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FDA/ISPE Continue Cooperative Efforts

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THIS ARTICLE SUMMARIZES SOME RECENT HIGHLIGHTS OF ISPE'S TAMPA AND AMSTERDAM CONFERENCES FEATURING THE INTRODUCTION OF TWO DRAFT GUIDANCE DOCUMENTS DEVELOPED IN COOPERATION WITH THE FDA.

ISPE presented two new draft documents developed in cooperation with FDA, "Guidance for Industry: Manufacturing Equipment Addendum to the Guidance for Industry for Scale-Up and Post-Approval Changes: Immediate-Release Products" (SUPAC-IR), and "Baseline™ Pharmaceutical Engineering Guide - Volume 2: Oral Solid Dosage Forms."

What is SUPAC?

The Scale-Up and Post-Approval Changes (SUPAC) guidance documents were developed by the Center for Drug Evaluation and Research (CDER) as a means of maintaining product safety, efficacy and quality, while providing substantial regulatory relief and flexibility to manufacturers.

The SUPAC guidance documents make recommendations to drug product sponsors who intend to make post-approval changes to the product in: the components or composition; the site of manufacture; the scale of manufacture; and/or the manufacturing process and equipment.

The guidance document resulted from: a workshop on the scale-up of immediate release drug products conducted by the American Association of Pharmaceutical Scientists, in conjunction with the United States Pharmacopoeial Convention and FDA; research conducted by the University of Maryland Baltimore County on the chemistry, manufacturing and controls of immediate release drug products, under the FDA/University of Maryland Manufacturing Research Contract; drug categorization research conducted at the University of Michigan and the University of Uppsala on drug substance permeability; and the SUPAC Task Force of the CDER Chemistry, Manufacturing and Controls Coordinating Committee.

The guidance defines: levels of change; recommended chemistry, manufacturing, and controls tests for each level of change; *in vitro* dissolution tests and/or *in vivo* bioequivalence tests for each level of change; and documentation that should support the change. This guidance outlines application information that should be provided to CDER to assure continuing product quality and performance characteristics of an immediate release solid oral dose formulation for specified post-approval changes.

What this means to industry is, in certain situations, manufacturers will be able to make changes in components, composition, site, equipment or process, *without prior approval*. Annual reports will be sufficient documentation of some changes. Clearly, this is a benefit in terms of both cost and time savings.

"THIS PROJECT HAS BEEN A REAL BREAKTHROUGH AS FAR AS FDA REGULATION IS CONCERNED. THIS IS A PARTNERSHIP WITH FDA; WE'RE IN IT TOGETHER, AND FDA HAS BEEN VERY COOPERATIVE."

RUSS SOMMA, PHD
NOVARTIS PHARMACEUTICALS CORP.
SUPAC STEERING COMMITTEE CHAIR

The concept of SUPAC is based on 21 CFR 314.70(a), which "provides that applicants may make changes to an approved application in accordance with a guideline, notice or regulation published in the *Federal Register* that provides for less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report)."

"Section 314.70 predated SUPAC," said FDA's Joseph Phillips, Deputy Regional F&D Director in the Agency's Mid-Atlantic Office in Philadelphia. "It provided the mechanism for firms to make the proper filing with the Agency. SUPAC provides guidance on how to make submissions to the Agency, reducing the burden to the company and making it much easier to effect change."

There are six SUPAC guidance documents currently in existence or development, and FDA has asked ISPE to produce addenda for these as well. In addition to the Immediate Release document, FDA has completed and ISPE has begun work on addenda to the Modified Release (SUPAC-MR) and Semi-Solids (SUPAC-SS) documents. Yet to come from FDA are documents addressing post-approval changes to transdermal systems (SUPAC-TDS), bulk actives (BACPAC), and aqueous solutions (PAC-SAS).

