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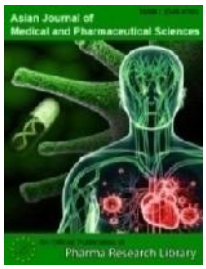

R E V I E W A R T I C L E

Common Deficiencies in Regulatory Submissions

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A B S T R A C T

This concludes our discussion on the commonly cited deficiencies for control of the drug product and stability. This is by far the most active area when it comes to deficiencies and comments cited to ANDA applicants. The prevalence of deficiencies speaks to the criticality of the information with respect to controls proposed for routine release and stability analysis of the drug product. Applicants should endeavor to provide sound scientific and regulatory justification for all specifications (tests, methods, and criteria) that are proposed.As stated in the beginning of the paper, this is not an exhaustive list of deficiencies in the drug product release and stability sections. However, the authors have attempted to provide the underlying reasons for common deficiencies related to the control of the drug product during release and stability testing. Our goal is to shed light on the rationale for citing these deficiencies and demonstrating how pharmaceutical development studies, performed during the initial development of the product, may reduce the instances of these deficiencies being cited.

Keywords: FDA, Common deficiencies.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Drugs which are marketed, distributed & used in any country should be registered with the national competent regulatory authority. Company success depends on reduction of time taken for a drug to reach market, Thus, Drug registration is essential factor of drug regulation. Every drug before getting market approval undergoes

rigorous scrutiny and clinical trials to ensure its Safety, Efficacy & Quality. Few deficiencies raised on ICH CTD Module 3 (Quality) are depicted in the article for reference of readers.

2. Drug Substances Deficiencies

- State if the blending of batches occurs during the proposed manufacturing process. If blending does occur, confirm that each batch will be fully tested and shown to comply with the approved API specification prior to blending.
- Stateiftherecoveryofany solventsoccurs andgivethedetailrecovery processalongwith the specification of recovered solvents.
- The molecule XXX is not acceptableas a starting material and it should be considered as a late intermediate inthe synthetic processof the finalAPI.You arerequestedtoredefine the starting material to a simpler molecule (as a synthetic precursor that isseveralsynthetic steps prior to the final keyintermediate).
- The applicant'sspecificationsfor the starting material YYYarenot acceptable: the specifications should contain limits for unspecified, specified and total impurities.
- Absence of discussion for Class1 solvent as contaminant of another solvent.
- A specific discussionaspartofoverall discussion on impurities should be provided with regard to Impurities with potential genotoxicity either produced by preparation of API or its degradation [reference guidance EMEA/ CHMP/ QWP/ 251344/206or USFDA recommended approaches December 2008].
- Thelimits setforresidualsolventsshouldbe tightened on the basisofactual results.
- Absence of comparison of the quality of the final substance obtained with starting materials from different suppliers.

3. Drug Product Deficiencies

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." 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).

Drug Substance:

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.

Manufacture:

Rreference 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.

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.

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.

Drug product composition information:

Very few deficiencies and comments are cited with regard to the information presented in the composition tables. If cited, these include not providing the percent of each excipient (e.g., w/w %) in the formulation. The intent of this question is to clearly provide the reviewer the intended function of the multifunctional excipients in the formulation at the proposed w/w % level. An applicant should provide a list, for each product strength where applicable, the quantitative composition, function of excipient, grade (e.g., Avicel PH 101 etc.), the standard (e.g., US Pharmcopeia, National Formulary, Food Chemicals Codex, etc.), and origin as applicable (e.g., vegetable or animal source) of each component.

Another issue that may need to be addressed is with regard to the justification of the excipient function in the formulation. The reported function should be based on documented evidence and the design of the product. For multifunctional excipients, the sponsor should provide the basis of the function intended in the proposed formulation. Based on the intended function, specific controls should be included in the excipient specifications. The assigned excipient function in the original filing will have regulatory implications with respect to post-approval changes depending on the function of the excipient (i.e., recommendations found is SUPAC-IR) (3). An example of a common multifunctional excipient is starch which may be used for multiple purposes (binder, disintegrant, etc.).

