PROCEDURES

OFFICE OF GENERIC DRUGS

Reviewer Determination of Major/Minor Amendments to Abbreviated New Drug Applications (ANDAs)

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PURPOSE

The purpose of this MAPP is to provide chemistry review staff in the Office of Generic Drugs (OGD) with expanded information regarding amendment requests to original and supplemental ANDAs. This information is meant to help reviewers determine whether an amendment should be categorized as major or minor to ensure consistency of those determinations across the chemistry review divisions.

BACKGROUND

In 2001, OGD issued a revised guidance to industry on *Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications* (Rev. 2, December 2001). OGD recently determined that its reviewers would benefit from additional information to clarify the type of amendment appropriate for the deficiencies identified. In response, a cross-section of OGD chemistry reviewers (led by a chemistry supervisor) developed a list of specific examples where a major or minor amendment would be appropriate as listed in the revised guidance.

PROCEDURES

OGD chemistry reviewers should apply the examples provided below to facilitate their determination of amendment request designations, and team leaders and chemistry supervisors should ensure that the designations are consistently applied and the amendment designations in the resulting deficiency letters (as applicable) are correct.

1. Clarification of when a new batch may result in a major amendment designation (as noted in II. Policy, Section B.1 of the revised guidance to industry on *Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications*):

   - ***Composition change or reformulation.*** Changes in composition or formulation that may not result in a new batch being required as a condition for approval, but only as a post-approval commitment, would not require a major amendment. Examples of such changes could include change of color (Yellow #5 to Yellow #10) or changes comparable to those designated as Scale-up and Postapproval Changes (SUPAC) Level 1 changes.[1]

   - ***Change in the source of a drug substance.*** This is a major amendment because a new batch of drug product is required.

   - ***Major change in the drug substance manufacturing process.*** Cases that result in a change to the ANDA holder's drug substance specifications (e.g., impurity profile, polymorphic form, etc.) would result in a major amendment.

   - ***Major change in drug product manufacturing process.*** This would result in a major amendment. An example is a change from dry to wet granulation (or vice versa). Refer to the guidance to industry on *Changes to an Approved NDA or ANDA* (April 2004) for additional examples of major manufacturing process changes that would result in a major amendment.

   - ***Change in manufacturing site.*** A change in the drug substance or drug product manufacturing site that requires an inspection would result in a major amendment.

   - ***Need for a new bioequivalence study (21 CFR 320.21).*** This always results in a major amendment.

   - ***New in vitro study for a specific product (e.g., metered dose inhalers).*** The need for this study demonstrates that the application requires a major amendment. Other products to which it applies are transdermal patches, nasal sprays, or novel dosage forms such as liposomal products and those with nanoparticles.

   - ***New strength of the product.*** This always results in a major amendment.

   - ***Unacceptable impurities or impurity levels (21 CFR 314.94(a)(9)).*** This results in a major amendment if the proposed impurity levels for individual impurity levels did not meet the requirements in the ICH *Q3A(R2) Impurities in New Drug Substances* and *Q3B(R2) Impurities in New Drug Products* guidance documents at product release and in stability testing. This includes observed levels that were

[1] The most recent versions of the SUPAC guidances are available on the FDA Drugs guidance web page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

higher than ICH Q3B(R2) qualification threshold (QT) and did not include any justification or qualification. On the other hand, such observations result in a minor amendment if the impurities were below ICH Q3B(R2) QT but higher than those in the reference listed drug (RLD). See the additional considerations below under "Failed stability data."

- ***Unacceptable excipients found during the review (21 CFR 314.94(a)(9)).*** This refers to excipients not previously used in an FDA-approved product or to excipients proposed at higher levels (based on the maximum daily amount of the excipient) than previously approved. If qualification data are not provided to support the safe use of the excipient, reformulation will be necessary—and thus would result in a major amendment.

- ***Failed stability data.*** Judgment in particular situations may be needed to determine the appropriate amendment category. For example, if the accelerated data fails, the reviewer should ask for intermediate data. If the intermediate and long-term data are acceptable, any additional data needed results in a minor amendment. However, if the data reviewed indicate that at least 12 months of real-time stability was needed, it may result in a major amendment.[2]

- ***Change in the container-closure system (other than solid oral dosage forms).*** This point deals with matters such as leachables and changes such as those for inhalation products and autoinjectable products. The examples of changes described as major and needing a prior approval supplement that are discussed in the guidance to industry on *Changes to an Approved NDA or ANDA* (April 2004) are appropriate descriptions for changes that result in a major amendment designation.

  These changes include:

  - For liquid products, a change to or in polymeric materials of primary packaging components not used before in a CDER-approved product for that dosage form.

  - For liquid products in permeable or semi-permeable containers, a change from an ink and/or adhesive used on the packaging never used in a CDER-approved product for the same dosage for and with the same type of permeable or semi-permeable packaging.