SUPAC-IR - Background

FDA developed the SUPAC Addendum on Manufacturing Equipment, with the assistance of ISPE. It is an adjunct to the FDA Center for Drug Evaluation and Research's Guidance for Industry: Immediate Release Solid Oral Dosage

"THE SUPAC GUIDANCE DOCUMENTS MAKE RECOMMENDATIONS TO DRUG PRODUCT SPONSORS WHO INTEND TO MAKE POST-APPROVAL CHANGES TO THE PRODUCT IN: THE COMPONENTS OR COMPOSITION; THE SITE OF MANUFACTURE; THE SCALE OF MANUFACTURE; AND/OR THE MANUFACTURING PROCESS AND EQUIPMENT."

Forms Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (SUPAC-IR) issued in November 1995.

The purpose of the document is to assist sponsors of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs) and Abbreviated Antibiotic Drug Applications (AADAs) for immediate release drug products in determining what documentation should be submitted to the Agency, regarding equipment changes made in accordance with recommendations in sections V [Changes In Batch Size (Scale-Up/Scale-Down)] and VI-A (Manufacturing) of SUPAC-IR.

FDA's New Jersey District Director Matt Lewis (now retired) and Joseph Phillips approached ISPE in mid-1996, requesting the Society's assistance with developing a list of "similar" equipment to accompany the SUPAC Addendum. "We felt ISPE had the expertise among its members to develop the list," Phillips said.

A Steering Committee comprised of experts in engineering and processing from generic and brand name pharmaceutical manufacturers was formed by then ISPE Executive Vice President Larry Kranking. In October, Russ Somma, PhD, Head of Process Development, Solids, for Novartis, assumed the Chair. Co-Chairing the committee is Adel Kheir-Eldin, Vice President of Quality for Zenith Goldline Pharmaceuticals. Also sitting on the committee were the FDA's Phillips and Paul D'Eramo, National Drug Expert from the Agency's Mid-Atlantic Regional Office.

Sub-teams of engineering and processing personnel from industry, with experience in specific processing operations, were assembled to formulate individual sections of the addendum.

Development of the Document

"At the October conference, we presented a draft of the concepts involved in the document and the rationale for selecting them," said Somma. "We then opened a comment period which ran through mid-November."

"We immediately encountered one problem, which was a difference in approach to the document between FDA and our group. We all were in agreement that a move within a sub-class could be accomplished quite easily, with the Agency notified of the change in the company's annual report. However, the Agency regarded a change from one sub-class to another within the same equipment classification as a move that would require that a request for prior approval be filed. Our position was that such a move should not require prior approval. In the ensuing weeks, this difference of opinion was resolved, with the result that a move between sub-classes would be allowed with the same notification via annual report, so long as the company could show its rationale for the change should the Agency question the move."

This was an excellent verification that the system of having the committee do a draft presentation, open it for wider comment, then more discussion with the FDA really does work.

"At the end of the comment period, the information collected was distributed to the team and we began recrafting the document for the February conference," Somma commented. "We knew that we had to have the project finished, and were working against a tight timetable. At any time, we had as many as 60 people working on this project."

The Addendum is organized by unit operations: Blending and Mixing, Drying, Particle Size Reduction/Separation, Granulation, Unit Dosing, Coating/Printing, and Soft Gelatin Capsules. Each section defines the specific operations within the unit (e.g. Blending and Mixing: Diffusion Blending, Convection Mixing, and Pneumatic Mixing), the operating principle or class for each operation, and its design characteristics or sub-classes (e.g. Diffusion Blending: baffles, geometric shape, axis of rotation, and discharge geometry).

Tables in each section list the classes and sub-classes, which, in most instances, include examples. As noted in the introduction to the guidance document, "...in some cases, specific equipment may not be listed. It (the document) does, however, include a representative list of equipment commonly used in the industry. The guidance does not address equipment that has been modified by a pharmaceutical manufacturer to fit its specific needs."

