Both industry and the FDA face significant challenges in meeting the expectations of timely approval of generic drug products. On FDA’s part, the number of new abbreviated new drug applications (ANDA) submissions is at historic levels. For industry, it is critical to bring new products to market and meet its own expectations for timely approvals. To promote an efficient review process for ANDAs and to reduce the time for ANDA approvals it is important that both FDA and industry work collaboratively. Hatch Waxman was created in 1984 increase the availability of more affordable generics into patient hands on the earliest possible date. Industry and FDA negotiated a user fee program known as GDUFA to help further resource FDA in carrying out its mission to provide faster generic drug approvals as well as improved safety through risk based inspections, including parity of foreign and domestic inspections, and improved transparency.

Industry can make significant contributions to an efficient review process by submitting applications that address all anticipated regulatory and technical issues.

Industry has the opportunity to reduce overall review time of ANDAs by submission of complete applications that properly address the numerous technical sections contained within an ANDA. The FDA has issued several guidances as well as developed a question-based review approach to assist applicants in submitting the necessary supporting information. Although these efforts by the Agency have been helpful, FDA has identified a number of recurring comments identified during the technical review process. Many of these recurring comments were identified and discussed in a four-part series of articles published in 2010 and 2011. These observations should be carefully assessed by ANDA applicants to help assure that applications consider and address these recommendations as appropriate. To further assist applicants, the Generic Pharmaceutical Association (GPhA) has summarized all recent publications made available by FDA to compile a summary of key repeating observations made by FDA in review of ANDAs.

Appreciating that reaching more timely reviews and ultimately a first cycle review system requires significant efforts on both industry as well as FDA, GPhA is continuing to work with FDA to identify areas of opportunity for the agency to further improve the quality and consistency of generic drug reviews as a whole.

GPhA strongly urges applicants to become familiar with the issues outlined in FDA’s articles cited in this summary of those publications. For applicants that receive substantive comments during the ANDA review process, becoming familiar with deficiencies frequently identified by FDA may assist you in preparing and submitting the most complete ANDA possible. Finally,
applicants are advised to closely monitor FDA’s guidance page for new or revised guidances intended to assist industry as well as additions or changes to the Office of Generic Drugs’ Filing Checklist. By carefully evaluating and effectively implementing procedures to assure that technical issues are appropriately addressed in ANDAs, FDA and industry will benefit by reducing the review cycles of ANDAs and conserving Agency and industry resources and achieving the goal of timely ANDA approval.

GPhA is providing this summary of common deficiency issues as an informational document and does not make any claim that the recommendations included in this paper will be found uniformly acceptable by FDA, nor does GPhA endorse the recommendations made by FDA. Not all recommendations made by FDA may apply for every ANDA. Depending on the facts and circumstances involved, good science may support a different approach. Applicants are encouraged to carefully evaluate the information that should be considered for each drug product.

These recommendations represent common deficiencies and/or recommendations. These questions should not be considered to be comprehensive and applicants are advised to carefully consider and submit relevant controls for the process and product.

**Drug Substance**

Section 2.3.S General Information

Q. 1. When describing Drug Substance (DS) properties, e.g. critical material attributes as they pertain to intended use or performance, formulation, manufacturing process, analytical methodology and product stability, what are some of the common aspects that applicants fail to include?

A. 1. Examples of the types of descriptive factors that are often not provided in this section include a relevant description of factors, such as, criticality of solubility, pH related solubility, hygroscopicity, moisture sensitivity, etc., that impact understanding and quality of process and product.

2.3.S.2 Manufacture

Q. 2.a. If the applicant performs a process of the API after receipt, should the effect of processing on the stability of the API be addressed?

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A. 2.a. Information should be provided assessing the impact of processing on stability.

Q. 2.b. In some cases, single or multiple API manufacturing sites may be used by a supplier. How should this be addressed in the ANDA?

A. 2.b. Report in the ANDA the possibility of receipt of API from multiple manufacturing sites and identify the specific sites.

2.3.S.3 Characterization

Q. 3. While most information related to impurities is contained in the DMF, are applicants expected to address impurities that may or may not be adequately controlled by the DMF holder? What are some common examples of information that may be requested from the ANDA applicants?