A topic that should also be addressed is related to the chosen dosage form. To be a generic, the dosage form must be the same as the approved RLD unless under an approved suitability petition, and this is clearly one of the main Quality Target Product Profile (QTPP) tenets. With this being said if the RLD is a capsule, the generic must also be a capsule, and also meet the definition in CDER Data Standards Manual (6). Similarly, a formulation may not be called a cream unless it meets the Data Standards Manual (monograph) definition of a cream (6).

Inactive Ingredients Database:

The information on the IIG website provides the highest level of an ingredient approved for a single unit (2). As the information is for single unit, we highly recommend that the ANDA sponsor exercise caution in using this information in formulating their drug product. The scope of the information provided in the IIG database is limited to the use of an excipient in the Center for Drug Evaluation and Research (CDER) approved product and for this reason it is imperative the sponsor do the requisite due diligence to justify the use of the excipient in their product line.

Ingredient composition:

Per 21 CFR 314.94 [(iii)(a)(9)(v)], the applicant is required to both identify and characterize the excipients in the proposed product demonstrating that they do not impact safety (7). This includes the composition or "make-up" of the ingredients. In many cases, complex coatings, colors, and flavors are proposed for use in the drug product. A composition should be provided in the ANDA or if the information is proprietary, a drug master file (DMF) reference or the composition of such components should be provided by the supplier directly to the Agency. With respect to the use of iron oxides, there are times that a sponsor is asked to justify that the use meets the requirements in the CFR. The ANDA sponsor should indicate that their product meets the 21 CFR 73.1200 requirements for exposure of NMT 5 milligrams elemental iron per day (10). It also is recommended that sponsors include the detailed calculation of total daily intake of iron based on the intended formulation.

Compatibility of excipients with API:

With respect to design of the intended product, the lack of understanding of the chemistry and performance of excipients is one of common causes for production failures and recalls. Thus, it is important to study the compatibility of the excipients with the API and understand the critical material attributes prior to finalizing the drug product formulation. Performance characteristics will be discussed in a later section in this article.

What evidence supports compatibility between the excipients and the drug substance.

In response to this question in 2.3.P.2.1.2 regarding the compatibility of the API with the excipients, the sponsors frequently provide justification for not conducting these studies based on the facts that the excipients are "common" for the given dosage form and the stability data for the exhibit lots are acceptable. Some of the sponsors are found to monitor only the change in the physical appearance of the mixture of API with the proposed excipients. An example of a so called "common" excipient significantly affecting the formulation, is lactose, when used in conjunction with APIs which are primary or secondary amines. The formation of "Amadori" complexes has been found to be detrimental to the stability of many drug products.

Justification for not performing excipient-API compatibility studies based on the fact that the formulation is similar to that of the reference listed drug has its flaws, too. It is often found that based on the grade and supplier, the impurity and residual solvents profile of the excipients may differ significantly. The sponsors are encouraged to identify the impurities and residual solvents in excipients which have the potential of adversely affecting the quality of the drug product. A few examples of impurities in excipients which may affect the product stability may be the following:

- Levels of methacrylic acid and divinyl benzene in polacrillin potassium
- Residual peroxides in povidone, crospovidone and/or polyethylene glycol
- Heavy metals or other metal reagents in talc.

Control of excipients:

There is only a single question in the QBR-QOS pertaining to control of excipients: "What are the specifications for the inactive ingredients and are they suitable for their intended function?" However, despite its apparent simplicity, the question is a poignant one and relates to a critical question in the pharmaceutical development section, 2.3.P.2.2, which plays a role in ensuring the quality of the drug product and its performance based on label claim over the shelf life.

How were the excipients and their grades selected?

Performance characteristics of excipients. One of the least understood questions in QBR-QOS is perhaps , where the sponsor is asked to justify the selection of the "grade" of the excipients. Overwhelmingly, the response to this question is that the excipients are USP/NF grade. Another common response is the verbatim information as found in the Handbook of Pharmaceutical Excipients (12) with no specificity to the intended use in the proposed drug product. This question in the QBR-QOS is intended to demonstrate the understanding of the performance characteristics (i.e., excipient performance or functionality related characteristics) of the excipients which may affect the manufacturability of the drug product. The performance characteristics of excipient are based on their form and their physical properties.