Draft Introduction

The conference introducing the draft Addendum drew 200 delegates in the US, most from pharmaceutical manufacturers. Speakers were a mix of industry and FDA personnel, all of whom had been involved in the development of SUPAC and/or the Addendum. In addition to Phillips and D'Eramo, Agency participants included: Charles Hoiberg, PhD, Director DNDC 1; Mohammed Hossain, PhD, Team Leader, Office of Pharmacology and Evaluation; Ajaz Hussain, PhD, Acting Deputy Director, CDER; Paul Schwartz, PhD, Team Leader, Office of Generic Drugs; Eric Sheinen, Director, Office of New Drug Chemistry; Douglas L. Sporn, Director, Office of Generic Drugs; and Kasturi Srinivasachar, PhD, Chair, Drug Substance Technical Committee.

In Europe, the draft was presented at an ISPE Conference in Amsterdam in late February, with Hoiberg, Phillips and D'Eramo representing FDA.

The draft was very well received by those in attendance, who see in it both another step toward further cooperation between FDA and industry, and a means of saving vast amounts of time and money in the manufacture of their products.

"The equipment listing answered a problem we had, on the spot," said Robert Lennahan of Bristol-Myers Squibb, one of the Tampa conference participants.

"At first, I thought the idea of an equipment list was a lousy one," said Leo Lucisano, Assistant Director of Regu-

latory Affairs for Glaxo Wellcome Inc., and one of the program speakers. "As it developed, though, it certainly is a useful companion document to the guidance document. I think ISPE's engineers took a very rational, scientific approach in developing the list."

"Everyone I talked to in Tampa felt positive about the changes made in the document since October," Lucisano added. "I tip my hat to ISPE and FDA for working so well together to make the changes on the issue of sub-class changes."

"I was happy we were able to get CDER and the generic division of FDA, and manufacturers, both generic and research, and vendors all in one room able to agree," said Richard Poska, Sr. Regulatory Affairs Scientist at Abbott Laboratories, and a member of the committee which developed the list.

At the time of the Tampa conference, ownership of the Addendum formally passed to FDA, which then opened a 60-day comment period on the document. Following the event, the Agency posted the draft on the Internet where it is available to anyone interested in reviewing it. The Internet address is:

http://www.fda.gov/cder/guidance.htm
then select *chemistry draft*

FDA also has referenced the Addendum in the *Federal Register*. Comments on the draft should be sent to Ted Sherwood, Office of Generic Drugs, Center for Drug Evaluation and Research, HFD-600, 7500 Standish Place, Rockville, MD 20855, telephone 301/594-0340. Any comments received after April 3, 1997, may not be acted upon by the Agency until the document is next revised or updated.

Next Steps

"Work is underway on an addendum for SUPAC-MR (Modified Release). The sub-teams have met, and will have the draft ready for introduction at the next ISPE/FDA SUPAC Conference, April 14 in Philadelphia," said Somma. "At the same time, we hope to have a first draft presenting the rationale for the addendum to SUPAC-SS (Semi/Solid)."

There have been changes to the Steering Committee makeup as well, with two new members added from the FDA's CDER.

"This project has been a real breakthrough as far as FDA regulation is concerned," Somma said. "This is a partnership with FDA; we're in it together, and FDA has been very cooperative. Joe Phillips has helped us a lot during this process."

"It also has been a very positive experience for all of us. When the conceptual difference developed in October, it became apparent that a group like ISPE was the one to go to in order to resolve some of these differences and encourage interaction between industry and the Agency."

According to Glaxo Wellcome's Lucisano, "The real benefit of the equipment grid is that it reinforces and clarifies the roles of industry, FDA field personnel, and the reviewing chemist at CDER."

Baseline® PHARMACEUTICAL ENGINEERING GUIDE

The Baseline™ Pharmaceutical Engineering Guides project was initiated by ISPE's Pharmaceutical Advisory Council, a group of upper management representatives from the major US pharmaceutical manufacturers. Following a joint meeting with FDA, a Steering Committee was formed to oversee the production of a series of guides aimed at controlling costs in the design and construction of new facilities, and providing a better understanding of the basics required for regulatory approval for these facilities.

