Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance

Packaging and Labeling Control

1. Do CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability-indicating?

No. Drug product stress testing (forced degradation) may not be necessary when the routes of degradation and the suitability of the analytical procedures can be determined through use of the following:

- data from stress testing of drug substance
- reference materials for process impurities and degradants
- data from accelerated and long-term studies on drug substance
- data from accelerated and long-term studies on drug product

Additional supportive information on the specificity of the analytical methods and on degradation pathways of the drug substance may be available from literature sources.

Section 211.165(e) of the CGMP regulations states that the accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented. Further, section 211.166(a)(3) requires that stability test methods be reliable, meaningful, and specific, which means that the content of active ingredient, degradation products, and other components of interest in a drug product can be accurately measured without interference, often called "stability-indicating."

The CGMP regulations do not specify what techniques or tests are to be used to ensure that one’s test methods are stability-indicating. However, evaluating the specificity of the test methods during forced degradation studies (i.e., exposing drug to extremes of pH, temperature, oxygen, etc.) of drug substance and drug product often is necessary to ensure that stability test methods are stability-indicating. But in certain circumstances conducting a forced degradation study of just the drug substance may be sufficient to evaluate the stability-indicating properties of a test method.

Generally, in determining whether it is necessary to conduct forced degradation studies of the drug product, the specificity of the test method should be evaluated for its ability to

assay drug substance, degradants, and impurities, in the presence of each other, without interference. The evaluation also should provide assurance that there is not a potential for interaction between drug substance, degradants, impurities, excipients, and container-closure system during the course of the shelf-life of the finished drug product.

Last, the rationale for any decision made concerning the extent of the forced degradation studies conducted as well as the rationale for concluding that a test method is stability-indicating should be fully documented.

References:

- 21 CFR 211.137: Expiration dating
- 21 CFR 211.165(e): Testing and release for distribution
- 21 CFR 211.166(a)(3): Stability testing
- Compliance Policy Guide, Section 480.100 (7132a.04), *Requirements for Expiration Dating and Stability Testing*

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2. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?

Yes. Generally, we believe that sampling in a typical drug manufacturing facility warehouse would not represent a risk to the container/closure or affect the integrity of the sample results. But whether the act of collecting a sample in the warehouse violates the CGMPs requirement that containers "be opened, sampled, and sealed in a manner designed to prevent contamination of their contents..." will depend on the purported quality characteristics of the material under sample and the warehouse environment. For container/closures purporting to be sterile or depyrogenated, sampling should be under conditions equivalent to the purported quality of the material: a warehouse environment would not suffice (see 211.94 and 211.113(b)). This is to preserve the fitness for use of the remaining container/closures as well as ensure sample integrity, if they are to be examined for microbial contamination. At a minimum, any sampling should be performed in a manner to limit exposure to the environment during and after the time samples are removed (i.e., wiping outside surfaces, limiting time that the original package is open, and properly resealing original package). Well-written and followed procedures are the critical elements.

Note that the CGMPs at 211.84 permit a manufacturer to release for use a shipment of containers/closures based on the supplier's certificate of analysis and a visual identification of the containers/closures. Once a supplier's reliability has been established by validation of their test results, a manufacturer could perform the visual examination entirely in the warehouse.

References:

- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures

- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.113(b): Control of microbiological contamination
- 21 CFR 211.122: Materials examination and usage criteria

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