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| Title: Post Approval Equipment Changes to API Manufacturing Processes | | | | | |
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Introduction

API equipment changes after the final intermediate only require a revision to registrations if the equipment has been explicitly described in a registration commitment or if pre-/post-change chemical and physical equivalence of the API cannot be demonstrated or if there is an effect on the drug product.

Practice

The expectations or requirements for API equipment changes defined in FDA or other Health Authority guidance DO NOT extend beyond the language of the registration commitment defined by the current registered API Regulatory Process Description (RPD) EXCEPT when appropriate chemical and physical equivalence of the API cannot be shown or when the change is shown to have an effect on the drug product. This position applies to API registration commitments described in NDAs, ANDAs, NADAs, ANADAs, Drug Master Files, Certificates of Suitability, Marketing Authorizations or equivalent regulatory documents.

Consistent with FDA BACPAC I Guidance, equipment changes prior to the final intermediate need not be reported even if the equipment has been specified in the approved registration. The elements of the site work process for API equipment changes after the final intermediate are:

- The sponsor of a proposed change prepares a protocol to demonstrate equivalency of the API before and after the change.
- The equivalency protocol is reviewed and approved by site Quality Operation, Process Technology and Manufacturing Services.
- A Product Change Proposal (PCP) is prepared and sent to Manufacturing Compliance describing the proposed change and requesting an assessment of the change against the language of the approved Regulatory Process Description (RPD) and any other registration commitments that describe API manufacturing.
 - If current process equipment is explicitly described in a registration commitment, a revision to the registration may be required prior to the site implementing the change.
 - If current process equipment is not explicitly described in a registration commitment and equivalence of the API and drug product can be demonstrated, no registration update is needed.
- The sponsor of the change decides whether or not to proceed based upon the regulatory assessment and results of the equivalency study.
- Once a particular type of equipment change has been established as equivalent for a given API process and the registration reviewed by Manufacturing Compliance and revised as needed, subsequent interchanges of such equipment for a specific API process may be handled at the site level and need not be reviewed by Manufacturing Services.

General Discussion

The filing requirements presented in guidance documents, such as FDA's Guidance to Industry –

Guidance 130 - Post Approval Equipment Changes to API Manufacturing Processes

should be included. If the phrase “isolated by filtration” is used, relevant examples should be included, e.g. basket centrifuges, Heinkel centrifuges, pressure filters and vacuum filters.

As API manufacturing process descriptions are updated, the terminology used should be assessed on a case-by-case basis, but there is no need to proactively update existing process descriptions that include the language “isolate by filtration.”

Other API operations, e.g. drying, de-agglomeration, milling, should also be defined or described generically in the RPD if the nature of the equipment, technology or conditions used to accomplish the operation are not critical. Where the language of our current regulatory commitment is generic or silent on the nature of the equipment used after the final intermediate, no revision to the registration is required unless pre-/post-change equivalence cannot be demonstrated.

An assessment of the impact of a change on the equivalence of the API should be performed, and an assessment of impact on the drug product(s) may also be necessary. The site Quality Operation function should require demonstration of chemical and/or physical equivalence of the API or drug product. When necessary, appropriate registration revisions must be made before the change may be implemented. Equipment changes to API manufacturing must be managed by the Product Change Proposal process and reviewed by Manufacturing Compliance to determine whether a regulatory filing will be required. Once a particular type of equipment change has been established as equivalent for a specific API process and the registration reviewed by Manufacturing Compliance and revised as needed, subsequent interchanges of such equipment for a particular API process may be handled at the site level and need not be reviewed by Manufacturing Compliance.

The content of this document focuses on post-approval equipment changes after the final intermediate in API manufacturing. This practice may be a model for other types of post approval changes that are transparent to the language of the API process information in the currently approved registration documents. Such changes should be addressed case-by-case using the Product Change Proposal work process and the principles discussed here.

References

- 1) Guidance for Industry – Changes to an Approved NDA or ANDA, U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), April 2004, Revision 1.
- 2) Guidance for Industry – BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post approval Changes: Chemistry, Manufacturing, and Controls Documentation, U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Centre for Veterinary Medicine (CVM) February 2001.