FDA Perspectives: Common Deficiencies in Abbreviated New Drug Applications: Part 1: Drug Substance

Team leaders in FDA's Office of Generic Drugs provide an overview of common deficiencies cited throughout the CMC section of abbreviated new drug applications.

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The ever increasing workload at the Office of Generic Drugs (OGD) within the US Food and Drug Administration's Center for Drug Evaluation and Research (CDER) has led the office to develop a number of strategies to streamline the review process. One such strategy was the introduction of Question-Based Review–Quality Overall Summary (QbR–QOS). Another strategy involves asking sponsors of abbreviated new drug applications (ANDAs) to provide a Pharmaceutical Development Report with their application.

The QbR is a platform for implementation of CDER's Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach and a springboard to quality by design (QbD). It also provides the sponsors with an opportunity to discuss the development of their product. The summary report in QbR-QOS can be referenced by the reviewers as a snapshot of the ANDA before they review the entire application (i.e., the body of data). Adequate information provided in the QbR–QOS and the Pharmaceutical Development Report reduces the application assessment time, minimizes transcriptional errors, and helps the review process at all levels (primary, secondary, and tertiary).

Examples of commonly cited drug-substance related deficiencies in ANDAs (as paraphrased by the authors)

Examples of commonly cited drug-substance related deficiencies in ANDAs (as paraphrased by the authors)

1. The Drug Master File (DMF) related to the drug substance is deficient, and the holder has been notified. Please do not respond until the DMF holder has responded to all the deficiencies.
2. The general properties section (S.1) of the ANDA fails to contain all relevant information. Please provide hygroscopicity, solubility as a function of pH, and melting range for the drug substance.
3. Please revise the characterization section (S.3) to include full IUPAC names, structures, and classification of the impurities as process related and/or degradation products.
4. Please tighten or justify the proposed limits for the specified impurities based on ICH Q3A on impurities in new drug substances recommendations taking into account maximum daily dose (MDD).
5. Please revise the unknown impurities criteria to be in-line with ICH Q3A recommendations based on the MDD. Impurities observed above the recommended identification threshold should be identified, and impurities observed above the recommended qualification threshold should be suitably qualified.
6. Residual solvent criteria should be in line with the DMF holder's limits, as they are process related impurities. Please consult your DMF holder and revise your criteria accordingly.
7. Please consult your DMF holder to ensure all potential process impurities (e.g., metal catalysts or reagents) are included or controlled in the proposed specifications.
8. Please add justified specifications for the full range of particle size distribution. Alternatively, please provide justification that particle size is not critical to the manufacturing process and drug product performance.
9. Based on the literature, multiple polymorphic forms are possible. Please provide the form used and add a suitable control to ensure consistency in the drug substance.
10. Please include a suitable test and justified criterion for water content of the drug substance.
11. Please add a quantitative control of the counter-ion in your drug substance.
12. Based on the chiral nature of the drug substance, please include a control for the relevant enantiomer and diastereomers.
13. In view of the chiral nature of the drug substance, please include a chiral identity.
14. We recommend a chiral assay of your drug substance, since it is prone to racemization on storage.
15. As validated methods were transferred from the DMF holder, please provide verification data to demonstrate that the methods can be performed at the proposed facility.
16. Please provide a USP cross-over study for the assay method to demonstrate the proposed method is equivalent or better than the compendial method.
17. We recommend that a chromatographic method be proposed for the analysis of drug substance assay.
18. Please revise the certificate of analysis to report impurity results as discrete numerical values instead of as "conforms." If results are below the method limit of quantitation (LOQ), please report as less than LOQ; and if results are below the limits of detection (LOD), please report as less than LOD or "none detected."
19. Please provide LOD and LOQ for all specified impurities and residual solvents.
20. Please provide information on all impurity reference standards used, including lot number, source of the standard, and purity.

Also, by seeking sponsors' responses to critical questions regarding the quality of their drug product, the QbR has helped to reduce the number of deficiencies cited for an application. This process of knowledge sharing has improved the overall review quality. However, it has not met the expectation of the Office of Generic Drugs (OGD) because applications are being submitted with minimal justification in establishing product quality. Despite OGD's efforts, the number of amendments submitted in response to FDA's deficiency letters, have still been staggering.

