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ADVICE AND GUIDANCE FOR MANAGERS IN FDA-REGULATED INDUSTRIES

COMPLIANCE BRIEFING

Chipping Away at the GMPs: FDA's Phase 1 Proposals

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In mid-January 2006, FDA proposed exempting phase 1 investigational drugs and biologics from the current good manufacturing practice regulation (21 CFR 210/211) in both a direct final rule and a proposed rule.^{1, 2} At the same time, it published draft guidance, *INDs — Approaches to Complying with CGMP During Phase 1*, to be used instead of the regulation when manufacturing phase 1 material.^{3, 4}

FDA stated in the direct final rule that it was taking this action “to streamline and promote the drug development process.”¹

On May 2, 2006, FDA withdrew the direct final rule because it received significant adverse comment.⁵ Under FDA's direct final rule procedures, the receipt of any significant adverse comment will result in the withdrawal of the direct final rule.⁶ The agency has stated that “comments received by the agency regarding the withdrawn rule will be considered in developing a final rule using the usual notice-and-comment procedures.”⁵ The draft guidance and the proposed rule have not, however, been withdrawn. The **IMMEL REPORT™** hopes that the agency will use the comments received to develop proposed GMPs for investigational drugs, as the agency had always considered doing.⁷

Immel Resources' comments to the agency on the direct final rule (with slight edits) follow.^{8, 9} These comments summarize some of the points presented in March 2006 during an international audioconference for *BioPharm* magazine and also in a tutorial at the 30th Annual GMP Conference at the University of Georgia, Athens.^{10, 11} We are deeply indebted to *BioPharm*, the GMP Conference, and members of the FDA for the opportunity to present these comments.

Puts patients at risk, and is not legally binding

It is our position that 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.¹² Guidance documents are not legally binding, and no one is required to follow them.¹³ They also cannot be enforced.¹³

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 has always considered proposing CGMPs for investigational drugs.⁷ 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.¹ This would mean that some phase 1 material would be made per CGMP regulation, and some may not be. Patients or healthy volunteers in phase 1 are already shouldering the biggest burden of

“Whatever you can do, or dream you can, begin it. Boldness has genius, power and magic in it.”

– Goethe

HIGHLIGHTS

- 1 Chipping Away at the GMPs: FDA's Phase 1 Proposals
 - Nuremberg Code
 - Product Development in a Nutshell
 - Exploratory IND Studies Guidance
- 8 Great Training Ideas
 - A Retreat
 - GMP Jeopardy
 - Popcorn Exercise
- 9 Environmental Health and Safety
 - Process Hazard Analysis for Pharmaceutical Operations
 - Checklist
- 12 Did You Know?
 - FDA Centennial
 - Frequently Requested 483s

to page 2 ►



Chipping Away at the GMPs - continued

any participants because they are the first humans to receive a compound.¹⁴ Of the patients who participate, many 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 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.”¹⁵ 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.”^{16, 17}

As you know, FDA has a detailed regulation governing preclinical (or animal) testing, which requires a Quality Assurance Unit.¹⁸ With this proposal, FDA is continuing to require that the 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 series of responses to tragedies that have occurred and attempts to prevent future tragedies from occurring.^{19, 48} 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.”²⁰

Questions: Is this true? Are the regulations truly burdensome? Are they the impediment to innovation? Or are they basic protections for all patients?

In the recent past, we have had two patient deaths in phase 1 trials conducted at leading medical research institutions, Johns Hopkins and the

“In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.”^{16, 17}

University of Pennsylvania.²¹ 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.”²² Nonetheless, it was administered by inhalation, resulting in the death of a healthy patient.^{23, 24} 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.²⁵⁻³⁰ Jesse subsequently died.²⁵⁻³⁰

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.^{31, 32} As you know, the Hippocratic Oath, which physicians must follow, states “Do no harm.”^{33, 34}

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.^{35,36} 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 after reading a 17-page guidance document?

The infant deaths were associated with intravenous solutions compounded by a pharmacy that were not sterile.³⁵ There have been several deadly recent class I recalls due to drugs compounded by pharmacists that have been contaminated, such as a

methylprednisolone injection contaminated with a rare fungus (*wangiella*), which caused meningitis in six patients and the death of one.³⁷ Other deadly recalls of pharmacy-compounded products included an albuterol inhaler for asthmatics that was contaminated with *Serratia liquefaciens*, which as you know may cause respiratory infections, sepsis, or death.^{38, 39} One patient was also recently blinded in one eye by using pharmacy-prepared eyedrops that were not sterile.³⁵

Medical Device Experience.

In the medical device industry, the number of deadly recalls has increased more than 300% since 1998.^{40, 41} The single largest group of FDA warning letters for noncompliance is currently being issued to medical device firms, including a large percentage going to sponsors, clinical investigators, and institutional review boards involved in device

to page 3 ▶



human clinical trials.^{40, 42, 43} 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.).⁴⁴

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.⁴ 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.¹² 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.⁴⁵ Even pharmacists learn that when compounding sterile or aseptic product, they must incorporate necessary checks and balances.⁴⁶

This approach does not appear to recognize the importance of an experienced and knowledgeable QC unit (or person) in safe manufacture of materials. The agency is undermining the QC unit, the one group inside organizations 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 to be used in human beings for the first time?^{12, 18}

Off mission

The mission of the U.S. Food and Drug Administration, mandated by Congress in the Food, Drug and Cosmetic Act 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.”⁴⁷ The direct final rule states that the agency is making this proposal “to streamline and promote the drug development process.”¹¹ 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.^{19,48} 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.⁴⁷

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.⁴ This is a violation of current good manufacturing practice.¹² 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, which resulted in the deaths of more than 100 patients, many of them children.^{19,49} 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.⁴ 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.”⁴ This is clearly insufficient.

