

April 3, 2006

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 Comments received on the direct final rule/proposed rule and draft guidance may be incorporated instead into a proposed rule on CGMPs for investigational drugs and biologics.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

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

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.

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

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

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

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 1 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 1, but keeping phase 1 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*