ohrt21.pdf>

- "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 Public, Critical Stages of Clinical Drug Development Now Easier, January 13, 2006, <http://www.fda.gov/oc/ohrt/ohrt21.pdf>

- "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/oc/ohrt/ohrt21.pdf>

- 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/cgmp/2002/04/2002-187.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/cgmp/2002/04/2002-187.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/cgmp/2002/04/2002-187.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/cgmp/2002/04/2002-187.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/cgmp/2002/04/2002-187.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/cgmp/2002/04/2002-187.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 produce 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/cgmp/cgmpcd/2002/06-353.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 produce 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/cgmp/cgmpcd/2002/06-353.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/cgmp/cgmpcd/2002/06-353.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/cgmp/cgmpcd/2002/06-353.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/cgmp/cgmpcd/2002/06-353.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/cgmp/cgmpcd/2002/06-353.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/cder/rdmt/indguid.htm>

- 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 Earlier Stages Of Clinical Drug Development More Efficient, January 11, 2006, <http://www.fda.gov/oc/ohrt/060111pr.htm>

- 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/cder/rdmt/indguid.htm>

- 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/cder/rdmt/indguid.htm>

- 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/cder/rdmt/indguid.htm>

- 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/cder/rdmt/indguid.htm>

- 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 I/O 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/rdmt/guidance/2086ht.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 phase 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/rdmt/guidance/2086ht.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/rdmt/guidance/2086ht.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)(4)(ii)).
- 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 (FDCA), 21 U.S.C. 301, <http://www.fda.gov/oc/ohrt/mission.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 (FDCA), 21 U.S.C. 301, <http://www.fda.gov/oc/ohrt/mission.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 Center: The Power of Strengthening Immel Resources LLC, earlier published as The BioPharm Guide to GMP History, by E. 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 NoPharm Guide to GMP History*, by G. 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/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 regard: (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/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 Association, *International Declaration of Helsinki on Ethical Principles of Medical Research Involving Human Subjects*, 1964 and 1979, <http://www.wma.net/e/ethics/helsinki.html> and <http://www.fda.gov/oc/ohrt/belmont.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
Source: FDA Warning Letter, <http://www.fda.gov/oc/ohrt/belmont.html>, FDA Enforcement Story J08, <http://www.fda.gov/oc/ohrt/belmont.html>, New Hope Magazine, February 2002, 71th & Trueman, <http://www.fda.gov/oc/ohrt/belmont.html>, FDA Clinical Investigation, <http://www.fda.gov/oc/ohrt/belmont.html>

- 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

Source: FDA Warning Letter, <http://www.fda.gov/oc/whistleblowers/whistleblowers.html>, FDA Enforcement Story 2005, <http://www.fda.gov/oc/whistleblowers/whistleblowers.html>, Johns Hopkins, Philadelphia, February 2005. Title: A Typographical Error on a Clinical Trial Form Led to a Fatal Error. FDA Disqualified a Contracted Research Unit for Clinical Investigations. <http://www.fda.gov/oc/whistleblowers/whistleblowers.html>

- 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

Source: U.S. Department of Justice Press Release, <http://www.justice.gov/opa/pr/2005/feb/05-cv-00011.html>, DOJ Press Release, February 10, 2005. Title: U.S. Department of Justice Announces Criminal Charges Against University of Pennsylvania Researchers. <http://www.justice.gov/opa/pr/2005/feb/05-cv-00011.html>

- 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

Source: U.S. Department of Justice Press Release, <http://www.justice.gov/opa/pr/2005/feb/05-cv-00011.html>, DOJ Press Release, February 10, 2005. Title: U.S. Department of Justice Announces Criminal Charges Against University of Pennsylvania Researchers. <http://www.justice.gov/opa/pr/2005/feb/05-cv-00011.html>

- 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, NCI, 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

Source: Pharmacy Compounding, <http://www.pharmacycompounding.com>, The Compiler Magazine, 31(1) Winter 2000. Title: Pharmacy Compounding: A Review of the Industry. <http://www.pharmacycompounding.com>

