Breakout Session: Changes Without Prior Approval
April 22, 2003

Goals and Objectives

Discuss the following:

- Scientific risk-based approaches for identifying low risk manufacturing changes that can be implemented without prior FDA approval
- Draft guidance on comparability protocols for small molecules and development of a comparability protocol guidance for proteins
  Effective use of development data and other information to justify less burdensome filing requirements for postapproval manufacturing changes

Background Information

Background information on the status of on-going postapproval change activities is attached.

Format

There will be four sessions on *Changes Without Prior Approval*. The intended format of the workshop is for all participants from one of the four business sectors (generic-human drug, innovator-human drug, animal drug, and biotechnology) to attend their assigned session. The discussions will be in a brain-storming format.

Focus

While it is important to recognize and understand current and past initiatives relating to postapproval changes, the breakout sessions are intended to focus on new opportunities and pathways. The breakout sessions will focus on four basic areas:

1 For postapproval changes, how do you define risk? How do you manage the risk? What risk-based approaches can you suggest for identifying low risk postapproval changes, drugs, or manufacturing processes?

  Real or perceived risks are associated with any decision making/change process. Furthermore, there are risks in not changing. We will explore how risk is viewed and managed for postapproval changes.

  Do you see comparability protocols as being useful to your company? Have you used comparability protocols in the past? Do you have an example of how one was successfully used?

  FDA has recently published a guidance on comparability protocols (http://www.fda.gov/cder/guidance/5427dft.pdf). We will discuss how comparability protocols

might be used in a company and to justify less burdensome filing requirements for postapproval changes.

3. How could development data and other information be used to justify less burdensome filing requirements for postapproval changes?

   A firm, through its development program, often has an in-depth understanding of how chemistry, manufacturing, and controls changes can affect its product. This information, if shared with regulators, could justify less burdensome filing requirements for changes justified as low risk by the development data. We will explore the opportunities for using development data or other information to justify less burdensome filing requirements for postapproval changes.

4. In addition to the current initiatives, can you suggest other risk-based approaches to justify less burdensome filing requirements for postapproval manufacturing changes? Have you experience with other approaches (e.g., other regulatory agencies) that might be adopted for reporting postapproval changes to FDA?

   This discussion will focus on gathering suggestions for different risk-based approaches that might be used by FDA to regulate postapproval manufacturing changes.

Closing: Can you recommend any next steps? Future workshops?

Status—Current Postapproval Change Initiatives

FDAMA 116

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (FDAMA) (Pub. L. 105-115). Section 116 of FDAMA amended the Federal Food, Drug, and Cosmetic Act (The Act) by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. Section 116 further provided that these requirements take effect upon the effective date of regulations promulgated to implement section 116 or 24 months after enactment of this provision, whichever occurs first.

FDAMA 116 affects CDER, CBER, and CVM. The Centers have been working together on updating general regulations and publishing guidance documents that provide more specific recommendations on the reporting mechanism of postapproval changes.

CDER

Regulation
On June 28, 1999, FDA published in the Federal Register a proposed rule revising 21 CFR 314.70 (64 FR 34608), with a limited number of changes updating 610.12 (CBER). Since November 21, 1999, and until the final regulation for § 314.70 publishes, section 506A is the sole basis for FDA's regulation of postapproval manufacturing changes for products approved in new drug (NDA) or abbreviated new drug (ANDA) applications. Publication of the final rule is pending.

Guidance
On June 28, 1999, FDA published in the Federal Register a notice of availability of a draft guidance entitled *Changes to an Approved NDA or ANDA* (64 FR 34660). CDER issued a final guidance on *Changes to an Approved NDA or ANDA* on November 19, 1999. Since November 19, 1999 the guidance has represented FDA's current thinking on how it will apply the requirements of section 506A of the Act for NDA and ANDA products. An updated version (conforming changes only) of this guidance will publish with the final rule. CDER intends to revise the guidance with substantive changes after 314.70 publishes.

Some of CDER products are covered under the CBER/CDER guidance *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products.*

CBER

Regulation
CBER's postapproval regulations at 601.12 are considered consistent with FDAMA 116. However, a limited number of changes were published along with the CDER rule revising 314.70 to promote consistency between the Centers.

Guidance
CBER's postapproval change guidances include:

- *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products.*

- *Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture*

CVM

Regulation
On October 1, 1999, FDA published in the Federal Register a proposed rule revising 21 CFR 514.8 (64 FR 53281). Publication of the final rule is pending.

Guidance
On October 1, 1999, FDA published in the Federal Register a notice of availability of a draft guidance entitled *Changes to an Approved NADA or ANADA.*

Comparability Protocols

A draft guidance (CBER/CDER/CVM) on comparability protocols published on February 25, 2003 (68 FR 8772). The comment period closes on June 25, 2003. A second comparability protocol guidance tailored to certain biologics drug products and proteins is planned.

SUPAC Guidances (all CDER; limited participation by CBER, CVM)

Updating of all published "SUPAC" guidances is warranted. Currently, updating of these guidances is a lower priority compared to other projects.

Published Guidances

- BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation (CDER/CVM)
- PAC-ATLS: Postapproval Changes - Analytical Testing
- SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation
  SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum
  SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation

- SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence

Planned Guidances

- APPAC: Analytical Procedures; Post Approval Changes
- BACPAC II: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation (CDER/CVM)
- PACPAC: Packaging; Post Approval Changes

Risk-Based CMC Review Program (CDER)

A background paper on this initiative that was prepared for a June 2001 workshop is provided (see attached file).