Sponsors may need to avoid using a specific grade of excipient in certain formulations, if its use is discouraged by the manufacturer of the excipient. It has been observed, that excipients have been used in a formulation, when the suppliers certificate of analysis (COA) clearly states that the grade is not intended for the particular dosage form. This is a serious flaw and needs to be clearly justified.

Transdermal delivery systems and locally acting patches: Although transdermal delivery systems (TDDS) and other patches are not currently common dosage forms, as these products become more popular deficiencies would be cited with respect to specific critical quality attributes (CQAs) if they are not addressed in the submission.

Adhesion is by far of the most critical attribute that should be addressed in applications. Product adhesion is a CQA related not only to product quality and performance, but to product safety. The applicant should be able to measure adhesion in the proposed product with an appropriate, justified test and they should be able to demonstrate that the proposed system shows consistent product quality, performance and safety in terms of adhesion. A good reference on the criticality of adhesion in TDDS is a recent review article (20). Additional literature and guidance is also available on critical attributes of TDDS and patches (21, 22).

General drug product information: There are a few pieces of general information that if not provided will lead to deficiencies. As stated previously, this is not intended to be an all-inclusive list. Common information not provided in the ANDAs that has led to deficiencies includes the following:

- Results for all strengths are not included.
- Quantitative results are not presented for numerical tests, but general terms such as "complies" or "meets limit" are reported.
- A USP <467> compliance statement along with option used is not included in the drug product specifications.
- In case of the drug product label having specific information regarding how the patient may use a drug product, additional controls may be requested in release and stability. For example, if the label of a chewable, dispersible tablet claims that it may be dissolved in water or juice completely before taking, a test may be needed to establish that the generic meets the same criteria.

Methods and validations:

There are a variety of common deficiencies regarding the analytical methods used for the drug product analysis, as well as, the associated method validation studies. One common question cited to applicants is related to insufficient method information being provided in the QBR-QOS, especially for non-compendial methods. The applicant should provide a brief summary of each non-USP method. This can be in a tabular or descriptive form and the information should include the critical parameters for the method and system suitability criteria, if applicable. Specifically for impurity methods, it should be clear that impurities (degradation products) are quantified using impurity standards or by the use of relative response factors (RRF).

In some submitted ANDAs, inadequate method validation information is provided. For in-house methods, validation protocols should include all the relevant tests as noted in USP <1225>, including method robustness (16). Some specific studies and information that is often lacking in submitted method validations reports include linearity studies that do not include the proposed limit or the LOQ; inadequate or irrelevant acceptance criteria in the validation protocol, and lack of spiking studies to assess method suitability for detecting specified degradation products that may increase over time. Additionally, stress studies often are insufficient to assess stability indicating nature of the method as no degradation is observed in stressed samples.

Stability: The sections of the QBR–QOS and the body of data in submitted ANDAs include information with respect to stability studies used to determine the shelf-life of the product. As stated previously, much of the information provided in the P.5 section is relevant to both release testing (P.5) and stability testing (P.8).

There are three QBR–QOS questions noted in P.8. These are as follows:

- What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?
- What drug product stability studies support the proposed shelf life and storage conditions?
- What is the post-approval stability protocol?
- This article will focus on the first two questions with respect to common deficiencies and comments cited in ANDA submissions.

Stability specifications:

Based on ICH Q1A(R2) (23) stability studies should include testing of attributes of the drug product that are susceptible to change during storage and may influence quality, safety, and/or efficacy of the drug product.

Modification of limits for stability:

In some cases, the relaxation of the limits of certain quality attributes in stability is necessary based on the nature of the drug product. Applicants should take great care in using realistic, as well as, scientific and regulatory approaches to setting acceptance criteria for the stability studies.

For example, when the API or one of the excipients is hygroscopic, the water content may increase during shelf life for solid oral dosage forms. Similarly, if a hydrolytic degradation pathway related to an API is well documented in literature, the resultant degradant may be controlled at a higher level in stability.