Insufficient aseptic or sterile information

The guidance, which 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.⁴ 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.⁵⁰ 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.¹² 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, it believes that “all of the entities affected by this rule have personnel with skills necessary to comply with requirements.”¹¹ This is illogical. The amount of training required for aseptic technique alone is substantial and not yet well described in the guidance.^{4, 50}

Based on assumptions; no data provided

The FDA acknowledges that it does not know how many entities may be affected by this rule and that it does not keep a database of firms affected by this rule.¹ Because FDA performs only limited inspections of phase 1 material manufacturers (such as “for cause” or during treatment INDs),⁵¹ what data

to page 4 ➤



Chipping Away at the GMPs - continued

does FDA have to support its 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 its 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.^{52, 53} ICH Q7A also has 57 detailed pages and is used to manufacture material that will be further processed before being delivered to patients.^{52, 53} 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, which could result in patient injury or death if the material is improperly prepared or contaminated.⁴ FDA also at least inspects API manufacturers, but again, the agency does not routinely inspect in phase 1 unless for cause (or in certain specified circumstances, such as for treatment INDs).^{51, 54}

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.^{1, 4} In addition, the potential costs (estimated at an additional \$810 per IND for chemical manufacturers and laboratories that 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.^{1, 4} The draft guidance does not yet discuss required equipment or facilities for these types of products, such as biosafety cabinets, isolators, and other equipment.⁴ Nor does it limit movement from an animal colony to the human manufacturing environment (which is required in the European Union

The Nuremberg Code ²⁴

The basis for ethics codes in research, the Nuremberg Code was published in 1947 and arose out of the Nuremberg War Crimes Trial. Some 23 Nazis, 20 of them physicians, were charged with conducting medical experiments — including systematic torture, mutilation, and killing — on thousands of concentration camp victims during World War II. Among other things, the Nuremberg Code made voluntary consent a requirement in clinical research studies and noted that risks should be minimized and not significantly outweigh potential benefits.

In 1964, the landmark Declaration of Helsinki elaborated on the ethical principles that should guide human subjects research, noting the need for a clearly formulated protocol reviewed by an independent committee.

CGMPs; not limiting this movement has caused contamination in facilities manufacturing material for humans).^{4, 45}

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, approximately 20,400 patients and volunteers would be affected.¹ 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 it using guidance documents or issues a rule that affects part of the rule (but not all), it causes a great deal of confusion in industry.⁵⁵⁻⁵⁷ I have already received one email message from a regulatory affairs executive who stated that from now on, when her company plans to use non-GMP material in a phase 1 trial, it will provide more data for FDA in its 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 it 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.^{1, 6} 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.¹

The draft phase 1 GMP guidance was apparently developed in

collaboration with the National Cancer Institute (NCI), the federal agency responsible for combating cancer.^{58, 59} FDA's Acting Commissioner, Andrew von Eschenbach, M.D., is both Director of the National Cancer Institute and also Acting Commissioner of the FDA.⁵⁹ Von Eschenbach has served as both NCI Director and also as FDA Acting Commissioner for the past 10 months. As we go to press, he just resigned from the National Cancer Institute. Dr. von Eschenbach is perhaps best known for his stated goal that NCI will eliminate the suffering and death due to cancer by 2015.⁵⁹ A bit of trivia is that the National Cancer Institute's proposed 2007 budget is \$4.7 billion, whereas FDA's proposed 2007 budget is \$1.9 billion.^{60, 61} (As you know, FDA regulates food, drugs, medical devices, blood, cosmetics, radiation-emitting products, and animal drugs — products accounting for 20 cents of every dollar spent by Americans.^{60, 61})

Illogical

The agency states in the direct final rule that it would regulate phase 1 material by means other than the CGMP regulation, namely by using the 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.^{1, 47} 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.¹ FDA also states in the direct final rule

to page 5 ►



Product Development in a Nutshell ⁷²

- From concept or idea — a drug or therapeutic biologic product moves into preclinical development, where it is subject to the following regulations:
 - Good laboratory practices (GLPs) (21 CFR 58)
 - Part 11 (21 CFR 11, Electronic Records, Electronic Signatures)
 - Investigational New Drug (IND) submission requirements (21 CFR 312)
- After submitting the IND to FDA, clinical trials may begin after 30 days if FDA has no objection. Throughout Phase I, Phase II, and Phase III clinical trials, the following regulations apply:
 - Good manufacturing practices (GMPs; 21 CFR 210/211)
 - Part 11
 - Good clinical practices (GCPs; 21 CFR 50, 54, 56)
- If the clinical trials are successful, the data are summarized, collated, and the marketing submission is made. The submission is made per the following regulations:
 - New drug application (NDA) (21 CFR 314), or
 - Biologics licensing application (BLA) (21 CFR 601)
- After the submission is made, the compound’s clinical and nonclinical safety and effectiveness will be reviewed by FDA reviewers.
- FDA will often inspect the facility in a preapproval (PAI) or prelicensing inspection (PLI).
- If the firm passes the inspection and the product is approved for marketing in the U.S. based upon its safety and effectiveness data — and the firm’s readiness to manufacture the product — GMPs and Part 11 will continue to apply throughout the lifetime of the product.
- Most companies will also test their compound in additional clinical trials (following GCPs) to see if the compounds may be useful for other indications. They may also conduct post-marketing (Phase IV) studies.
- All material produced for clinical or commercial use must be produced following GMPs.

that it may terminate an IND if it discovers that the manufacturing of the investigational material is inadequate.¹ Obviously, however, many of these actions may occur after the fact and well after patients have been injured in a trial.