  - Change in the primary packaging components for any drug product when the primary packaging components control the dose delivered to the patient.

[2] Determinations made about acceptable impurities, etc., might affect whether the stability data would be found acceptable. However, such determinations are covered in the bulleted item, "Unacceptable impurities or impurity levels."

- Any change that may negatively affect drug product sterility assurance, as determined by a microbiology review.

- Deletion of secondary packaging components intended to provide additional protection to the drug product or change in the composition or addition of secondary packaging that may affect the impurity profile of the drug product.

- Change to a new container/closure system if the new system does not provide the same or better protective prosperities as the approved container closer system.

2. Clarification of instances when new analytical methods and/or full validation data (as noted in II. Policy, Section B.3 of the revised guidance to industry on *Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications*) may result in a major amendment:

   - If the existing methods have not been shown to be stability indicating. For example, if the firm uses thin layer chromatography or titration for its assay with no information about related substances and does not have a corresponding stability indicating method.

   - If the existing method lacks mass balance so degradation products cannot be quantitated accurately.

   - If the existing method is not sensitive enough to adequately quantify genotoxic impurities and others types of toxic impurities.

   - However, if only method verification is needed, the amendment could be categorized as minor.

3. Examples of situations that describe an application as being of "overall poor quality" (as mentioned in II. Policy, Section B.3 of the revised guidance to industry on *Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications*) and thus result in a major amendment:

   - As appropriate, an application missing any of the basic quality by design (QbD) elements such as the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA), Critical Process Parameters (CPP), and Control Strategy could result in a major amendment. Without such information, it would not be clear in the application that the sponsor had adequate product and process understanding. In some instances, the applicant may provide enough justification for this to result in a minor amendment.[3]

[3] This point will be applicable once QbD is fully implemented in 2013.

- If, after several review cycles, a drug master file (DMF) holder has not been able to provide adequate information in the DMF (e.g., unacceptable impurity levels or need for pharm-tox consult) to support ANDA approval, it would be necessary to issue a major amendment.

- There is a lack of consistency between Modules 2 and 3 in an application that would result in a major amendment.

- If the reviewer finds data from an ANDA that is different from or unrelated to the ANDA purportedly under review, a major amendment could be issued. Such lack of quality oversight may call into question the firm's quality management system and raise questions about the quality of the manufacturing process.

4. Examples of situations that apply to the "not all-inclusive" phrase (as mentioned in II. Policy, Section B of the revised guidance to industry on *Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications*) and thus result in a major amendment[4]:

    - The API differs from the description in the United States Pharmacopeia (USP) in terms of polymorph or waters of hydration (without petitioning USP to incorporate the differences via the flexible-monograph approach).

    - There is a lack of or inadequate critical in-process and release controls such that the firm cannot demonstrate it has the ability to consistently manufacture a high-quality product.

    - The firm does not follow significant recommendations in guidance to industry or does not provide any rationale as to why it did not follow the available guidance to industry. This point is of particular interest with more complex products (e.g., inhalation, transdermal).

    - There are unacceptable levels of extractables or leachables originating from the packaging of susceptible dosage forms such as injectables and other solutions.

    - The need for a pharmacology/toxicology consult exists because of high impurity or solvent levels or use of solvents not included in ICH *Q3C(R5) Impurities: Guideline for Residual Solvents.* Applicants should meet ICH Q3C(R5) and USP <467> Residual Solvents/Organic Volatile Impurities requirements with respect to solvents. If not, a major amendment will be requested.

    - There is a lack of environmental assessment when it is needed for plant-derived products.

[4] This point includes ANDAs that are missing studies or critical information, but do not need a new batch.

- There are issues with physical attributes that affect patient acceptance, compliance, or safety in a drug product that would result in a need for reformulation or significant process development work, and thus need new batches. Examples of such issues include very large tablets or capsules that affect swallowing; large, extended-release minitablets in a capsule that is labeled to allow administration by sprinkling its contents onto food; undesirable smells from residual solvents; excessive tablet friability; inappropriate scoring (i.e., scoring when the RLD is unscored or no scoring when the RLD is scored); or a lack of coating if the coating protects against irritation in the digestive tract.

REFERENCES

1. Guidance to Industry, *Changes to an Approved NDA or ANDA,* April 2004
2. Guidance to Industry, *Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications,* December 2001
3. ICH Guidance to Industry, *Q3A(R2) Impurities in New Drug Substances,* June 2008
4. ICH Guidance to Industry, *Q3B(R2) Impurities in New Drug Products,* July 2006
5. ICH Guidance to Industry, *Q3C(R5) Impurities: Guideline for Residual Solvents,* February 2011
6. SUPAC guidances, available at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
7. USP <467> Residual Solvents/Organic Volatile Impurities, June 2007

EFFECTIVE DATE

This MAPP is effective upon date of publication.