

Docket No. 2006N-0525

15 February 2007

Dear Sirs,

Please find hereunder the comments from:

DSM Anti-Infectives
P.O. Box 425
(mail-stop 530-0373)
2600 AK Delft
The Netherlands

Contact person: Chris Oldenhof, Ph.D.
Manager External Regulatory Affairs
Tel: +31 15 2792361
Fax: +31 15 2793632
e-mail: chris.oldenhof@dsm.com

DSM Anti-Infectives, a Business Group of the Dutch company DSM, is one of the world's leading manufacturers of antibiotic APIs and -intermediates. Our Business Group has eleven wholly- and partly owned manufacturing sites worldwide, and is the holder of about twenty US DMFs (many of which were formerly approved AADAs for bulk) submitted to and in majority previously reviewed and found acceptable by the FDA. We highly appreciate this opportunity for submitting our comments on the revision of 21CFR 314.70 that is of great importance to our products and operations.

The current regulatory system forms a high barrier to continuous improvement and innovation in particularly the dedicated manufacture of APIs. The barrier to improvement is highest with regards to dedicated manufacturers of the older, mainstay APIs that are being supplied to multi-customer environments. We understand that a key objective of the FDA Pharmaceutical Quality Assessment System (PQAS) in the 21st Century is to encourage continuous improvement and innovation in pharmaceutical manufacture, including APIs. Another FDA objective is to drastically bring down the total number of manufacturing Supplements with up to 80%. Both objectives can probably only be achieved if the regulatory system for APIs will be drastically adapted.

The revision of 21CFR 314.70 will be a key step in reaching these objectives. The current DMF-based structure for submitting information on dedicated API manufacture implies that one change in an API DMF may trigger up to hundreds of (A)NDA Supplements. This causes extensive duplication of submissions and review or - much more often- it results in the decision by the manufacturer to refrain from implementing the improvement at all. Even worse: If an involved company would be one with insufficiently high ethics it may also result in implementation of the change without any notification at all, neither to FDA nor to the (A)NDA holders.

FDA's current review approaches normally require that the impact of each change to API manufacture will be assessed separately for each final drug product i.e. in relation to

each affected (A)NDA. For this reason the approval of DMFs is until now not being regarded by the FDA as a fully realistic option (even though such option has existed for antibiotic APIs via bulk AADAs, until the FDAMA was implemented).

The challenge is to define a new approach with regards to APIs that on the one hand will foster improvement and innovation in API manufacture and on the other hand will continually secure (or even improve!) the safety of medicines. If from a 21st Century PQAS point of view neither DMF approval, nor limiting down the level of detail in DMFs down to ca. 10% of what is the usual approach today would be acceptable options, then the only way forward lies in a large shift from post-approval change oversight through review of submitted paperwork to oversight through on site inspections.

For situations in which the producer of an API and the producer of the dosage form are two different companies important focus of inspections will then need to be on the adequate functioning of the interface between these companies. If both companies adhere to modern quality management systems and -philosophies the management of change at such interface will normally receive high priority from both sides.

In multi-customer systems the shift to an inspectional approach will of course still imply the existence of multiple interfaces between an API producer and its customer companies. The appropriate management of change through such multiple interfaces is a difficult task but -as opposed to operating via fully DMF/ANDA-based oversight- a feasible one.

Filling in the details of the paradigm shift from reviewing paperwork to including change oversight firmly within on site inspections goes beyond the scope of these comments.

We believe that the above approach will be fully in line with the basic philosophy for the 21st Century PQAS. It would imply that drastic relaxation of regulatory oversight on information in DMFs should only be available to companies that have committed to the 21st century PQAS principles (Q8-Q9-Q10-PAT) and that have proven to comply with those.

We also believe that by removing barriers to continuous improvement and innovation in API manufacture and by thus creating a workable system the dilemmas for industry that may come down to the choice of going "Out of Business vs. Out of Compliance" will be resolved. The chance of companies deciding to choose for unnotified implementation of changes in API manufacture would thus decrease strongly. Therefore, the proposed new approach will not only consolidate the current level of safety of our medicines: It will most probably significantly improve it. The current post-approval change authorization system is inadequate and is malfunctioning with regards to protecting the patient. The need to create something better is evident.

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