The agency was given inspectional authority for a reason, and that is because paper reviews are insufficient.^{19, 48} Questions: Is the agency throwing in the towel (because it 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?^{20, 62, 63} Common sense dictates that you drive quality into the process as early as possible—not reduce the basic quality required up front.⁶⁴

All people want a cure for cancer before the scourge visits *them*. People dying of cancer volunteer their bodies to test proposed cures, not to vet the quality of researchers’ production practices. Are we in such a rush that we are willing to subject the afflicted to even greater dangers?

Exploratory IND Studies guidance

FDA issued a final guidance on *Exploratory IND Studies* simultaneously with the draft phase 1 guidance.⁶⁵ FDA defines an *exploratory IND study* as a clinical trial that “is conducted early in phase 1, involves very limited human exposure, and has no therapeutic or

diagnostic intent (e.g., screening studies, microdose studies).⁶⁵ You may hear people talking about “phase 0” studies, or studies “prior to traditional drug development phase 1 trials”⁵⁸ — they are what this guidance addresses.

This guidance contains several controversial points, such as allowing the same batch of candidate material to be used for both animal toxicology studies and early phase 1 human testing, and allowing less, or different, preclinical support (or testing) than that needed for traditional IND studies.⁶⁵ The guidance adds, “Sponsors are encouraged to discuss any need for an exemption from GLP provisions with the FDA prior to conducting safety related studies, for example, during a pre-IND meeting. Sponsors must justify any nonconformance with GLP provisions (21 CFR 312.23(a)(8)(iii)).”⁶⁵ As a reality check, I asked two experienced and well-respected regulatory affairs consultants (both former executives) whether they would advise a client to ask FDA for a GLP exemption. Both said no, not for required animal toxicology testing.⁶⁶

A word to the wise: Although FDA guidance documents may provide the agency’s current thinking, they are not legally binding. The **IMMEL REPORT™** recommends that all organizations developing or manufacturing investigational drugs and biologics follow all applicable regulations, which include good laboratory practices, good manufacturing practices, and good clinical practices. Until such time that the regulations themselves are revised, the current regulations must be followed.

May delay products to market

Proponents of this proposal believe that it will speed products to market. My experience suggests that it may *delay* products to market. Phase 1 material is the foundation of clinical trials and is used to prove the safety of a compound in humans.¹⁴ 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, you must also ensure the necessary viral

to page 6 ➤



Chipping Away at the GMPs - continued

inactivation or clearance, detoxification of bacterial toxins, and so on.^{12, 50, 51, 67, 68}

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 its 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.^{51, 67, 68} If 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.^{19,69} 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.^{70,71} 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.⁷

In the aftermath of the death of the formerly healthy 24-year-old Ellen Roche as a direct result of her participation in a 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.”²⁴

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.”²⁴

For Further Reading

To read all of the comments received by the agency on the direct final rule, see FDA’s web site at <http://www.fda.gov/ohrms/dockets/dockets/05n0285/05n0285.htm>. Comments received by FDA on the draft phase 1 GMP guidance are available at: <http://www.fda.gov/ohrms/dockets/dockets/05d0286/05d0286.htm>. The proposed rule and draft guidance may be found at <http://www.fda.gov/ohrms/dockets/98fr/06-350.htm> (proposed rule) and <http://www.fda.gov/cber/gdlns/indcgmp.pdf> (draft guidance).

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Note

“A Brief History of the GMPs: The Power of Storytelling” and “Chipping Away at the GMPs Tutorial,” a PowerPoint presentation delivered at the 30th Annual GMP Conference, University of Georgia and earlier as an audioconference for *BioPharm* magazine, were attached to my original comments to FDA.⁸⁻¹¹ You can find them on the Immel Resources website under “What’s New” at www.immel.com.

REFERENCES

1. Current Good Manufacturing Practice Regulation and Investigational New Drugs, Direct Final Rule, U.S. FDA, January 17, 2006, <http://www.fda.gov/ohrms/dockets/98fr/06-353.pdf>.
2. Current Good Manufacturing Practice Regulation and Investigational New Drugs, Proposed Rule, U.S. FDA, January 17, 2006, <http://www.fda.gov/ohrms/dockets/98fr/06-350.htm>.
3. Draft Guidance for Industry on Investigational New Drugs, Approaches to Complying with GMPs During Phase 1: Availability, U.S. FDA, January 17, 2006, <http://www.fda.gov/ohrms/dockets/98fr/06-352.htm>.
4. Guidance for Industry, INDs: Approaches to Complying with GMPs During Phase 1, Draft Guidance, U.S. FDA, January 2006, <http://www.fda.gov/cber/gdlns/indcgmp.pdf>.
5. Current Good Manufacturing Practice Regulation and Investigational New Drugs, Withdrawal, U.S. FDA, May 2, 2006, <http://www.fda.gov/OHRMS/DOCKETS/98fr/06-4091.htm>.
6. Guidance for FDA and Industry: Direct Final Rules; Notice, U.S. FDA, November 21, 1997, <http://www.fda.gov/cber/gdlns/drcfnrl.pdf>.
7. Preamble to Title 21, Subchapter C, Human and Veterinary Drug, Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs, U.S. FDA, <http://www.fda.gov/cder/dmpa/preamble.txt>.
8. Letter to U.S. FDA, Docket 2005N-0285, from Barbara Immel, Immel Resources LLC, April 3, 2006, <http://www.fda.gov/ohrms/dockets/dockets/05n0285/05n0285-EC4-Attach-1.pdf>.
9. Letter to U.S. FDA (with attachments), Docket 2005N-0285, from Barbara Immel, Immel Resources LLC, April 3, 2006, <http://www.fda.gov/ohrms/dockets/dockets/05n0285/05n0285-c000007-01-vol1.pdf>.
10. Chipping Away at the GMPs: Understanding FDA’s Proposal to Exempt Material for Phase 1 Clinical Trials from CGMP Regulation, Barbara Immel, March 9, 2006, *BioPharm* audioconference, http://www.gmptrainingsystems.com/asp/bp_store_060309.asp.
11. Chipping Away at the GMPs: Understanding FDA’s Proposal to Exempt Material for Phase 1 Clinical Trials from CGMP Regulation, and New Draft Guidance, Barbara Immel, Instructor, March 16, 2006, 30th Annual GMP Conference, University of Georgia, Athens, What’s New, http://www.immel.com/Whats_New.html#FDA_phase1.

