



Division of Dockets Management
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Food & Drug Administration
5639 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

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Comments on the Revision of 21CFR 314.70 on Supplements and Other Changes to an Approved Application

Please find hereunder the comments from APIC:

Introduction

CEFIC is the European organization of the chemical industry representing national federations, companies and more than 100 affiliated associations and sector groups, located in Europe. All together CEFIC represents directly or indirectly more than 29,000 large-, medium- and small chemical companies in Europe, which employ about 1.7 million people and account for nearly a third of the world chemical production.

APIC is one of CEFIC sector groups, comprising European producers of active pharmaceutical ingredients (APIs) and intermediates. This product range implies that APIC is a major stakeholder regarding new FDA regulations and guidelines, in particular for those that affect APIs and intermediates.

We, therefore, highly appreciate this opportunity for submitting our members' comments on the upcoming revision of 21CFR 314.70 that is of direct relevance and in fact of enormous importance to our industry sector.

APIC Comments

1. A revision of 21CFR 314.70 in line with a more risk based and quality systems oriented approach for regulatory postapproval CMC changes would be valuable because it would be consistent with the FDA Pharmaceutical Quality Assessment System aimed at promoting continuous improvement and innovation in API manufacture.

It should therefore provide flexibility for API manufacturers to assume their own responsibility, especially also in cooperation with their customers (the dosage form manufacturer) for many of their post-approval changes. There is very much room for improvement here because the current post-approval change authorization system is in many situations unworkable, especially within „multi-customer systems“ in which an API is supplied to a multitude of dosage form manufacturers.

2. Considering risk-based approaches and manufacturing process understanding, manufacturers should be primarily responsible for ensuring product quality based on commitment to adhere to PQAS principles (Q8-Q9-Q10-PAT)
3. Drastically redefining which (major) manufacturing changes would require prior approval should significantly reduce the regulatory burden on the pharmaceutical industry as well as the workload for FDA. Flexibility should be adopted that will make it possible to submit non-major changes in Annual Updates / Annual Reports or to entirely remove the need for submission of those changes and instead require that all information on the appropriate management of such changes will be available for on-site inspections. In situations that the API manufacturer and dosage form manufacturer(s) are different companies the inspection focus should include the proper functioning of the management of change at the interface(s) between the companies.
4. The simplification of regulating post approval CMC changes would be advantageous for all stakeholders regarding the regulatory process, i.e. for the manufacturer, the regulatory authorities and last but not least for the patients.
The greater regulatory flexibility should be such that it will promote:
 - the consistent production of high quality, safe and efficacious product
 - the use of quality by design
 - the adoption of risk management approaches
 - the harmonization with other quality management systems throughout society
5. We believe that removing barriers to continuous improvement and innovation in API manufacture will be a crucial step for increasing the safety of medicines: A post-approval change system that will be workable for all parties involved will be the way forward towards preventing that certain companies might choose for the potentially very harmful approach of unnotified implementation of changes in API manufacture.

We trust that you will take our comments into consideration and look forward to hearing from you soon.

With our best regards,

Pieter van der Hoeven
APIC Secretary General
Cefic (European Chemical Industry Council)
E-mail: pvd@cefic.be
Phone: +32.2.676.72.02
Fax: +32.2.676.73.92