The draft of the first in the series, Volume 1: Bulk Pharmaceutical Chemical (BPC) Facilities, was presented at ISPE's 1995 Annual Meeting. Following a comment period, the first edition was published last year.

In all, there will be 11 guides. Nine "vertical" publications will provide guidance on the engineering issues for specific types of facilities, ranging from BPC to R&D Laboratories or Medical Device facilities. Two "horizontal" guides will address issues that apply to all types of facilities: pharmaceutical water systems, and commissioning and validation.

At the present time, work is underway on guides for Pharmaceutical Water and Steam and Sterile Manufacturing Facilities.

"VALIDATION VERSUS QUALIFICATION IS A CONCEPT THAT SOME PEOPLE HAVE A DIFFICULT TIME UNDERSTANDING. THIS IS AN AREA THAT ALWAYS CAUSES SOME CONFUSION."

JOSEPH PHILLIPS, FDA

Baseline™ Guide: Oral Solid Dosage Forms

The draft of the second in the series of Baseline™ Pharmaceutical Engineering Guides, Volume 2: Oral Solid Dosage Forms, also found an appreciative audience.

As was the case with the BPC Guide, the Oral Solid Dosage Forms (OSD) draft was developed by a Task Team of industry volunteers working in concert with FDA. Chairing the Task Team charged with developing the OSD Guide was Gregory Cierpial, Senior Manager with Hoffmann-La Roche, Inc.

"There were very few problems in preparing the Guide," Cierpial said. "We actually had it drafted, and might have been able to introduce it at the Annual Meeting (November 1996 in San Diego), but we wanted to take some extra time in its review. Conceptually, it was easy to do because of past experience with the BPC Guide. From this experience, we knew better how to work both as a team and with FDA, and Paul D'Eramo and Joe Phillips also had a better idea of how to move the project forward."

Guide Contents

The OSD Guide is comprised of 11 chapters:

1. Introduction
2. Concepts and Regulatory Philosophy
3. Product and Processing Considerations
4. Architectural
5. Process, Support and Utility Systems
6. HVAC
7. Electrical
8. Instrumentation and Controls
9. Other Considerations
10. Commissioning and Qualification
11. Definitions

"One item in the Guide that touched off a lot of discussion during the Tampa presentation was in Chapter 2," commented Cierpial. "The Guides take the position that only 'critical' systems which are in direct physical contact with the drug product or are used to measure, monitor or record critical parameters need be validated. For support systems, such as utilities, qualification and good engineering practice are often sufficient. Joe Phillips and Paul D'Eramo spent 25 minutes speaking on this issue of validation versus qualification during the workshop."

"Validation versus qualification is a concept that some people have a difficult time understanding," said Phillips. "This is an area that always causes some confusion."

"The section on process considerations (3.3) where the color key weights requirements for each type of equipment is really helpful," said Bristol-Myers Squibb's Robert Lennahan, a program participant. "You can get an idea of the impact each one of these things will have on design and design costs." (Sample figure on page 43.)

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ROBERT LENNAHAN, BRISTOL-MYERS SQUIBB
A PROGRAM PARTICIPANT

Table 3-1

		GMP ISSUES					ECONOMIC				
		Cleanability	X-contamination	Validation	Calibration	Maintenance	Eqpt cost	Installation	Validation	Operational	Maintenance
Weigh/	Conventional	Red	Red	Green	Yellow	Green	Green	Green	Green	Green	Green
Dispensing	Laminar flow	Red	Yellow	Green	Yellow	Green	Green	Green	Green	Green	Green
	Isolator	Green	Green	Red	Yellow	Yellow	Red	Green	Green	Yellow	Yellow

		PROCESS			FACILITY					
		Throughput	Yield	Changeover	Space Reqmt	Containment	HVAC	Dust Collection	Arch. Finish	Process Utilities
Weigh/	Conventional	Green	Green	Green	Green	Red	Red	Red	Red	Green
Dispensing	Laminar flow	Green	Green	Green	Green	Yellow	Yellow	Yellow	Yellow	Green
	Isolator	Red	Green	Red	Red	Green	Green	Green	Green	Yellow

Continued on page 44.