In case of water content, in the example noted above, it needs to be demonstrated that the proposed relaxation is not detrimental to the product quality in any way, leading to change in appearance, physical attributes or impurity levels. In case of degradants, the relaxed limit is acceptable as long as it is within the ICH Q3B (R2) qualification threshold (QT) and the impurity is not a structural alert for genotoxicity. However, if a limit higher that the QT is proposed, it needs to be justified by comparison with several lots of RLD, close to or at expiration date. In case of artifacts arising due to interaction of the API with the excipients, the levels need to be at ICH Q3B (R2) proposed QT or adequately justified based on safety data.

Accelerated stability data on RLD samples:

Deficiencies are often cited when the relaxation of specifications of impurities in stability is justified by comparison with RLD, which has been subjected to degradation under accelerated stability conditions. Since accelerated storage conditions are not the normal storage condition of the drug product, it is recommended that the comparative batch analysis is conducted at controlled room temperature conditions to demonstrate similarity of behavior between the RLD and the generic.

Specific studies or tests on stability samples:

Water loss. Per ICH Q1A(R2) (23), it is recommended that aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss during stability studies. Deficiencies have been cited with respect to applicants using semi-permeable containers with no evaluation of potential water loss. It is recommended that the ICH Q1A guidance approach be used with respect to performing studies under low relative humidity conditions. Alternative approaches to determine water loss based on differing stability conditions can also be used, per the guidance.

Dissolution:

The responsibility of reviewing the adequacy of the dissolution specification rests with the Division of Bioequivalence (DBE). However, a frequent deficiency provided to the applicants is to update the drug product release and stability specification based on DBE recommendations. It is also imperative that the applicants conduct the dissolution test by using the DBE recommended method on retained 3rd month accelerated stability samples for all packaging configurations and ensure that the exhibit batch meets the proposed specification. If accelerated stability samples are not available, testing should be conducted on samples placed in controlled room temperature. In this case, typically, the age of the samples at the time of testing will be the tentative expiration dating period that OGD will grant to the drug product. As such, updated stability protocols should be provided reflecting the reduced tentative expiration date. To avoid the reduction of shelf life, it is recommended that samples, which have already been taken out from the accelerated stability study chamber be retained until approval of the ANDA.

Photo stability studies:

The information regarding photostability studies for the drug product is often absent from the application. As ICH Q1B (24) states, the studies on the photostability of drug product need to be done in a sequential manner, starting with the fully exposed product and proceeding, if necessary to the immediate pack and then to the marketing pack, until results demonstrate that the drug product is adequately protected from exposure to light. In some cases, the ANDA holder justifies not performing photostability studies for the drug product based on the fact that the drug substance did not show photo-degradation during the forced degradation studies. Alternatively, if the applicant demonstrates that the generic product packaging provides a comparable level of protection to the RLD packaging, photostability studies may be exempted.

Thermal cycling:

Thermal cycling studies or freeze-thaw cycling studies are recommended for certain dosage forms such as solutions, suspensions and emulsions to ascertain the effect of extreme temperature fluctuations during shipping through various climatic zones, seasonal fluctuation in temperature and mode of transport on the physical stability of the drug products. These studies are generally desirable for those drug products which may undergo phase separation, loss of viscosity, precipitation, and change in particle size distribution.

Diluent studies:

Stability testing of the pharmaceutical product after constitution or dilution, where applicable, should be conducted based on the information in the labeling of the RLD. This testing should be performed on the constituted or diluted product through the proposed in-use period on exhibit batches as part of the ANDA submission.

Accumulated data/studies:

Usually, satisfactory results of three months accelerated studies justify a tentative expiration date of 24 months. However, based on trends observed in the accelerated stability data, the expiry date for some products may be based solely on the accumulated full long-term stability data.