to page 7 ➤



12. 21 CFR 210, Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General, and 21 CFR 211, Current Good Manufacturing Practice for Finished Pharmaceuticals, U.S. FDA, <http://www.fda.gov/cder/dmpg/cgmpregs.htm>.
13. Administrative Practices and Procedures; Good Guidance Practices, Final Rule, U.S. FDA, September 19, 2000, <http://www.fda.gov/OHRMS/DOCKETS/98fr/091900a.htm>.
14. Inside Clinical Trials: Testing Medical Products in People, From Test Tube to Patient, A Special Report from FDA Consumer Magazine, U.S. FDA, <http://www.fda.gov/fdac/special/testtubetopatients/trials.html>.
15. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979, http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4178b_09_02_BelmontReport.pdf.
16. Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, 1983 Version, <http://www.fda.gov/oc/health/helsinki83.html>.
17. The World Medical Association Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, 1989 Version, <http://www.fda.gov/oc/health/helsinki89.html>.
18. 21 CFR 58, Good Laboratory Practice for Nonclinical Laboratory Studies, U.S. FDA, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=58&showFR=1>.
19. A Brief History of the GMPs: The Power of Storytelling, Barbara Immel, published in *BioPharm* magazine (August 2000 issue, and November 2002 Supplement, *The BioPharm Guide to GMP History*) and *Pharmaceutical Technology* (July 2001 issue), also available from Immel Resources LLC, Petaluma, CA, www.immel.com.
20. FDA Issues Advice to Make Earliest Stages of Clinical Drug Development More Efficient, FDA Press Release, January 12, 2006, <http://www.fda.gov/bbs/topics/news/2006/NEW01296.html>.
21. Current Regulatory Environment, **IMMEL REPORT™**, May–June 2005, Immel Resources LLC, Petaluma, CA, www.immel.com.
22. FDA Warning Letter to Dr. Alkis Togiias, Johns Hopkins Asthma & Allergy Center, March 31, 2003, http://www.fda.gov/foi/warning_letters/g3936d.pdf.
23. Human Research Reinstated at Johns Hopkins, With Restrictions, Linda Bren, *FDA Consumer Magazine*, U.S. FDA, September–October 2001, http://www.fda.gov/fdac/features/2001/501_john.html.
24. Trials and Tribulations, *Johns Hopkins Magazine*, Dale Keiger and Sue DePasquale, February 2002, Johns Hopkins University, <http://www.jhu.edu/~ihumag/0202web/trials.html>.
25. Human Gene Therapy: Harsh Lessons, High Hopes, Larry Thompson, *FDA Consumer Magazine*, September–October 2000, http://www.fda.gov/fdac/features/2000/500_gene.html.
26. FDA NIDPOE Letter to James Wilson, Institute for Human Gene Therapy, University of Pennsylvania, November 30, 2000, <http://www.fda.gov/foi/nidpoe/n121.pdf>.
27. FDA Notice of Opportunity for Hearing Letter to James Wilson, Institute for Human Gene Therapy, University of Pennsylvania, February 8, 2002, <http://www.fda.gov/foi/nooh/Wilson.htm>.
28. FDA Warning Letter to James Wilson, Institute for Human Gene Therapy, University of Pennsylvania (GCP violations), March 3, 2000, http://www.fda.gov/foi/warning_letters/m3435n.pdf.
29. FDA Warning Letter to James Wilson, Institute for Human Gene Therapy, University of Pennsylvania (GLP violations), July 3, 2000, http://www.fda.gov/foi/warning_letters/m3897n.pdf.
30. U.S. Settles Case of Gene Therapy Study that Ended with Teen's Death, U.S. Attorney's Office, Philadelphia, PA, February 9, 2005, http://www.usdoj.gov/usao/pae/News/Pr/2005/feb/UofPSettlement_release.html.
31. TeGenero Drug Too Perilous to Test on Healthy People, Bloomberg.com, May 2, 2006, http://www.bloomberg.com/apps/news?pid=10000100&sid=a.kk3_aFltJ4&refer=germany.
32. Q&A: Drug Trials, BBC News, March 16, 2006, <http://212.58.240.36/1/hi/health/4808090.stm>.
33. Hippocratic Oath, *Primum non nocere*, Wikipedia, http://en.wikipedia.org/wiki/Hippocratic_Oath.
34. The Hippocratic Oath, bbb.co.uk, <http://www.bbc.co.uk/dna/h2g2/A1103798>.
35. Pharmacy Compounding: Customizing Prescription Drugs, Tamar Nordenberg, *FDA Consumer Magazine*, U.S. FDA, July–August 2000, http://www.fda.gov/fdac/features/2000/400_compound.html.
36. FDA Talk Paper, Nationwide Alert on Injectable Drugs Compounded by Urgent Care Pharmacy, November 15, 2002, <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01171.html>.
37. Testimony by Steven K. Galsion, U.S. FDA, before Senate Committee of Health, Education, Labor and Pensions, Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients, October 23, 2003, <http://www.fda.gov/ola/2003/pharmacycompound1023.html>.
38. *Enforcement Story 2003*, Center for Drug Evaluation and Research, Internet Enforcement Activities, Pharmacy Compounding, U.S. FDA, http://www.fda.gov/ora/about/enf_story/archives/2002/ch3/cder2.htm.
39. Serratia, eMedicine, Web MD, <http://www.emedicine.com/med/topic2103.htm>.
40. Downregulating the FDA, Part 1: Inspections, **IMMEL REPORT™**, September–October 2005, Immel Resources LLC, Petaluma, CA, www.immel.com.
41. Class 1 Recalls Break Record: FDA Begins Product-Specific Inquiries, *The Silver Sheet*, February 2005, F.D.-C Reports, Chevy Chase, MD.
