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September 29, 2000



Dockets Management Branch (HFA-0305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**RE: Docket No. 00D-1418: International Conference on Harmonization;
Draft Guidance on Good Manufacturing Practice for Active Pharmaceutical
Ingredients**

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$2 Billion annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

Merck supports and adheres to the ICH Q7A guidance which was developed for Good Manufacturing Practice (GMP) for active pharmaceutical ingredients (API). We, however, have these following comments for consideration.

SPECIFIC COMMENTS:

Line 200: 3.12 Training should be regularly conducted by qualified individuals and should cover as a minimum the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. The practical effectiveness of the training should be periodically assessed.

Comment: It is unclear as to how one is to assess "the practical effectiveness of training" and what is meant by "periodically". This assessment is not required in finished product GMPs.

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Line 518 **6.40** To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

Comment: A system in which the quality unit approves changes to master production instructions should be sufficient. In this case a signature by a person in the quality unit on the production instruction master may not be needed.

Line 633 **Section 7.1 General Controls (7.11, 7.13 and 7.14)**

Comment: The term 'critical material/critical raw material' are used in this section. These terms should be defined in the glossary.

Line 655 **7.22** If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. ..Means of providing assurance could include one or more of the following:

- Certificates of cleaning
- Testing for trace impurities
- Audit of the supplier

Comment: It is suggested that the sentence be revised to state that the listed are examples of means of providing assurance of no cross-contamination, however, other documents (eg letters of guarantee) may also be appropriate. the important point is to verify cleanliness / cross-contamination control

Line 668: **7.30** At least one test to verify the identity of each batch of material should be conducted with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis may be used in place of performing other tests provided that the manufacturer has a system in place to evaluate suppliers.

Comment: It may be appropriate to include exceptions for inter-site movement of materials within the same company. This exception should apply to API used for marketed product and clinical supplies (See **Section 19.40**).

It is recommended that intra-company shipments of intermediates should be exempt from testing requirements, including identity testing, if the seals on the containers are intact.

Line 673 **7.31** Supplier approval should require an evaluation including adequate evidence (e.g. past quality history) that the supplier can consistently provide material meeting specifications.

Comment: It is recommended that the term 'supplier' be replaced by 'manufacturer' since the supplier may only distribute the material.

Line 742 **8.15** Any deviation should be documented and explained. Any critical deviation should be investigated.

Comment: It is recommended that the first sentence requiring any deviation to be documented and explained be deleted. The important point is that critical deviations should be documented and investigated. Deviations from controls established for safety and environment purposes do not need to be documented as GMP deviations. If it is not acceptable to entirely remove this sentence, then the phrase 'where appropriate' should be added to the sentence.

Line 885 **9.42** For intermediates or APIs with a retest date, the retest date should be identified on the label and/or Certificate of Analysis.

Comment: It is recommended that for intermediates, the inclusion of the retest date on the label should only be necessary if the intermediate is to be transferred outside the control of the manufacturer's material management system. Currently, it is not clear in the guidance if this applies to all intermediates including isolated intra-site intermediates destined for further processing. Alternate systems of control are normally used within a site processing unit.

Line 953 **11.16** Out of specification results obtained should be investigated and documented according to a procedure.

Comment: OOS investigations should exclude tests of a non-GMP nature, e.g. deviations from controls established for safety and environment purposes. Additionally, the following exception to the requirement for investigation of out-of-specification results should be included: Results from in-process tests that are carried out for the purpose of monitoring the process, e.g. pH and KF results prior to end point being reached (See section 8.20).

Line 997 **11.40** Authentic Certificates of Analysis should be issued for each batch of intermediates or API on request.

Comment: This needs to be clarified to indicate that a Certificate of Analysis should not be needed for intermediates or APIs which remain within the control of the manufacturer's material management system, (i.e. are not shipped off-site).

Line 1007 **11.43** "Certificates should be dated and signed by authorizedthe original manufacturer."

Comment: The information required on the Certificate of Analysis is too detailed. Instead, it is recommended that this section be rephrased to state that 'Certificatesshould show the identity of the original manufacturer' instead of the 'name, address and telephone number of the original manufacturer.'

Line 1460: **Section 18. Specific Guidance for APIs Manufactured by Cell Culture/Fermentation**

Comment: This section contains a significant amount of detail much of which may go beyond the scope of GMPs. The discussion takes on a more operational tone which might be found in a Standard Operational Procedure.

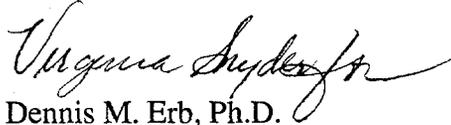
This section also seems to be silent on the unique nature of certain raw materials that may be utilized in fermentation operations (e.g., lard water). It may be appropriate to include some latitude relative to the release requirements (e.g., based on manufacturer's analysis or guarantee) for these types of materials, especially when meaningful testing relative to API quality may not be available.

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Line 1634 19.40 Raw material used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing.

Comment: It may be appropriate to include exceptions for inter-site movement of materials within the same company. This exception should apply to API used for marketed product and clinical suppliers. (See Section 7.30)

Sincerely,



Dennis M. Erb, Ph.D.
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