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Division of Dockets Management (HFA-305)
Food and Drug Administration
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The following comments relate to the June 2010 *draft Guidance for Industry: CMC Postapproval Manufacturing Changes Reportable in Annual Reports.*

Please provide objective criteria for the following points. In every case, the FDA is saying that a change should be reported in an annual report, not a CBE 30 or a PAS, provided that the company feels in good faith that there is no impact. No company has ever made a change while believing that the change would have an adverse impact on quality. Determining whether a change has impact is the proper role of a regulatory agency.

I understand that some changes are categorically riskier than others. The final guidance should have objective criteria instead of appealing to good faith. Objectionable sections are the following, all from Appendix A.

1.3 "New supplier of inactive ingredients that have a minimal effect on product performance in the drug product." This section should include, "with the exception of functional excipients that act as a preservative or that determine the release rate of modified release formulations."

2.1. "Modification of an approved manufacturing facility that does not affect a product manufacturing area or sterility assurance and does not change product quality or specifications." This section should be stricken. As written, a company could obtain approval for one facility, then build an entirely new facility at the same address, and the FDA would find out during the next annual report. With this sentence, FDA is abdicating pre-approval jurisdiction over all facility design issues. Quickly, some the industry will inevitably learn that they can obtain approval for a showcase facility, then move their production to a swamp post-approval (provided that the company felt that the swamp did not change product quality). Since FDA seldom inspects plants overseas, and FDA reviews annual reports only cursorily, an unethical company could get away with this strategy for years.

4.6 “Replacement of blend uniformity and in-process homogeneity tests with other appropriate testing that assures adequacy of mix.” FDA should specify appropriate tests. Again, a company can obtain approval with a stringent blend uniformity test, change their equipment (3.3), change the scale (3.2), and then change their test. As long as the company believes in good faith that the blend uniformity test is good enough, FDA will not know about the change before a year’s worth of batches are on the market.

4.9. “Deletion of the homogeneity test as a routine test from the application, provided the applicant has process controls in place to demonstrate the product’s homogeneity.” This section should be heavily qualified or stricken. As argued before, a smart company will file a homogeneity test, then immediately remove the test after approval. With this sentence, FDA removes the requirement to perform any tests of homogeneity in-process (provided that the company believes in good faith that their “process controls” are appropriate). FDA should specify the nature of necessary process controls that can substitute for a homogeneity test.

6.2. “Reduction of expiration dating for a drug product for reasons other than stability failures.” FDA should specify which reasons are appropriate. If a product is near failure but has not actually failed yet, a company’s decision to reduce the expiration dating should be reviewed by FDA.

It seems that FDA wrote the guidance with particular scenarios in mind, but the proposed wording allows unethical companies far too much leeway. In the real world, unclear guidance means everything goes.

Sincerely,

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