With this as prologue, a series of articles are forthcoming in an effort to be more transparent and to assist sponsors to submit applications with adequate justification for drug substance and drug product (DS and DP) specifications, in-process controls, choice of formulation, product design, and manufacturing processes. Our experience shows that having justification in the original submission reduces the number of deficiencies and provides assurance to the agency in the sponsors' ability to manufacture high quality drug products.

These articles will attempt to clarify the intent and criticality of some of the common deficiencies cited throughout the Chemistry, Manufacturing, and Controls (CMC) portion of ANDA submissions. Sponsors may use this information to build quality into their submissions. As background for this work, the authors have surveyed a representative sample of deficiency letters issued by each chemistry team within OGD over the past six months. The surveyed deficiencies were cited for ANDAs submitted in the QbR–QOS format. However, this article is not intended to be a discussion of all common deficiencies in ANDAs. The article focuses exclusively on the drug substance portions of the ANDA submissions using the Common Technical Document (CTD) and QbR format as a guide. For a partial list of some common drug substance related deficiencies, see the sidebar "Examples of commonly cited drug-substance related deficiencies."

One area that will not be expanded on in this article is the common deficiency that the referenced Drug Master File (DMF) is inadequate and, as such, the ANDA sponsor should not respond until they have been informed that the DMF deficiencies have been addressed. The deficiency in itself is rather clear and its criticality is obvious as the drug substance is the key ingredient in the product. However a recommendation to ANDA sponsors is that they "do their homework" when selecting a DMF partner and be aware of the information available to them with regard to drug-substance characterization, properties, purity, and methodology as well as the regulatory history of the DMF holder. The upcoming International Conference on Harmonization (ICH) Q11 guideline on drug substances should provide clarity for both DMF holders and ANDA sponsors with respect to the critical aspects of the drug substance. Schwartz provides another helpful resource with respect to critical information to be gleaned from the referenced DMF (1).

A second topic not discussed in this article is the issue of polymorphism. It is again a frequently cited deficiency where the ANDA sponsor has been requested to include information and a control for polymorphic identity and its impact on the performance of the drug product. The sponsors are highly recommended to address criticality of controls of polymorphism in the drug substance and/or the drug product based on an evaluation of drug substance characteristics, proposed formulation, proposed manufacturing process, and its impact on the product performance. For more details on the significance of polymorphism in ANDAs, please refer to the following publications (2, 3).

2.3.S / 3.2.S Drug Substance

2.3.S.1 General Information[1] . The second question in the QbR–QOS pertains to drug-substance properties. This question is inconsistently answered by the sponsors of most applications. A full understanding of the drug-substance properties is essential in the development of formulation,

manufacturing process, analytical methodology, and product stability. In many instances, this critical information is lacking and triggers a question requesting the identification of crucial aspects of the drug substance that are essential in making a quality drug product. An understanding of the drug-substance properties is paramount to ascertaining the critical material attributes (CMA). The properties may or may not be CMAs based on the intended use or performance, the formulation, manufacturing process, analytical methodology, and product stability. Examples are as follows:

Solubility may be critical to determining the formulation, the process, and the performance of the product. A study of pH-related solubility and solubility in various organic solvents can also be used to justify manufacturing process steps and in providing information useful for developing suitable analytical methods.

Knowledge of hygroscopicity may have an impact on choices made in the formulation or the manufacturing process; and may also provide insight into potential stability challenges if the drug substance or the formulation is sensitive to moisture.

Providing an answer to this question and identifying the drug-substance aspects that are critical to product quality can eliminate this request coming from the reviewer.

2.3.S.2 Manufacture. With respect to section 2.3.S.2, reference is usually made to the associated DMF(s). If questions are asked regarding the manufacturing of the drug substance, it is because of additional processing of the drug substance by the ANDA sponsor such as micronization. If the ANDA sponsor performs post-DMF drug substance processing such as micronization, the effect of such processes on drug substance stability should be addressed.

