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December 15, 2005

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

RE: Docket No. 1998D-0266

Dear Sir or Dear Madam:

The opportunity to comment on the draft guide for PET drug CGMP is appreciated. I consult on a regular basis with a major commercial PET drug firm, and to a lesser extent, with several other firms. I have had an opportunity to participate in the management of their quality systems, and thus, to observe intimately their progress in complying with the draft 2002 CGMP guidance. I commend the Agency's revision in response to public comments in 2002. I offer the following comments:

V.A. QA Regulatory Requirements.

On line 286 the guidance states "that all errors are investigated and corrective action is taken." A more appropriate statement would recommend that a firm would determine the need for an investigation and conduct them, when necessary.

V.B.4 Control of Components, Containers and Closures

Beginning on line 694, the guidance allows acceptance of listed items based on meeting internal specifications and examining a CoA. A notable exception to this list is microbial growth media, opening the way for an unnecessarily required Growth Promotion Test (GPT). It is inconsistent with FDAMA and an unnecessary hardship for PET firms to conduct a GPT for commercial media. Firms would have to establish microbiological labs at each site at considerable expense of manpower and resources. Growth media is a robust product with a conservative expiration date. If the Agency is not confident with commercial media suppliers, I suggest that they be brought under Agency oversight. Please add this item to the subject list.

XI.B. Finished Drug Product Controls: Finished Product Testing

Section B, beginning on line 1185 and other parts of Part XI, imply that every specification listed in an NDA would be tested for every batch of product, except sterility testing, when indicated. Agency policy recognizes that historical data and verification testing are more important than individual tests. Consider the following statement from the Tests and Assays section of General Notices of USP 28:

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"Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for ensuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards."

I strongly recommend a revision of this section to recognize the value of in-process controls and process validation and to allow a manufacturer to omit an analytical test in the presence of overwhelming data that supports the safety and efficacy of a batch of PET drug product.

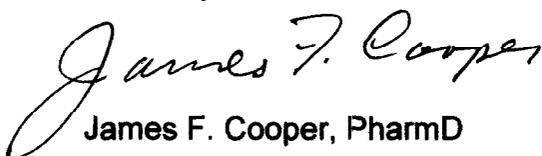
XI.B. Finished Drug Product Controls: Conditional Final Release

Under the time constraints of PET drug production, there will be invalid suitability tests, equipment malfunction and other invalidity issues that will occur and delay the timely release of a PET drug product. In my four-year experience of working with a major PET drug supplier and reviewing non-conforming results, I have learned that these incidents relating to conditional release are common, probably in the range of 1% of all batches. The Guidance statements that these occurrences are rare or extremely infrequent, as stated in line 1263, are simply untrue and out-of-touch with reality. PET drug producers know which analytical tests are essential to verify safety and efficacy and which tests are done simply to verify that product attributes are consistent with historical data. It is essential to recognize that the unnecessary delay or cancellation of a PET drug study due to inappropriate conditional release criteria impacts adversely on patients scheduled for imaging procedures. I recommend the following revision to replace this section:

"When one of the required finished product tests cannot be completed due to a breakdown of analytical equipment, inconclusive result or an invalid test condition, proposed 212.70 (f) allows PET producers to release the drug product for human use. Written procedures would specify which finished product tests meet the criteria for conditional release, what action is taken to resolve the cause of an omitted test and how the conditional release action is documented. If equipment is properly maintained, breakdowns should be infrequent. We recommend that PET producers determine if an omitted test adversely affects the safety and effectiveness of the PET drug product. All activities of conditional release should be properly documented."

I may be reached at jimandfran@att.net for further interaction.

Sincerely,


James F. Cooper, PharmD