A. 3. Common recommendations include:
- Summary of potential impurities (organic and inorganic), related substances, residual solvents and residual reagents
- IUPAC names, structures and classification and/or degradation impurities
- Provide justification for any potential impurities that are process specific and not specified in the drug substance specifications

2.3.S.4 Control of Drug Substance

Q. 4. Control of Impurities
   a. Organic impurities

Q. 4.a. Please provide “best practices” for applicants as it pertains to addressing organic impurities.

A.4.a. Align product specs with the DMF, but specifications must comply with USP monographs and ICH Q3A(R2). USP and ICH Q3A should be cited as justification. See *Guidance for Industry, ANDAs: Impurities in Drug Substances (R1)* (June 2009).

For non-USP articles, other compendia (EP, JP), comparison to the RLD or safety studies may be used to justify limits.

For highly toxic materials, e.g., genotoxic or carcinogens materials, additional advice can be found in the draft CDER guidances on genotoxic impurities for justification(s). Unidentified and unspecified impurities should be controlled at or below the ICH Q3A (R2) threshold. Provide
documentation to demonstrate efforts towards identifying impurities based on synthetic process before classifying as unidentified or unspecified impurities.

b. Residual Solvents
Q. 4.b. FDA has advised that the DMF holder and the Applicants should have a complete understanding of the effect of residual solvent levels on product quality. What are some of the common deficiencies related to the adequacy of justification?

A. 4.b. Controls should be implemented based on ICH Q3C criteria and USP <467>. If proposed limits are less stringent than ICH Q3C or USP <467>, adequate justification is required. See CDER guidance (Residual Solvents in ANDAs: Questions and Answers, October 28, 2008 and Guidance for Industry, Residual Solvents in Drug Products Marketed in the United States, November, 2009).

c. Metal impurities
Q. 4.c. USP <231> may not be considered to be adequate to cover all metal impurities that may be present in the drug substance. What other sources should be considered?


d. Other inorganic impurities and reagents
Q. 5.d. How should industry address other inorganic impurities or reagents related to the drug substance?

A. 5.d. Generally, applicants need to control the drug substance inorganic impurities and reagents and establish limits justified on good science. Applicants should refer to appropriate industry guidance for specific recommendations.

Drug Substance Identity

a. Control of counter ions
Q. 6.a. ICH Q6A states that test procedures and acceptance criteria for APIs and drug products that are salts should have identification testing specific for individual ions. How is this best addressed?

A. 6.a. Typically, an ID test that is specific to the salt should be adequate. However, FDA may request quantitative control of counter ions. Quantitative control of the counter ion may establish the completeness and reproducibility of the manufacturing process.

b. Control of chirality
Q. 6.b. How should applicants best address chirality?


APIs that are optically active may need specific ID testing or performance of chiral assay. It is recommended that ANDAs containing enantiomeric and racemic APIs should include a stereochemically specific identity test and/or a stereochemically selective assay methods. The selection of the controls should be based on the substances method of manufacture and stability characteristics.

A chiral ID is highly recommended for chiral APIs in addition to control of chiral impurities. If the amount of chiral impurities is high and API is prone to racemization over shelf life, a chiral assay method may be desirable in addition to ID.

c. Identity tests for USP articles
Q. 6.c. FDA often issues comments to applicants when alternate ID tests are proposed for USP articles. Please advise on how best to avoid comments related to identity tests for USP articles.

A. 6.c. Failure to meet the USP identification test may indicate that the article is mislabeled. It is recommended that the USP identity tests are part of the proposed API specifications regardless of the inclusion of alternate ID tests.

d. Physical attributes of the drug substance

Particle size
Q. 7. What are some of the routine considerations related to particle size that may not be addressed by applicants?

A. 7. Consider controls for particle size of the API when it may impact the manufacturability or performance of the drug product. For APIs prone to agglomeration, it is recommended to include controls and report distribution and ranges if possible.

Polymorphs
Q. 8. What are common deficiencies related to polymorphs?
A. 8. Water content may or may not be a CMA but a control should be proposed. If water content is a critical control for the API and it may be present in a variety of forms, a range may be proposed. If the API is hygroscopic, water content may be critical for manufacturability of the product and should be controlled.