42. *Enforcement Story*, 2001–2003 editions, U.S. FDA, http://www.fda.gov/ora/about/enf_story/archives/.
43. FDA's Electronic Freedom of Information Reading Room, Warning Letters and Responses, <http://www.fda.gov/foi/warning.htm>.
44. 21 CFR Parts 808, 812, and 820, Medical Devices: Current Good Manufacturing Practice (CGMP); Final Rule, U.S. FDA, October 7, 1996, <http://www.fda.gov/cdrh/fr1007ap.pdf>.
45. Volume 4, Medicinal Products for Human Use: Good Manufacturing Practice, European Commission, <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm>.
46. Compounded Sterile Preparations: An Overview of the New Standards in USP 79, Angela V. Ackerman, Vol. 29, No. 4, April 2004, http://www.uspharmacist.com/index.asp?show=article&page=8_1252.htm.
47. Federal Food, Drug, and Cosmetic Act, Section 903, U.S.C. 393, U.S. FDA, <http://www.fda.gov/opacom/laws/fdcaact/fdca9.htm>.
48. History of the FDA, John Swann, U.S. FDA, <http://www.fda.gov/oc/history/historyoffda/default.htm>.
49. Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident, Carol Ballentine, *FDA Consumer Magazine*, June 1981, <http://www.fda.gov/oc/history/elixir.html>.
50. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, U.S. FDA, September 2004, <http://www.fda.gov/cber/gdlns/steraseptic.pdf>.
51. FDA Compliance Program Guidance Manual 7346.832, Pre-Approval Inspections/Investigations, April 5, 2005, <http://www.fda.gov/cder/gmp/PAL-7346832.pdf>.
52. ICH Harmonised Tripartite Guideline, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Q7, International Conference on Harmonization, 10 November 2000, <http://www.ich.org/LOB/media/MEDIA433.pdf>.
53. Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, August 2001, U.S. FDA, <http://www.fda.gov/cder/guidance/4286fnl.pdf>.
54. FDA Compliance Program Guidance Manual 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection, February 13, 2006, <http://www.fda.gov/cder/dmpa/7356-002F-CDER.pdf>.
55. Part 11: New Guidance Provides Little Guidance, Barbara Immel, *Medical Device & Diagnostic Industry*, January 2004, <http://www.devicelink.com/mddi/archive/04/01/001.html>.
56. FDA Withdraws Jan. 17 Rule Relaxing Phase 1 Standards, Doug McCormick, *Electronic Newsletter of Pharmaceutical Technology*, May 4, 2006, <http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=324103>.
57. From the Editor in Chief: GMPs and Drug Development, Laura Bush, *BioPharm*, April 1, 2006, <http://www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=317573>.
58. The Critical Path Initiative: One Year Later, Janet Woodcock, *Medical Imaging and Drug Development*, U.S. FDA, May 5, 2005, <http://www.fda.gov/cder/regulatory/medimaging/woodcock.ppt>.
59. About the Director, National Cancer Institute, <http://www.cancer.gov/directorscorner/about-the-director>.
60. Statement on Fiscal Year 2007 Budget Request, Testimony Delivered April 6, 2006, before the U.S. House Subcommittee on Labor-HHS-Education Appropriations, to discuss the NCI Budget Request for Fiscal Year 2007, John Niederhuber, NCI and Richard Turman, HHS, <http://www.cancer.gov/aboutnci/FY07-budget-request>.
61. Performance Budget Overview, U.S. FDA, Office of Management, Budget Formulation and Presentation, FY 2007 Table of Contents, <http://www.fda.gov/oc/oms/ofm/budget/2007/HTML/1PerformanceBudgetOverview.htm>.
62. Challenge and Opportunity on the Critical Path to New Medical Products, U.S. FDA, March 2004, <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>.
63. FDA Unveils Critical Path Opportunities List Outlining Blueprint to Modernizing Medical Product Development by 2010, FDA Press Release, March 16, 2006, <http://www.fda.gov/bbs/topics/news/2006/NEW01336.html>.
64. Guidance for Industry: Q8, Pharmaceutical Development (ICH Q8), May 2006, U.S. FDA, <http://www.fda.gov/cder/guidance/6746fnl.pdf>.
65. Guidance for Industry, Investigators and Reviewers: Exploratory IND Studies, U.S. FDA, January 2006, <http://www.fda.gov/cder/guidance/7086fnl.pdf>.
66. Telephone conversations with Meggi Raeder, Ph.D., Regulatory Solutions, and Bonnie Horner, Regulatory Consulting, March 2006.
67. Guidance for Industry: Guideline for the Preparation of Investigational New Drug Products (Human and Animal), U.S. FDA, March 1991, <http://www.fda.gov/cder/guidance/old042fn.pdf>.
68. FDA Compliance Program Guidance Manual 7356.002M, Inspections of Licensed Biological Therapeutic Drug Products, October 20, 2003, http://www.fda.gov/cder/dmpa/7356_002M.pdf.
69. Giving Thalidomide a Second Chance, Herbert Burkholz, *FDA Consumer Magazine*, September–October 1997, U.S. FDA, http://www.fda.gov/fdac/features/1997/697_thal.html.
70. Epidemiological Notes and Reports Nosocomial Bacteremias Associated with Intravenous Fluid Therapy, CDC *MMWR Weekly*, December 26, 1997, <http://www.cdc.gov/mmwr/preview/mmwrhtml/00050554.htm>.
71. Personal conversation with Ron Tetzlaff, formerly with FDA, now Corporate Vice President, Parexel Consulting, March 2006.
72. Advanced CGMPs Course, Barbara Immel, Immel Resources LLC, Petaluma, CA, www.immel.com.