There are drug products, due to their inherent nature show a significant change during the accelerated stability studies. In these cases, the expiration date is based on the long term stability data, though the ANDA holder may demonstrate that the RLD exhibits similar behavior under accelerated stability conditions. In cases were significant changes occur in accelerated conditions, applicants may also need to demonstrate (e.g., intermediate storage conditions) that excursions in temperature during routine shipping and storage have no detrimental impact on the product quality.
FDA is meeting or exceedingits goals for 510(k)review times agreed to withindustry under theMedical Device UserFee Act (MDUFA). FDA reviews 90% of 510(k)s within 90 days, and 98% of those devices within150 days. Devices submittedundera510(k) accountfor 95% ofthe more than 4,000submissions subjecttouserfee performance goals that FDA reviews each year. Review–has increased primarily due to companies taking more time to respond to requests for additional information (see Chart 1).

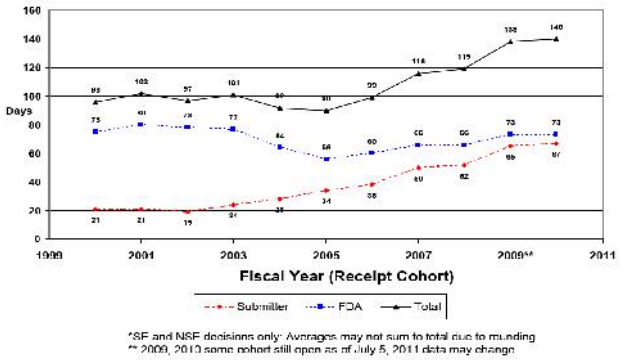

Figure 1: Average Time to 510(k) Decision

Once a submission is received, the review clock forFDA begins. When a submissioncontains insufficient information anda reviewer identifies a need for additional information, the reviewer will either call the submitter (Interactive Review) or prepare a letter outlining the additional information needed (Additional Information (AI) Letter). These letters include bothformal letters sent viaU.S. mail as well as “telephone hold” memosande mails. These letters include acomprehensive list of deficiencies associatedwith incoming original 510(k) submissions. Once an AI Letter is sent, the submissionto whichthe letter pertains is placedon "hold"andisnotconsideredto be under active review whilethe reviewer is waiting for a response. In other words, the clock stops during this time. A I Letters request a responsewithin 30 days. If additional time is needed, sponsors mayrequestan extensionupto 180 days. The more quickly the sponsorisableto respondtothe AI Letter,theshorterthe total review time will be. As is demonstrated by Chart 1, above, average industry time in responding to these types of requests has significantly increased over the past few years. When deficiencies that a reviewer believes can be quickly and easily resolved are noted, there viewer may choose to use the Interactive Review process rather than send an AI Letter. The review clockdoes notstop whilethe reviewer awaits a response from the sponsor. The InteractiveReview process maybe used at any point during the review process, even before a comprehensive list of deficiencies is identified.1 Total review time to reacha510 (k) decision can include more than one review cycle if the company did not submit all the required information or the information submitted raised new questions, such as when the results of the company’stestingsuggestthere is anewsafety riskor thecompany changes the device’s indications foruse. Acycle ends each time the review clock is stoppedwhileareviewer waits to receive additional information, and a new cyclebegins when the sponsor submits a responsetoan AI Letter.

Drug development:

The process of bringing a new drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research (microorganisms/animals) and clinical trials (on humans) and may include the step of obtaining regulatory approval to market the drug.

4. Conclusion

This concludes our discussion on the commonly cited deficiencies for control of the drug product and stability. This is by far the most active area when it comes to deficiencies and comments cited to ANDA applicants. The prevalence of deficiencies speaks to the criticality of the information with respect to controls proposed for routine release and stability analysis of the drug product. Applicants should endeavor to provide sound scientific and regulatory justification for all specifications (tests, methods, and criteria) that are proposed. As stated in the beginning of the paper, this is not an exhaustive list of deficiencies in the drug product release and stability sections. However, the authors have attempted to provide the underlying reasons for common deficiencies related to the control of the drug product during release and stability testing. Our goal is to shed light on the rationale for citing these deficiencies and demonstrating how pharmaceutical development studies, performed during the initial development of the product, may reduce the instances of these deficiencies being cited.

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