An additional question that is often asked by reviewers in this section is whether the drug substance will be manufactured at multiple manufacturing sites. It is recommended that the DMF holder be consulted to address which site will be used to supply commercial material and if multiple sites will likely be used. This fact should be included in the exhibit batch information (i.e., the possibility of manufacturing multiple exhibit batches). If there is a possibility of a change in source site after approval, this information should be included in the ANDA sponsor's regulatory strategy.

2.3.S.3 Characterization. For drug-substance characterization information, the ANDA sponsor typically refers to the applicable portions of the referenced DMF. This section, however, also provides the introduction to potential impurities that may or may not be adequately controlled by the DMF holder. A summary of the potential impurities (organic and inorganic), related substances, residual solvents, and residual reagents should be included in this section (see section 2.3.S.4 below for a discussion of criteria for the impurities). Many times, the information with respect to International Union of Pure and Applied Chemistry (IUPAC) names, structures, and classification as process related and/or degradation impurities is missing from the ANDA. This type of information is part of a complete response to the QbR question found in section 2.3.S.3. Additionally, justification should be provided for any potential impurities including, in some cases compendial impurities (e.g. USP monograph specified impurities), that are process specific and are not specified in the drug-substance specifications.

2.3.S.4 Control of Drug Substance. Common questions with respect the control of the drug substance can be grouped into four major categories. These categories include: control of impurities (i.e. organic, inorganic, residual solvents, and residual reagents), drug substance identity, physical characteristic controls, and analytical methodology. Each category will be expounded upon with respect to common questions asked after the reviewer assesses sections 2.3.S.4 and 3.2.S.4.

Control of impurities

The authors noted above that two common question topics regarding the drug substance are polymorphism and DMF inadequacy. Other than these two, the most commonly asked question regards control of impurities. Impurity controls are critical for ensuring the quality of the drug substance. The control of impurities is directly linked to the route of synthesis, choice of solvents, and other reagents used in the synthesis. This control is also essential to developing a good understanding of the drug-substance manufacturing process.

Generally, organic impurities should be in line with the DMF holder's criteria; however, compliance with United States Pharmacopeia (USP) monographs and the ICH Q3A(R2) guideline on impurities in new drug substances is crucial in providing justification (4). For details, the sponsor is referred to the OGD guidance on impurities in drug substances (5). For non-USP articles, other compendia (e.g., European Pharmacopoeia (EP) or Japanese Pharmacopoeia (JP)), comparison to the reference listed drug (RLD), or safety studies may be used to justify limits for impurities. For highly toxic impurities (e.g., genotoxic, carcinogens), additional considerations such as those found in the draft CDER guidance on genotoxic impurities are necessary in providing justification (6). It is advocated that the unidentified and unspecified impurities be controlled at the recommended ICH Q3A (R2) threshold (5). It is also recommended that documentation be provided to demonstrate efforts made toward identifying the impurities based on the synthetic process before classifying them as unidentified or unspecified impurities.

Residual solvents are directly linked to the synthetic process and, as such, should be controlled based on the criteria in ICH Q3C (impurities in residual solvents) and USP <467> (7, 8). However it is recommended that the DMF holder and the sponsor have a complete understanding of the effect of the residual limits on product quality rather than accepting the limits recommended in ICH Q3C and USP <467>. If the sponsor wishes to set a less stringent limit, they need to justify it adequately. Additional guidance for CMC reviewers and industry is also found in the OGD questions and answers on residual solvents in ANDAs document and the CDER guidance on residual solvents (9, 10).

Specific questions are often asked with regard to residual metals from the synthetic process. The current USP <231> test and criteria are not comprehensive and do not cover all potential metal impurities that may be present in the drug substance. It is thus recommended that sponsors follow the European Medicines Agency (EMEA) guidance for metal catalysts or the Stimuli article, General Chapter on Inorganic Impurities: Heavy Metals, published in the Pharmacopeial Forum (5) in establishing the specifications (11, 12). Similar to the case for residual solvents, the intended use of the product should be taken into account when proposing a criterion.

In addition, other inorganic impurities (e.g., cyanide or thiocyante) and reagents (e.g., triethylamine, alkyl halides, etc.) may need to be controlled in the drug substance, and established limits must be justified based on good science. Guidance for setting meaningful criteria may be found in many of the same guidance documents noted throughout this article.