GREAT TRAINING IDEAS

GXP Training Ideas

Host a retreat for your group.

Schedule a mini-retreat for your department to discuss group goals, get to know each other better, and provide refresher training. Offer the session off-site at a local hotel or conference center or in the quietest conference room you can find. Announce the event well in advance to allow people to easily attend, distribute a copy of the proposed agenda in advance, and provide attendees with a phone number where they can be reached during an emergency. Really make it a useful and fun session. If you're offering a full-day or longer session, provide continental breakfast, lunch, and an afternoon snack each day.

Begin with the agenda for the day. (For multi-day sessions, provide a new agenda at the beginning of each day and a summary at the end of each day.) Provide a brief overview on company or organizational goals and follow it with an exercise to brainstorm group goals and a refresher GXP training session. For a day (or longer) retreat, consider inviting an experienced facilitator from human resources or an outside consultant to lead an exercise or class (to identify leadership skills, build teamwork, or review GXPs). Individuals should gain some knowledge about themselves, as well as information about the group and the other team members.

For a brainstorming exercise to identify group goals or areas for improvement, provide colored index cards to all participants. Ask them what they would like to work on during the year, or ask them: What's driving you crazy? What concerns you the most about the group's compliance with GXPs? Alternatively, you can review recent deviation, nonconformance, or out-of-specification result trends within the department (no individual names, please) and ask for the group's help in thinking of ways to address them.

After everyone has a chance to record their thoughts on the cards, ask participants to get into small groups to discuss them. Ask them to not only commiserate with one another, but also

to suggest possible ways to address the issues. Discussion should continue until all participants have had a chance to discuss all of their cards, or all of the ones they feel comfortable discussing. Ask each group to organize the cards into topics, and give each group a chance to discuss its findings with the overall group. As facilitator, lead the overall group in discussing and identifying the goals that participants most want to work on during the year.

For the GXP refresher session, present an overview of all the regulations applicable to your group. Or discuss current trends in regulatory compliance or an important new topic. Don't forget to ask everyone to sign a training form so each person receives credit. During this session, consider showing and discussing current FDA 483s or warning letters or compliance policy guidance manuals (how FDA inspects). Adults love to see real-world examples. FDA makes a number of redacted documents available on its web site (with confidential information removed) through the Freedom of Information Act (FOIA). Frequently requested FDA 483s are available at <http://www.fda.gov/ora/frequent/default.htm>, FDA warning letters are available at <http://www.fda.gov/foi/warning.htm>, and FDA Compliance Policy Guidance Manuals are available at <http://www.fda.gov/ora/cpgm/default.htm>.

Host GMP Jeopardy or another game show. This suggestion requires lots of lead time in planning and organizing. Ask for a well-organized volunteer to lead the preparations. Ask for volunteers (or recruit members of your QA or compliance departments) to write Jeopardy questions. All questions should be reviewed by an experienced compliance person, with correct answers for each question confirmed and double-checked. Also, invite a "game-show" host, assistant, and if desired, people who will help with the promotion, game show "booths" or tables, and buzzers. (One of the first active pharmaceutical ingredient plants I ever worked with had

a full-time trainer who in a previous life had performed with the Ramones, and he always wore a tuxedo when he served as game-show host.) Promote the event and book the conference room well in advance. Consider inviting individual participants to compete, or if you prefer, two-person teams. We've found that two-person teams work the best — it's also easier to find contestants.

Present the "Popcorn" Exercise.

Credit for this oldie-but-goodie exercise belongs to Linda Noffke, a former compliance trainer with Boehringer-Ingelheim in Connecticut and now a trainer with the Visiting Nurses Association. With Linda's permission, we modified the original manufacturing exercise to include packaging as well and prepared a manual that is now in the public domain. (If you'd like a copy, call us at (707) 778-7222, or write us at immelman@immelman.com. Ask for the "Popper" exercise, and we'll send it to you.)

In this exercise, teams compete to manufacture and package as much popped corn as they can during a 30-minute production period. They must properly gown (hair nets, lab coats, beard covers, gloves, shoe covers) and follow GMPs during production and packaging, including creating their own labels for the product.

This exercise also requires advance preparation. If you have never presented it before, consider doing a "dry run" with a few members of your department to get the timing down, work out any "kinks," and gain sufficient confidence before it's show time.

Collect or borrow enough hot air popcorn poppers, extension cords, gowning supplies (hair covers, beard covers, lab coats, shoe covers, gloves), bowls for manufacturing and packaging, measuring cups, plastic sandwich bags (for individually packaging product), labels, markers and/or ink pens for creating labels, a mock batch record, and a mock packaging record (with sufficient

to page 9 ➤



Process Hazard Analysis for Pharmaceutical and Biotechnology Operations

by John P. Farris, CIH, President and CEO, SafeBridge Consultants, Inc.

materials and copies for each team). During class, organize the class into teams, provide the materials, and discuss the allotted time for each activity. Allow time for a planning period, a production period, and an inventory and debriefing period.

During the planning period, each team will assign roles (Production Manager, QA Manager, etc.). During the exercise, all individuals will have to complete the necessary documentation thoroughly and completely. When the heat is on and production is in full swing, remind the teams of the time remaining in the production period. Variations of the exercise include doing a packaging exercise only and packaging M&Ms, small candies, cookies, etc. Some teams may become quite competitive during the exercise, but there is usually good-natured joking. A very important tip is to remind each team to follow the preheating instructions supplied with its popcorn popper (you'll want to repeat these in your batch record). If a team overheats its popper, it will malfunction and be out of commission for the whole exercise (much like the very real scenario when production equipment malfunctions in a manufacturing plant). At the end of class, debrief the overall group, inventory the completed "packaged" product that met its specifications, and ask participants what they learned and observed during the event.