"THE TASK TEAM FOUND TWO MAJOR TRENDS. THE GUIDE EXAMINES THE TREND AWAY FROM SINGLE PRODUCT PLANTS TO MULTI-PRODUCT FACILITIES WITH MULTI-USE EQUIPMENT.
IT ALSO ADDRESSES THE FACT THAT THERE ARE A LOT MORE PRODUCTS OF VERY HIGH POTENCY OR TOXICITY TODAY..."

GREGORY CIERPIAL, HOFFMANN-LA ROCHE, INC.
TASK TEAM CHAIR

"The 'Materials Finishes' section in Chapter 4 is another extremely useful item," said Cierpial. "It gives a very clear description of what types of materials and finishes are acceptable at each protection level."

Chapter 5 defines the types of utility systems involved in an OSD facility, breaking them out into process, support and utility categories. Generally, process systems are those which either contact the product directly or contact materials which will become or come into contact with the product, and are considered "critical," meaning they will require validation.

In Chapter 8, the Guide analyzes the critical and non-critical issues involved in instrument and controls systems, while Chapter 9 reviews regulations from the National Fire Protection Association and Occupational Safety & Health Administration which apply to oral solid dosage facilities.

"Good Engineering Practice, as defined in Chapter 10, is an important aspect of the Guide," Cierpial noted. "It outlines the required documentation and execution of the design process."

Trends in OSD Facilities

"The Task Team found two major trends," said Cierpial. "First, the Guide examines, fairly explicitly, the trend away from single product plants to multi-product facilities with multi-use equipment."

"It also addresses the fact that there are a lot more products of very high potency or toxicity today, but treats this as another processing variable or consideration, as opposed to providing specific guidance on dealing with toxic compounds. The team spent a lot of time debating and discussing this issue, and came to the conclusion that the fact that you are dealing with materials that are toxic may change the way you handle them, but not necessarily the GMP design aspects of the facility."

TABLE 4-1 Material and Finish Selection Guidance

Architectural Element	Level I	Level II	Level III
Floors	Standard construction practice is generally appropriate. Typical materials include sealed concrete, epoxy coatings, coatings with a high level of wear resistance	Standard construction practice is generally appropriate. Typical materials include sealed concrete, epoxy coatings, VCT, seamless vinyl	Surfaces should be smooth and cleanable. Typical materials include sealed concrete, epoxy coatings, VCT seamless vinyl, chemically resistant coatings
Interior Walls	Not required to separate operations, if installed typical materials include wiremesh, gypsumboard, CMU. Note that as a method of separating stored materials devices such as stanchions/chains and moveable partitions are acceptable if proper material identification procedures are in place.	Standard construction practice is generally appropriate. Typical materials include CMU, gypsumboard, metal panels (with a finish material appropriate to the durability and cleanability requirements), glazed tile Note that softer materials such as plastic curtains also can be used as a secondary method for preventing contamination, e.g. in conjunction with HVAC systems.	Wall construction should provide a solid, non-porous surface. Typical substrate materials include CMU, gypsumboard, metal panels (finished with epoxy paint), resinous coatings, metal or PVC type cladding
Exterior Walls	Typical building materials and systems that give a neat appearance are generally acceptable. This includes masonry block and exterior insulated finish systems.	The interior surfaces of external walls should be of the same quality as required for internal walls.	The interior surfaces of external walls should be of the same quality as required for internal walls.