Drug substance identity

Common questions that arise during ANDA reviews regarding drug substance identity include control of counter ions, stereospecific identity or assay tests, and compliance with USP identity tests.

Control of counter ions. In ICH Q6A, test procedures and acceptance criteria for new drug substances and new products, it is recommended that, for drug substances that are salts, the "...identification testing should be specific for the individual ions. An identification test that is specific for the salt itself should suffice" (13). However, there are cases where quantitative control of counter ions is requested by FDA. This request may be due to the information available regarding the route of synthesis for drug substance based on the DMF. For example, in some cases, an intermediate with a specific counter ion is converted to the final drug with another counter ion. Thus, the chemist may request a quantitative control of the counter ion to establish the completeness and reproducibility of the manufacturing process. The above approach is consistent with our current effort to establish critical control points based on process understanding.

Control of chirality. With respect to identity of chiral compounds, the authors recommend that both ICH Q6A and the CDER guidance on the development of new stereoisomeric drugs be consulted (13, 14). ICH Q6A recommends that "drug substances that are optically active may also need specific identification testing or performance of a chiral assay." In the referenced CDER guidance for stereoisomeric drugs, it is recommended that "applications for enantiomeric and racemic drug substances should include a stereochemically specific identity test and/or a stereochemically selective assay method. The choice of the controls should be based upon the substance's method of manufacture and stability characteristics" (14).

In many ANDA submissions, suitable tests are not proposed for control of stereoisomeric drug substances, and deficiencies are often cited. A chiral identification is highly recommended for chiral drug substances in addition to the control of chiral impurities. However, if the amount of chiral impurities is significantly high and the drug substance is prone to racemization over shelf life, a chiral assay method may be desirable in addition to identification.

Identity Tests for USP Articles. Often, alternate identity tests are proposed for drug substances that are official USP articles. We reference the USP General notices, section 5.40 Identification Test, specifically noting that the "failure of an article to meet the requirements of a prescribed Identification test may indicate that the article is mislabeled" (7). It is recommended that the USP identity tests are part of the proposed drug substance specifications.

Physical attributes of the drug substance. Particle size: Reviewers may ask questions regarding control of particle size when particle size of the active pharmaceutical ingredient (API) has a significant effect on the manufacturability of the drug product and its performance. There are also APIs that are prone to agglomeration, thus requiring particle-size control. It is recommended that the firms report the distribution and ranges, if possible. A soon-to-be published paper will provide regulatory perspectives on particle size specifications (15).

Polymorph: See above.

Water content: Based on the nature of the drug substance, water content may or may not be a CMA. However, the ANDA sponsor needs to justify the proposed control. Water content becomes a critical control for drug substances, which may be present in any of a variety of forms: anhydrous or one of several hydrated forms, and a specific hydrate is used. In such cases, a range may be proposed. For hygroscopic drugs, the water content may be critical in determining the impact on the manufacturability of the product.

Analytical methods related to the drug substance. Verification of compendial methods: If a compendial analytical method is used, the ANDA sponsor is not required to provide complete validation. However, documentation of suitability of use needs to be established based on 21 CFR 211.194(a)(2) of the current good manufacturing practice (CGMP) regulations, which states that "the suitability of all testing methods used shall be verified under actual conditions of use" (16). ANDA sponsors are requested to refer to USP <1226> for verification of compendial methods (8).

USP methods versus in-house methods: In cases where there is an USP monograph for the drug substance and the sponsor decides to use an in-house method, a comparison to demonstrate the equivalence of the methods is considered valuable. Again, the impurity profile of the API used by the sponsor may be significantly different from the source of the USP monograph, based on the synthetic route. Thus, it is important to demonstrate that the USP method is capable of separating all the possible process impurities and degradants since in the event of any dispute the USP method is considered the method of resolution.

Adoption of DMF holder's method: ANDA sponsors frequently state that they have adopted the DMF holder's methods for analysis of the drug substance and refrain from providing the details of validation. It is acceptable to adopt the DMF holder's methods for analysis of the API. However, because the ANDA is a standalone document, the information regarding validation of the method needs to be complete. The sponsor may provide details of the validation from the DMF holder with additional information regarding its own verification of the method.