Do you have a GXP training idea that you're particularly fond of and would be willing to share? Full credit will go to you as the trainer, and to your organization as well, for submitting the idea. We'll send you a free **IMMEL REPORT™** mug and two complimentary issues of the **IMMEL REPORT™** to thank you for your trouble. Write us at immel@immel.com, or call us at (707) 778-7222. Fame and fortune await! ➦

The **IMMEL REPORT™** is not intended to replace the advice of an experienced quality assurance or regulatory compliance professional. Please ensure that you are following all applicable regulations, and consult with an experienced quality assurance or regulatory compliance professional regarding any questions that you may have.

Pharmaceutical and biotechnology manufacturing operations use physical processes, machinery, and drug or biological substances that present potential biohazards and risks of fire, explosion, and injury or illness to people, the manufacturing plant, and the environment. These risks can only be properly managed by using a thorough engineering or scientific analysis and allowing knowledgeable and qualified professionals to work as a team to review all aspects of hazard mitigation during process design. Anything less invites an incident or disaster that could have serious financial effects on a company through injury to people, destruction of the physical plant, or interruption of manufacturing.

Process hazard analysis (PHA) comprises a methodical, comprehensive review of all aspects of process design using the combined knowledge and efforts of specialists representing all relevant disciplines. Normally, the interests and viewpoints of management, R&D, manufacturing, process engineering, employee health and safety, maintenance, and environmental protection must be sought, heard, evaluated, and accommodated in this process. PHA is not a single event, but rather a series of reviews that should occur beginning at the conceptual stage of process design and continue through design development to pre-startup review and post-operational verification. Each stage builds on the information and risk management decisions made by the team at the preceding stage.

At the **conceptual stage**, the team gathers and evaluates all process safety information and decides whether it needs any additional information to allow the PHA to be done properly. Data or information needed at this stage include but are not limited to:

- proposed equipment list
- proposed process flow description

- preliminary instrumentation and control diagrams
- chemical and physical or biological hazard characteristics of the materials to be processed, including:
 - animal and human toxicology
 - occupational exposure limits (OELs)
 - airborne contaminant sampling and analysis methods
 - reactivity and stability
 - explosion severity
 - minimum explosive concentration
 - ignition temperature
 - minimum ignition energy
 - volume resistivity
 - environmental effects

Information gaps will undoubtedly be identified at the conceptual stage, and the team should make plans to conduct the necessary testing to obtain the information. A sample PHA checklist (for a pharmaceutical operation) is shown on pages 10-11.

At the **design development stage**, the team evaluates information from the conceptual stage and uses it to guide the proposed design. At this point, team members evaluate the suitability of the specific machinery to be used, check ergonomic factors, decide on mitigation measures, and agree on the *basis of safety*. The basis of safety is the overall safety argument establishing the rationale for why the system can be considered to be safe and providing the relationships to any underlying evidence supporting the conclusion. For example, the basis of safety to prevent the hazard of an explosion in a fluidized bed dryer/granulator could be explosion suppression, rendering the gases inert (also known as *inerting*), venting, or containment. This rationale is sometimes referred to as the *safety case* (particularly in Europe) and includes the documentation of the structured safety process undertaken. This process should



Sample Process Hazard Analysis Checklist Pharmaceutical Operations

be supported by sound scientific and/or engineering principles. The process design is finalized in accordance with the safety case, and then the equipment or process is constructed or installed, and procedures and batch records or worksheets are written. The final review at this stage consists of a look at the procedures and batch worksheets to ensure that they incorporate the necessary operational controls required by the predefined safety case.

The PHA team should complete a **pre-startup** review after the processing train is completed and all equipment is in place to ensure that the installation has been completed in accordance with the design. At this time, such checks as motor rotation direction, adequacy of static electricity bonding and grounding, oxygen concentrations (if the system is inerted), ergonomics, process containment, materials handling, waste handling, and so on are reviewed and placebo batches are run. If everything is found satisfactory, the process is permitted to start up.

A quick **post-operational** review should be performed after several months of operation to determine how the process is running and to ensure that needed operational procedure changes are evaluated and documented.

The PHA is a systematic process to identify and analyze the hazards of an operation, the associated potential consequences and risk of accidents and incidents, and the adequacy of measures taken to eliminate, control or mitigate the hazards. This process includes the development of thorough documentation to establish the basis for safety. This is best accomplished by organizing a complete team of competent professionals in the scientific and engineering disciplines mentioned above. A useful tool to get started is a process analysis checklist that can drive the systematic approach and ultimately lead to sound decisions and complete documentation. When properly implemented and followed to

Process: _____

Reviewers: _____

PROCESS CONCEPTUAL STAGE

Gather and evaluate process safety information.

| | On Hand | Need | Not Applicable |
|---|---------|------|----------------|
| Proposed equipment list | | | |
| Proposed process flow description | | | |
| Preliminary instrumentation and control diagrams | | | |
| Chemical and physical hazard characteristics of the materials to be processed | | | |
| Animal and human toxicology | | | |
| Occupational exposure limits (OELs) | | | |
| Industrial hygiene (IH) sampling and analysis methods | | | |
| Reactivity and stability | | | |
| Explosion severity | | | |
| Minimum explosive concentration | | | |
| Ignition temperature | | | |
| Minimum ignition energy | | | |
| Volume resistivity | | | |
| Environmental fate and effects | | | |

PROCESS DESIGN DEVELOPMENT STAGE

Evaluate information from the conceptual stage and use it to guide the proposed design.

