



Fresenius Medical Care NA

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

February 13, 2004

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**SUBJECT: Docket No.: 2000N-1449
Guidance for Industry—Changes to an Approved NDA or ANDA**

**RE: Comments from Fresenius USA Manufacturing,
Inc. (dba Fresenius Medical Care North America)**

Dear Sir or Madam:

Fresenius USA Manufacturing, Inc. (dba Fresenius Medical Care North America --FMCNA) respectfully submits the following comments in response to the Food and Drug Administration's notice published in Federal Register as Docket No. 2000N-1449, dated December 19, 2003.

INTRODUCTION:

FMCNA commends FDA on its continuing efforts to optimize a "least burdensome" filing mechanism for reporting manufacturing changes to drug products. We, a manufacturer of peritoneal dialysis drugs, continually seek quality/process improvements and risk reduction by utilizing currently available state-of-the-art, process technologies and analytical methodologies applicable to our products. In doing so our drug products maintain their approved identity, strength, quality, purity and potency thus, assuring the continued manufacture and delivery of safe and effective drug products to our customers. We welcome this opportunity to comment on Section 506A (21 U.S.C. 356a).

COMMENTS:

We believe there are ways to reduce the current burden for notification of post approval changes, and so offer the following comments on reporting major manufacturing changes to an approved NDA or ANDA.

1. ESTABLISH SUB-CATEGORIES for DRUGS BASED UPON RISK

We would like to see FDA create sub-categories of drugs, under the current drug categories. Such sub-categories would further tier drugs according to their risk profile.

2. CORRELATE the SUPAC CHANGE LEVEL with the DRUG'S RISK PROFILE

We believe, as a start, there is an opportunity for a greater use of a correlation between the SUPAC level of change, and a drug's risk profile. Such that changes consider the tier of a drug, along with the potential for risk and type of change to the drug. A risk profile could place certain sub-categories of drugs into a low tier category, with the result that most--if not all--changes to this specific sub-category of drug would be annual reportable.

2000N-1449

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**Example: Category -- Injectables:**

An intravenous drug solution would be placed into a different sub-category of drug than a lower risk/tiered intraperitoneal drug, e.g. a dialysis solution.

Note: Changes that create a new drug (non-equivalent product), or require clinical studies are not the subject of this comment.

3. SUBMIT DRUG COMPARABILITY PROTOCOL and RISK PROFILES**A) LOW RISK DRUGS**

Expand the SUPAC Guidance to allow manufacturers to submit a comparability protocol that covers a current prior approval SUPAC change. The protocol would be accompanied by a scientifically valid risk profile of the product, such as an FMEA, HACCP or other FDA-specified acceptable method.

B) MODERATE RISK DRUGS

Expand the SUPAC Guidance to allow manufacturers to submit a SUPAC prior approval change with a comparability protocol that covers the same change. Each protocol would be accompanied by a scientifically valid risk profile of the product, such as an FMEA, HACCP or other FDA-specified acceptable method.

C) HIGH RISK DRUGS

No change recommended to SUPAC, at this time.

4. APPROVAL OF COMPARABILITY PROTOCOLS and/or RISK ASSESSMENTS

Considerations supporting the approval of comparability protocols for low risk changes/drugs could also be based upon determinants such as:

- CDER's experience reviewing the drug,
- The drug chemical structure and intended use,
- The industry experience with the manufacture of the drug in the dosage form,
- The drug's safety history (recalls, alerts),
- Availability of data, for the currently approved drug, for comparison to the chemical/physical characteristic, specification and/or method being changed, and
- The cGMP status of the manufacturer.

Example: Manufacturing Process: (SUPAC VII B2)

Currently "*Changes in sterile load configurations that are outside the range of previously validated loads*" are prior approval change. We'd suggest, that the above considerations applied to low risk/tier drugs, could reduce this change to annual reportable if validation studies, conducted per an FDA-approved comparability protocol, prove acceptable distribution, penetration and lethality.

4 REDUCE the REPORTING LEVEL FOR PRIOR APPROVAL CHANGES

A) LOW RISK DRUGS---Once a manufacturer submits and gains FDA approval for a comparability protocol for the SUPAC major change, changes made under the protocol would be annual reportable.



B) MODERATE RISK DRUGS---When the prior approval supplement and the associated comparability protocol received FDA approval, the manufacturer---having demonstrated proper understanding for and collection of the required data for the specific major change---would be approved for conducting this specific change under the approved comparability protocol, and any subsequent changes similar to the specific SUPAC change for the A/NDA drug becomes annual reportable for the manufacturer.

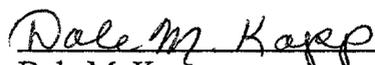
5 OTHER CHANGES SUGGESTED FOR SUPAC:

The Components & Composition Section currently states "*Moderate or minor changes may be covered in other guidance documents*". We request that CDER provide a risk-based guidance, or create a specific SUPAC-SAS guidance for these changes.

The Specifications Section currently states, "*Establish a new regulatory analytical procedure*". We believe FDA should clarify the term "new". FDA applies the interpretation of "new" to mean a change to a procedure/method that is not approved in the drug application. We believe the meaning should refer to a non-USP or non-industry known analytical method. In essence if an analytical method, for example ISE, is recognized as currently used in the industry for the same analysis, we would not consider the method "new". Here we suggest reducing this major change to an annual reportable change.

Fresenius Medical Care North America believes the above comments are just a beginning, and one approach for improving the application of the SUPAC post approval supplement change control process. Thank you for the opportunity to participate in the dialogue on this guidance.

Sincerely yours,



Dale M. Kapp
Supervisor; Drug Regulatory Affairs

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