HPLC method versus titration for assay of the active pharmaceutical ingredient: It is generally recommended that a specific, stability-indicating procedure is included for assay of the API. In many

cases it is possible to employ the same procedure (e.g., high-performance liquid chromatography) for both assay of the API and quantification of impurities.

In some cases where use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance, the combination of the assay and a suitable impurities test could be used. However, there may be occasions, when a non-specific titration assay is not preferred due to the inherent nature of the API and the impurities. For example, when the API is basic in nature and so are most of the impurities, a perchloric acid titration may yield to a "false–high" assay result due to non-specific titration of the API and the major impurities. In these cases, the ANDA sponsors may be requested to revert to a specific assay method.

Reporting results. ANDA sponsors frequently report results of analysis as "conforms" versus providing the quantitative figures. This may only be acceptable in case of limit tests. In all quantitative analysis, results above limit of quantitation need to be reported accurately.

Occasionally, sponsors provide quantitative values that are below the limit of quantitation (LOQ). We recommend that sponsors in these cases not report numerical values below the LOQ, as they have minimal significance. Additionally, the limit of detection (LOD) and limit of quantitation (LOQ) should be provided for all methods used to control impurities and residual solvents in the API.

2.3.S.5 Reference Standards

Most ANDA sponsors provide satisfactory information when it comes to API reference standards. However, one common deficiency is cited with respect to the impurity reference standard used in the proposed methods and/or the standards used during method validation. The sponsor should provide at a minimum the source, lot number, and purity of the impurity standards. This information is often found in the method validation report, and if this is the case, a reference to the relevant section or report can be provided in section 2.3.S.5.

Two other common questions from the reviewers' regard standard spectra and revision of secondary or qualified standard specifications. Representative spectra and chromatograms should be provided for reference standards used. With respect to revision of secondary or qualified standards, any applicable changes to the drug substance specifications should be made to the specifications of the reference standard. An additional recommendation is that reference standards meet all relevant acceptance criteria.

2.3.S.6 Container Closure System and 2.3.S.7 Stability

With respect to the last two sections of 2.3.S, questions are not routinely asked as these portions usually reference the associated DMF(s). Questions that do arise regarding the drug substance container closure

systems (section 2.3.S.6) are often prompted by "repackaging" of the drug substance by the ANDA sponsor. This action shifts the responsibility of storage and stability of the drug substance from the DMF holder to the ANDA sponsor, and the sponsor may have to provide detailed information and justification for the proposed container closure system and its effect on the drug substance's stability. Stability studies used to support the container closure system should be included in sections 2.3.S.7 and 3.2.S.7 of the ANDA. Additionally, if storage conditions differ from what is recommended (e.g. temperature, inert atmosphere, etc.) and/or justified by the DMF holder, drug substance stability data are recommended to support the conditions.

An additional question that arises in section 2.3.S.7 asks the ANDA sponsor to provide the justification for the retest or expiry date if these are not supported by the DMF holder information provided. For example, if the DMF holder certificate of analysis reports a 2-year expiry date and the ANDA sponsor lists a 5-year retest date, the discrepancy will need to be clarified and justified. Sometimes, based on DMF review, the chemist is aware that the expiration date proposed by the DMF holder is not justified by the information submitted in the DMF. In these cases, the deficiency cited to the ANDA sponsor may be commensurate to that cited by the DMF holder.

Conclusion

It is well known that successful development of a drug product begins by understanding the drug substance's physico-chemical characteristics as well as adequate control of the properties, which are critical to the drug product's quality, efficacy, and safety. The authors hope that the information provided in this article will shed some light on the common deficiencies cited during the review of ANDAs. The information provided herein is intended to assist ANDA sponsors in building quality into their submissions so that they may convey meaningful drug-substance information to FDA, with the goal of reducing instances of these common deficiencies from being cited.

1 Numbering in section heads correspond to those in the Common Technical Document (CTD).

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Disclaimer

The views and opinions expressed in this article are only those of the authors and do not necessarily reflect the views or policies of FDA.

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