- 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

Source: FDA Warning Letter, <http://www.fda.gov/oc/whistleblowers/whistleblowers.html>, FDA Enforcement Story 2005, <http://www.fda.gov/oc/whistleblowers/whistleblowers.html>, Johns Hopkins, Philadelphia, February 2005. Title: A Typographical Error on a Clinical Trial Form Led to a Fatal Error. FDA Disqualified a Contracted Research Unit for Clinical Investigations. <http://www.fda.gov/oc/whistleblowers/whistleblowers.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 (*varigella*) 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: *United Report*, "Downregulating the FDA - Part I: Response 2001," September-October 2005 Issue, Medical Device Current Good Manufacturing Practices. <http://www.fda.gov/oc/whistleblowers/whistleblowers.html>

- 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 they 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 1 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?
- Will "GMP Lite" really improve drug development?

Recommendations

- I hope that the agency will consider withdrawing the direct final rule, and keeping phase 1 material for humans under the protection of the CGMP regulation.
- One option would be issuing proposed GMPs for investigational drugs as FDA had originally considered. If so, the draft guidance could be used as a start to those proposed GMPs.
- Another option is that the draft guidance could be finalized and replace the earlier 1991 guidance as planned, but with no exemption of phase 1 material from CGMP regulation.
- A third option would be proposing and taking the phase 1 guidance through the ICH process.
- Your opinion may differ. My hope is that individuals and organizations with experience manufacturing clinical and commercial product will take the time to think about and send in any written comments that they may have to the agency.

What You Can Do

- Read FDA proposals and draft guidance, discuss them with your staff, and send any written comments your organization has, if you choose to do so, to FDA by the comment due dates.
- When submitting comments, please be specific.
- If you are commenting on the proposed or direct final rule, state if you are for or against the rule, and why.
- Use reasoning, logic, and good science.
- Attach any references.
- Include the docket number.
- Ensure all comments are relevant.
- State why the rule is inappropriate.
- Provide a challenge to the rule's underlying premise or state why the rule is ineffective or unacceptable.
- Issues should be serious enough to warrant a substantive response from the agency, and should sufficiently challenge the agency's view that the rule is needed.

What You Can Do

- To comment on the **draft guidance**, Docket 2005D-0286, send your comments by March 20, 2006.
- You may send them electronically to:
<http://www.accessdata.fda.gov/scripts/oc/dockets/comments/SEARCHRESULTS.CFM>
- Or send two copies of your written comments to:
 - Docket No. 2005D-0286
 - Division of Dockets Management (HFA-305)
 - Food and Drug Administration
 - 5630 Fishers Lane, Rm. 1061
 - Rockville, MD 20852

What You Can Do

- To comment on the **proposed or direct final rule** to exempt phase 1 material from CGMP regulation (these rules are identical; any comments received will be applied to both) or Docket 2005N-0285, send your comments by April 3, 2006.
- You may send them electronically to:
<http://www.accessdata.fda.gov/scripts/oc/dockets/comments/SEARCHRESULTS.CFM>
- Or send two copies of your written comments to:
 - Docket 2005N-0285
 - Division of Dockets Management (HFA-305)
 - Food and Drug Administration
 - 5630 Fishers Lane, Rm. 1061
 - Rockville, MD 20852

Recommended Reading

- Direct Final Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
<http://www.fda.gov/cgmp/dockets/98fr/06-353.htm>
- Proposed Rule, Current Good Manufacturing Practice Regulation and Investigational New Drugs,
<http://www.fda.gov/cgmp/dockets/98fr/06-350.htm>
- INDs - Approaches to Complying with CGMP During Phase 1 Draft Guidance, January 2006,
<http://www.fda.gov/cder/dockets/98fr/05d-0286-gdl0001.pdf>
- Exploratory IND Studies Guidance, January 2006,
<http://www.fda.gov/cder/guidance/2086fnl.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

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 Immell is president of Immell Resources LLC, where she helps pharmaceutical, biopharmaceutical, and medical device companies improve their quality systems and compliance track records. Since 1996, Immell Resources LLC has worked with more than 100 firms.
- Barbara is currently editor of the *Immell 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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