**PDA commentary on:**

***Guidance for Industry: Content and Format for Submission of Drug Products for Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Abbreviated Antibiotic New Drug Applications (AANDAs), February 6, 1996.***

Explanatory Note:

In early 1996 FDA/CDER provided copies of the above draft guidance to PDA and other organizations for the purpose of informal feedback. The following comments were submitted back to CDER on July 8, 1996.

PDA staff contact: James C. Lyda, x121
July 1996

July 8, 1996

Dr. Albinus M. D'Sa
Food and Drug Administration
5600 Fishers Lane (HFD-170)
Rockville, MD 20857

Re: *Content and Format for Submission of Drug Products for Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Abbreviated Antibiotic New Drug Applications (AANDAs)* , draft, February 1996

Dear Dr. D'Sa:

Enclosed are PDA's comments on the above-referenced draft guidance. These comments are provided in response to the February 21, 1996 meeting with CDER's CMC CC. Most PDA members are associated with companies and products regulated by the Center for Drug Evaluation and Research (CDER) and will be affected by this guidance. For this reason we appreciate the opportunity to provide suggestions on its utility.

For your information, PDA is a nonprofit, international association for pharmaceutical science and technology. The Association was founded in 1946 and specializes in quality assurance and manufacturing issues for pharmaceuticals, biopharmaceuticals and related health care products. Our 7,700 worldwide members include scientists and technical representatives of manufacturers, academia, regulators and suppliers of equipment and services.

PDA will be represented at the July 10, 1996 CDER meeting in which this guidance will be discussed. If you have any questions please contact me.

Sincerely,

Edmund M. Fry
President

Enclosure

PDA Commentary on draft FDA Guidance for Industry:
***Content and Format for Submission of Drug Products for Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Abbreviated Antibiotic New Drug Applications (AANDAs),***
draft, February 1996

We commend FDA on the comprehensiveness of this draft guidance document (referred to as 'the guidance'). It is a useful document that provides a detailed and thorough list of important points to be considered in the preparation of IND, NDA, ANDA and AANDA submissions. The guidance is consistent with the goal of both industry & FDA to submit complete & consistent applications

that meet requirements for market approvability.

PDA's comments on the guidance stress over-arching principles on how it should be regarded and used by *both* those submitting/filing applications and reviewers within FDA. While the Association has included several specific comments, we did not try to catalog each and every discrepancy or technical issue.

**A. Purpose and Use of the Guidance**

**Background:**

The guidance provides a large amount of detailed information and recommendations which could be problematic if applied rigidly. For industry the guidance will be most helpful if the recognized intent is to facilitate technical decisions & application planning. Similarly, FDA should avoid using it as a checklist for application review, requiring applications to address every point. Not every test, specification, or recommendation in the guidance is appropriate for every product, given the diversity of pharmaceuticals today. Specific examples that illustrate this point follow:

- Osmolality or osmolarity test for parenteral solutions (p.24). This test may be appropriate for products with significant amounts of osmolality adjusters or iso-osmotic claims. Osmolality is often assessed during development evaluations, however, such a non-specific test has minimal technical value for routine control for most parenteral solutions.

- Test for extractables (p.24). A routine control test for extractables is not appropriate for most parenterals. Testing is often conducted prior to application submission to demonstrate the suitability of non-glass containers precluding the need for routine control testing.

- Friability (p.19). While such a test may be of value for in-process control of manufacturing, friability is frequently not appropriate or used as a release test.

- Dissolution testing (p.11). Dissolution testing often has no value for oral suspensions as recommended.

**Recommendation:**

Section I, *Introduction,* should be amended to include a paragraph describing the flexible application of this guidance, as follows:

> **FDA recognizes that this guidance offers detailed information which may not be applicable to each and every product or dosage form. The applicant should consider the information in the guidance when applications are being prepared, incorporating information in concordance with the guidance when appropriate for the drug product. Similarly,**

**manufacturers may need to include information not covered in the guidance for some drug products.**

**B. Setting/Changing Specifications:**

**Background:**

At the time of approval of an NDA or an ANDA the applicant usually has a very limited database for use in setting specifications. Typically for an NDA, a small number of pilot scale batches, and 1-3 production scale batches have been manufactured. For an ANDA there may be one or more test batches at the time of submission, which may or may not be production scale. The limited data frequently represents tighter limits and ranges than would be expected in normal production. In addition, applicants frequently encounter what seem to be arbitrary FDA challenges of specifications proposed for new products, resulting in specifications being further tightened.

The net effect is that specifications initially approved in NDA's and ANDA's are frequently set much tighter than necessary to ensure safety, efficacy and potency of the drug product, and also tighter than the new manufacturing process is capable of meeting regularly. Potentially, this sets the stage for unnecessary and costly production batch rejection based on failure to meet specifications over the shelf life of the product.

This scenario has little relation to safety, efficacy or quality of the drug product. Rather it reflects a *process* which results in specifications being set overly tight too early in the drug products market life. Compounding this problem is the difficult & lengthy process of *widening* specifications after they have been approved.

**Recommendation**:

PDA proposes the guidance provide for 'initial' or 'interim' specifications at approval. To set such specifications, applicants should evaluate available batch and stability data, as well as a history of comparable products, to design specifications which are appropriate to ensure the quality of the product over the shelf life. The resulting 'initial' or 'interim' specifications could then be reviewed periodically under a formalized protocol approved in the NDA. If the product history indicates a potential for tighter specifications the applicant would commit to supplementing the NDA/ANDA accordingly.

**C. Other Comments**

1. **Target Composition/Formulation**.

Section II.A.1.d., *Targeted Composition*, states that the quantitative composition "should be formulated with the active targeted at 100% of the labeled claim with any deviation clearly justified and supported." This should be changed to "...not less than 100%..." or otherwise qualified in recognition of 21 CFR 211.101(a), "The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient." This language may help avoid confusion when overages under Section II.A.f. are contemplated, where the new target would be in excess of 100%

This same comment applies to Section II.A.2.a., *Targeted Formulation*.

2. **SUPAC**

The guidance should reflect the recent *SUPAC-IR* guidance issued by CDER, and should be revised as necessary as new SUPAC guidance documents are issued. The ability to readily implement certain component/composition, scale-up/scale-down, and manufacturing process and equipment changes after approval of an original application could have a profound impact on the content of an original application.

3. **Validation of Sterile Processes**.

The guidance restates FDA policy that requires data for validation of sterile processes, either aseptic fill or terminal sterilization, be submitted with the application, and references the December 1993 (republished November 1994), *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

PDA restates its position that validation of sterilization processes should be handled much as the validation of other processes/process changes, i.e. validation data reviewed through field GMP inspections without submission of voluminous data with the application. A copy of PDA's January 31, 1994 comments, amended on April 4 of the same year, is enclosed.

4. **Re-processing operations**.

Section II.3.a. *Reprocessing Operations, Supplemental Applications* requires a pre-approval supplement for any 'reprocessing procedure due to deviations not anticipated in the original application.' This may be excessive, and we suggest the manufacturer can validate and conduct such reprocessing using a change being effected supplement. That supplement could contain all information listed in II.3.b.i.(a-g).

5. **Specifications, Dose Form Specific, particle size limits.**

There are references to limits for *both* upper and lower particle sizes, e.g. *Oral Suspensions/Powders for Suspension* (p.22), *Injectable Suspension*, (p.25). Lower limits are technically troublesome and generally have very limited value. We suggest that upper limits be required, but lower limits be required only "where appropriate and necessary."

- End of Comments -

PDA thanks the following experts who prepared these comments:

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