Note: The published guidances mentioned in this document can be found on the Internet at:

- CDER: http://www.fda.gov/cder/guidance/index.htm
- CBER: http://www.fda.gov/cber/guidelines.htm
- CVM: http://www.fda.gov/cvm/guidance/guidance.html

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Risk-Based CMC Review Program
(Reducing CMC Filing Requirements for Drugs of Low Risk with respect to Quality)

Summary of a New CDER Initiative (updated 1-28-01)

1. Objectives

   a) Elimination of most NDA/ANDA manufacturing supplements for low risk drugs: All CMC changes except those listed in FDAMA section 116* (i.e., changes of Drug Substance (DS)/Drug Product (DP) specifications and DP components/compositions, and changes requiring an in-vivo study) will be reported through the AR of an approved NDA/ANDA for those low risk drugs that are on a list to be published in an Agency Guidance. However, for sterile products on the list, changes to the sterilization process will continue to be filed in accordance with existing post approval changes (PAC) guidance (i.e., submission of supplements may not be waived for certain changes affecting sterilization assurance).

   b) The Annual Report (AR) of an approved NDA/ANDA for those low risk drugs on the published list will contain reduced CMC information and data. The content of such AR will be described in an Agency Guidance (See item 3).

   c) An original ANDA for those low risk drugs on the published list will consist of the same reduced CMC information and data as required for the AR of the approved NDA/ANDA for the same drug (See item (b) above). Such an ANDA will be called a truncated ANDA (TANDA). Bioequivalence (BE) requirement of a generic drug filed under a TANDA may be waived based on BCS guidance. The provision of TANDA system will require changes of current FDA regulation

   * In accordance with SUPAC and other PACs where down regulations are provided

2. The process of defining the Risk-Based CMC Review program includes three phases.

(a) First phase: To establish a list of products meeting sound scientific criteria for low risk with respect to quality. Examples of attributes and acceptance criteria for determining low risk are:

(i) Drug Substance:

Attributes	Acceptance Criteria
Chemical Structure	Well characterized (smaller molecules, single molecule substance, chemical structure readily

		determined by common analytical tools, containing no or low # of chiral centers), others (to be defined)
	Synthetic Process	Simple process (a well-defined/optimized/repeatable process, others), others (to be defined) Adequate specifications (ICH standards), impurities and degradants described, known not to contain toxic impurities, others (to be defined)
	Physical Property	Polymorphism (defined and controlled), Particle sizes (defined and controllable), others (to be defined)
	Stability	Stable substances (long shelf life, stable under accelerated/stressed conditions? not requiring special packaging, others)
	Manufac. History	# of years (or # batches made) on the market (SUPACs definition?), reprocessing/rework records, demonstrating reproducibility over # of years, ICH Q7A, others (to be defined)
	Others	To be defined
(ii)	Drug Product:	
	Attributes	Acceptance Criteria
	Dosage form	Oral dosage form (Immediate Release, solid and liquid), including simple sterile solutions? excluding low strength drugs? others (to be defined)
	Manufac. Process	Easy to manufacture, robust/reproducible process, been manufactured by multiple processes? excluding sterilization process? others (to be defined)
	Quality	Adequate specifications (ICH standards), impurities and degradants well defined, others (to be defined)
	Stability	Stable products (long shelf life, stable under accelerated/stressed conditions? not requiring special packaging, others)
	Manufac. History	# of Years (or # of batches made) on the market (SUPAC definitions?), reprocessing/rework records, demonstrating reproducibility over # of years, others (to be defined)
		To be defined

(b) Second phase: To evaluate based on its clinical usage and safety the list of drugs that meeting low risk criteria with respect to quality. Clinical concerns may include but not limited to narrow therapeutic drugs, or drugs for critical care or with high toxicity

(e.g., certain cancer drugs). Drugs with serious clinical concerns will be removed from the list.

(c) Third phase: To determine the eligibility of a manufacturer for the program based on cGMPs consideration. Examples of attributes and acceptance criteria for cGMPs consideration are:

Attributes	Acceptance Criteria
Manufac. History	No recall due to quality reason? No consumer complaints on quality? others (to be defined)
DS Manufacturer	Acceptable cGMP status/record (to be defined)
DP Manufacturer	Acceptable cGMP status/record (to be defined)
Others	(To be defined)

3. The content of AR and TANDA: To draft a Guidance describing the reduced CMC information and data to be submitted at a one-time basis to the AR of the approved NDA/ANDA for the listed drugs. Such information and data may be modeled after Quality Summary of CTD-Q (e.g., a flowchart of synthetic process in lieu of detailed description, structure characterization, identification and qualification of impurities (monograph and new), composition and components of DP, DS and DP specifications, etc.). Reporting subsequent CMC changes under a supplement (See 1.a above) or in next AR will be limited only to those changes affecting the information and data provided in the updated AR. The same reduced CMC information and data required for an AR will be adequate for a TANDA for the same listed drug.

3. Under this program, the following requirements are not changed:

a) There will be no reduction on the requirements of validations, assessment studies, supporting data, and documentation that manufacturers need to perform or generate so to ensure the identity, purity, strength/potency, and quality of the product. These data and documentation will be kept on site and available for FDA inspection.

b) There will be no change to the Pre-Approval Inspection program for TANDA

4. To implement the program successfully, the Agency will

   a) provide training to industry and reviewers,

   b) form joint inspection team (reviewer and Field investigator) to randomly audit the scientific and validation data of those products regulated under this program, and

   c) work through CDER's Product Quality Research and PQRI to modify the "attributes and acceptance criteria", and to expand the drug list expanded in future.

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