Chemistry, Manufacturing, and Controls

Reducing the Regulatory Burden

Background Information

Advisory Committee for Pharmaceutical Science Meeting

November 15, 2000

Rockville, MD

Risk Based CMC Review
(Reducing CMC Requirements for Drugs of No or Little Risk with respect to Quality)

A Summary of the New CDER Initiative
Yuan-yuan Chiu, Ph.D.

1. Objectives

a) Elimination of most NDA/ANDA manufacturing supplements for no/little risk drugs: All CMC changes except those listed in FDAMA section 116***** (i.e., changes of DS/DP specifications, DP components/compositions, changes requiring an in-vivo study) will be reported through the AR of an approved NDA/ANDA for no/little risk drugs on a list to be published in an Agency Guidance. However, for sterile products on the list, changes to the sterilization process will be filed in accordance with PAC guidance (i.e., may require supplements).

b) The AR of an approved NDA/ANDA for a drug on the published list will contain reduced CMC information and data to be described in an Agency Guidance (See item 5).

c) An original ANDA (TANDA (Truncated ANDA)) for a drug 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). BE may be waived based on BCS. This change will require rule making.

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

2. To establish a list of products meeting sound scientific criteria for no or little risk with respect to quality, for examples:

(a) Drug Substance:

Attributes	Acceptance Criteria
Chemical Structure	Well characterized, others (to be defined)
Synthetic Process	Simple process (to be defined)
Quality	Adequate specifications, known not to contain toxic impurities others (to be defined)
Physical Property	Polymorphism? Particle sizes?
Stability	Stable substances (to be defined)
Manufacturing History	10? years on the market, others (to be defined)
Others	(To be defined)

(b) Drug Product:

Attributes	Acceptance Criteria
Dosage form	Oral dosage form (Immediate Release), simple sterile solutions, others (to be defined)
Manufacturing Process	Easy to manufacture (to be defined), Simple sterile solutions excluding changes that may affect sterility assurance
Quality	Adequate specifications, others (to be defined)
Stability	Stable products (to be defined)
Manufacturing History	10? years on the market, others (to be defined)
Others	(To be defined)

3. The drug list compiled based on the established scientific criteria will be evaluated based on safety:

Attributes	Acceptance Criteria
BCS (?)	Highly soluble and highly permeable?
Clinical Concerns	Non-NTI drug? not for critical care?
Others	(To be defined)

4. The eligibility of a manufacturer to be under this program will be based on GMPs considerations:

Attributes	Acceptance Criteria
Manufacturing History	No recall due to quality reason? others (to be defined)
DS Manufacturer	Acceptable GMP status/record (to be defined)
DP Manufacturer	Acceptable GMP status/record (to be defined)
Others	(To be defined)

5. 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, specifications, etc.). Only changes to this CMC information and data will need to be reported under a supplement (See 1.a above) or in a subsequent AR. The same reduced CMC information and data will be adequate for an original TANDA for the listed drugs from a generic drug manufacturer if determined to be eligible for this program based on GMP consideration.

6. The following requirements are not changed:

a) There will be no reduction of studies, data, and documentation that companies need to perform and 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

7. To achieve the objective of this project, the following process and timelines are proposed:

a) Initial working group to propose "attributes and acceptance criteria" (done)
b) Y. Chiu to brief OPS Chemistry DDs who will then inform chemistry team leaders (done)
c) Initial working group to brief Dr. Woodcock (done, 7/17/00)
d) Initial working group to present to CCC (done, 7/18/00)
e) Initial working group to present at Field/Drug Committee meeting (done)
f) Initial working group to meet with ORA representatives (done)
g) To form a technical working group(s) including OC and ORA staff to refine "attributes and acceptance criteria" and to plan for scientific workshops (done). CMCCC will have oversight of the technical working group. (done)
h) To inform RPS on rule making for TANDA (done)
i) Internal discussion at ONDC Scientific Rounds on September 25, 2000 (done)
j) Presenting at Trade meetings in October, 2000 (done)
k) Seeking input from ACPS in November, 2000
l) Scientific Workshop co-sponsored with AAPS in June-July of 2001 to discuss "attributes and acceptance criteria"
m) To seek MPCC input on safety concerns.
n) In 1st quarter of 2002 to publish draft Guidance on "attributes and acceptance criteria", and to propose rule permitting TANDAs
o) To form a technical working group to draft a Guidance on the reduced CMC information for the one time AR submission of an approved NDA/ANDA and an original TANDA, as well as the documentation of CMC changes filed through an AR of an NDA/ANDA/TANDA

p) In 4th quarter of 2002 to publish finalized Guidance on "attributes and acceptance criteria" and a draft Guidance proposing a list of drug candidates, the one time AR submission for an approved NDA/ANDA with reduced CMC information required and for an original TANDA, as well as documentation and reporting changes through an AR of an NDA/ANDA/TANDA

q) In 3rd quarter of 2003 to publish the finalized Guidance on drug list and reporting requirements for implementation, and final rule permitting TANDA.

8. To implement the program successfully, the following things will be done:

   a) Training to industry and reviewers will be provided.

   b) Joined inspection team (reviewer and Field investigator) will be formed to randomly audit the scientific and validation data of those products regulated under TANDA and AR for CMC changes.

9. To work through CDER's Product Quality Research and PQRI, and with outside "system engineers", the "attributes and acceptance criteria" can be modified and the drug list expanded.