Analytical methods
Q. 9. Verification of compendial methods is the common expectation from FDA. However, what are areas for which applicants should consider ‘verifying’ compendial methods?

A. 9. Applicants must provide documentation of suitability for compendial methods (Ref USP <1226>, 21 CFR 211)

Q. 10. What are the key comments when applicants decide to use in-house methods?

A. 10. If applicants decide to use an in-house method, a comparison to demonstrate the equivalence of the method is expected. It is important to demonstrate that the USP method is capable of separating all possible process impurities and degradants since the USP methods will be considered the regulatory methods in case of a dispute.

Adoption of DMF holder’s method
Q. 11. Applicants often adopt the DMF holder’s methods. What are some of the key considerations for applicants when utilizing DMF methods?

A. 11. Adoption of the DMF holder’s methods is acceptable however, information regarding validation of the method must be included in the ANDA. Information may include details of the validation from the DMF holder along with applicants information on its verification of the method.

HPLC method vs. titration for assay of the API
Q. 12. Applicants may propose different approaches for assay, e.g., HPLC vs. titration. Please describe recommended considerations/common deficiencies related to assay methods.

A. 12. Specific stability indicating methods are recommended. When 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 API, the combination of the assay and a suitable impurities test could be used.

Reporting results
Q. 13. Applicants continue to receive deficiencies related to reporting test results. What are some examples of common deficiencies related to reporting of test results?
A. 13. Reporting “conforms” may only be acceptable in the case of limit tests. In all quantitative analysis, results above the limit of quantitation need to be accurately reported. Applicants need not report numerical values below LOQ. Provide the LOD and LOQ for all methods used to control impurities and residual solvents in the API.

2.3.S.5 Reference Standards

Q. 14.a. What are some common deficiencies related to impurity reference standards used in proposed methods and/or standards used during method validation?

A. 14.a. Applicants should provide at a minimum the source, lot number and purity of impurity standards. If this information is provided in the method validation report, a reference to the relevant section or report can be provided in 2.3.S.5.

Q. 14.b. Standard spectra and chromatograms are often noted in comment letters. What are some of the common omissions in ANDAs?

A. 14.b. Representative spectra and chromatograms should be provided for the reference standards used in the testing.

Q. 14.c. What are some “best practices” when there are revision of secondary or qualified standards?

A. 14.c. Any applicable changes to API specifications should be made to the specifications of the reference standards. Reference standards should meet all relevant acceptance criteria.

2.3.S.6 Container Closure System and S.3.S.7 Stability

Q. 15.a. Repackaging of APIs can be performed by the applicants. When an applicant repackages the API, what information should be provided in the ANDA to assure stability?

A. 15.a. Applicants should provide detailed information and justification for the proposed container closure system and its effect on stability.

Q. 15.b. What are common deficiencies related to Stability studies for APIs?

A. 15.b. Stability studies to support the container closure system should be included in sections 2.3.S.7 and 3.2.S.7. If storage conditions differ from DMF holder, API stability data to support
Q. 15.c. What are common deficiencies issued to ANDA applicants when the retest or expiry date if not supported by DMF holder information?

A. 15.c. Additional data may be needed to support proposed retest/expiry date. For example, if the DMF CoA reports a 2-year expiry and the ANDA applicants reports a 5-year retest data, the difference should be clarified and justified. In cases where the DMF holder has not justified its proposed expiry, the ANDA applicants will receive a similar comment.
Section 2.3.P.1 Description and Composition of the Drug Product

Q. 1. Should the percentage of each excipient in the formulation be provided?

A. 1. Yes. For example, the w/w% of each excipient in the formulation should be included and is typically provided in the composition table(s). This information assists the reviewer in understanding the intended function of each excipient. This information is also critical in assessing the dose proportionality of a range of strengths for multi-strength products.