| | Acceptable | Improve | Not Applicable |
|---|------------|---------|----------------|
| Suitability of the specific machinery | | | |
| Actives weighing methods | | | |
| Procedure review | | | |
| Batch records review | | | |
| Personal protective equipment | | | |
| Product transfer methods | | | |
| Waste collection, handling, and treatment | | | |
| Ergonomic factors | | | |
| Medical surveillance | | | |
| Hazard awareness training | | | |
| Basis of safety (describe below) | | | |

The basis of safety for this process is

Fire/Explosion: _____

Health: _____

Design changes required: _____

to page 11 >



Sample Process Hazard Analysis Checklist Pharmaceutical Operations (continued)

PRE-STARTUP REVIEW

Ensure that the installation is completely in accordance with the design.

| | Acceptable | Improve | Not Applicable |
|--|------------|---------|----------------|
| Hazard awareness training conducted | | | |
| Mill motor rotation direction | | | |
| Adequacy of static electricity bonding and grounding | | | |
| Oxygen concentrations (if the system is inerted) ____% | | | |
| Ergonomics | | | |
| Containment and control of actives | | | |
| Materials handling | | | |
| Waste handling | | | |
| Personal protective equipment | | | |
| Room pressure relationships | | | |
| Local exhaust ventilation flow rates | | | |
| Cross-contamination control | | | |
| Maintenance and test of explosion control equipment | | | |
| Industrial hygiene (IH) sampling plan | | | |
| Dry walk-through | | | |
| Placebo test | | | |

Changes required before startup: _____

POST-OPERATIONAL REVIEW

Check that the process is running according to the design.

| | Acceptable | Improve | Not Applicable |
|--|------------|---------|----------------|
| Bonding continuity | | | |
| Process tightness (from industrial hygiene sampling results) | | | |
| Design oxygen concentrations attained (if inerted) | | | |
| Evaluation and documentation of operational procedure changes | | | |
| Implementation of improvements indicated by industrial hygiene (IH) sampling results | | | |

Other comments: _____

completion, the PHA process creates a safe working environment in advance of operations and accomplishes this in a non-reactive manner that best serves the respective organization.

John P. Farris is president and chief executive officer of SafeBridge Consultants, Inc., (650) 961-4820, ext. 229, john.farris@safefridge.com. He is also a member of the Editorial Advisory Board of the **IMMEL REPORT™**.

This article is part of the syllabus from the SafeBridge course "Potent Compound Safety Training for the EH&S Professional," also known as "Potent Compound Safety Bootcamp," a comprehensive two-day course to train EH&S professionals on critical technical concepts and proactive safety programs. To learn about the next scheduled course, please see the SafeBridge web site, www.safefridge.com.

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D I D Y O U K N O W ?

... that FDA is celebrating its 100th anniversary in 2006? The Federal Food and Drug Act was passed on June 30, 1906. The Bureau of Chemistry, U.S. Department of Agriculture (the forerunner of the FDA), led by Dr. Harvey Wiley, was given the authority to enforce the new Act. FDA has a wonderful history web page that provides articles and useful information about the agency that you can use in your training classes, including milestones in FDA history, FDA commissioners and their predecessors, current laws enforced by FDA, and web sites with historical information related to FDA, with beautiful, historical pictures and illustrations! The web site is at <http://www.fda.gov/oc/history/default.htm>. The FDA also has an FDA Centennial web site which includes a nice feature on "This Week in FDA History" at <http://www.fda.gov/centennial/default.htm>. Here's an excerpt from one of the available articles, "The History of the FDA," by John Swann, FDA Historian:

The agency grew from a single chemist in the U.S. Department of Agriculture in 1862 to a staff of approximately [10,000 employees and a budget of \$1.8 billion in 2005], comprising chemists, pharmacologists, physicians, microbiologists, veterinarians, pharmacists, lawyers, and many others. About one-third of the agency's employees are stationed outside of the Washington, D. C. area, staffing over 150 field offices and laboratories, including five regional offices and 20 district offices. Agency scientists evaluate applications for new human drugs and biologics, complex medical devices, food and color additives, infant formulas, and animal drugs. Also, the FDA monitors the manufacture, import, transport, storage, and sale of about \$1 trillion worth of products annually at a cost to taxpayers of about \$3 per person. Investigators and inspectors visit more than 16,000 facilities a year, and arrange with state governments to help increase the number of facilities checked....

The modern era of the FDA dates to 1906 with the passage of the Federal Food and Drug Act; this added regulatory functions to the agency's scientific mission. The Bureau of Chemistry's name changed to the Food, Drug, and Insecticide Administration in July 1927, when the non-regulatory research functions of the bureau were transferred elsewhere in the department. In July 1930, the name was shortened to the present version. FDA remained under the Department of Agriculture until June 1940, when the agency was moved to the new Federal Security Agency. In April 1953, the agency again was transferred, to the Department of Health, Education, and Welfare (HEW). Fifteen years later, FDA became part of the Public Health Service within HEW, and in May 1980, the education function was removed from HEW to create the Department of Health and Human Services, FDA's current home. To understand the development of this agency is to understand the laws it regulates, how the FDA has administered these laws, how the courts have interpreted the legislation, and how major events have driven all three.

(Thanks, John, for allowing us to reprint part of your article.)

... that FDA provides copies of frequently requested 483s and other regulatory documentation on its web site? Copies are redacted (with confidential information removed) and are available on FDA's Office of Regulatory Affairs (field organization) web site at <http://www.fda.gov/ora/frequent/default.htm>. These materials are made available to the public through the Freedom of Information Act (FOIA). We recommend downloading and discussing these documents in training classes or staff meetings to remain current with what FDA investigators are finding during inspections. Most of the 483s posted are for GMP issues; however, several concern GLP and GCP violations. As we go to press, 483s are posted for organizations manufacturing or processing medical devices, pet food, blood, human drug products, vaccines, and human tissue. There are also 483s concerning an institutional review board, human subjects committee, clinical investigator, and one GLP 483 concerning a sponsor.

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