Q. 2. What are the common omissions in ANDAs related to composition related to excipients?

Q. 2. Commonly identified deficiencies include:
- Quantitative composition
- Function of excipient
- Grade (e.g., Avicel PH 101, etc.)
- Standard (e.g., USP, NF, Food Chemicals Codex, etc)
- Origin as applicable (e.g. vegetable or animal source)
- The list should include all materials used throughout the process including organic and aqueous solvents and processing aids used in the manufacturing process and are removed during the process (e.g., water, alcohol, nitrogen, etc.)
- Information for all ingredients including specifications and CoA’s should be provided in 3.2.P.4
- Quantitative information for unit dose must specify a unit of measure for all other ingredients contained in the product

Q. 3. What type of information should be addressed to support excipient function?

A. 3. Function should be based on documented evidence and design of the product. For multifunctional excipients, the applicants 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 formulation. These assigned excipient functions in the original ANDA will impact regulatory decisions with respect to post-approval changes depending on the function of the excipient.

Q. 4. Are there additional considerations for complex products, such as, modified-release products, etc., with multiple processing steps?

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A. 4. It is recommended that applicants provide the composition of “intermediates” (e.g., granules, tablet cores or beads) be separated out to reflect each major process step in the composition table for ease of review. It should also be noted which ingredients will be added intragranularly or extragranularly.

Q. 5. How should applicants address overages of active ingredients?

A. 5. Generally overages are only acceptable when the ANDA applicant demonstrates that the same overage exists in the RLD. It is not acceptable to propose an overage to increase shelf life. If applicants wish to justify an overage compared to the RLD, comparative assay data on the test and reference products throughout shelf life as well as comparative impurity/degradant levels demonstrating similar level is recommended.
Manufacture 2.3.P.3 and Container Closure System 2.3.P.7

Section 2.3.P.3 Manufacture

Q. 1. Does OGD request that the actual manufacturing formula for the exhibit batch and the proposed commercial batch be provided in this section?

A. 1. The formula for the exhibit batch and proposed commercial batch should be provided. It is recommended that the quantities of all raw materials used in the formulation, including those which do not appear in the formulation be provided. For ease of comparison, this information should be provided in a clear tabular format. If any overages are proposed, those should be clearly identified and justified.

In-Process Controls and Results

Reconciliation

Q. 2. Please advise on expectations for reconciliation documentation.

A. 2. The Agency is especially concerned about unjustified, low reconciliation of exhibit lots. Applicants should include a table for reconciliation in the QbR-QOS and in the body of data. The yield should be cumulative and all losses accounted for. A rationale for the losses should be provided as well.

Applicants are frequently asked to demonstrate how the low reconciliation cited for the exhibit batch will be corrected or addressed for the commercial process. It is also advised to include a reference to any applicable investigation of losses.

In-Process Tests

Q. 3. Is it sufficient to identify in-process controls by referencing the batch records?

A. 3. No. Applicants are advised to provide a detailed description of the stages of manufacturing at which sampling is performed for in-process controls. This information should be included in the QOS and as technical section of the ANDA. Applicants should also note the frequency of testing during compression or similar processes should be proposed and justified based on bath size and type of equipment used.

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Q. 4. What is the general view of in-process controls compared to drug product release criteria?

A. 4. The Agency generally expects that in-process controls not be more relaxed than the drug product release specifications.

Q. 5. Are there special considerations for in-process controls when release criteria are tighter than the usual range of 90.0 – 110.0%?

A. 5. Applicants should consider establishing a composite blend assay with a range that is similar to the assay of the drug product for release analysis.

Q. 6. Does OGD find issues with parenteral fill volume that should be carefully considered by industry?

A. 6. Firms should follow USP<1> and <1151> to assess excess fill volume. It is possible to justify quantities less than recommended in USP <1151> based on data from multiple containers demonstrating that the intended volume can be removed the container or by inclusion of a routine extractable volume test. Overfills greater than USP <1151> need to be justified.

Manufacturing Process

Q. 7. FDA frequently raises questions related to blend homogeneity, especially for dry blend processes. What general recommendations should industry consider in order to appropriately address potential concerns?

A. 7. Applicants should confirm a good understanding of the blending process and the potential for powder segregation. This information should be included in the pharmaceutical development section (3.2.P.2). Firms may need to integrate additional controls for a blend, such as, particle size distribution of the components, particle size distribution of the final blend, flow characteristics, density, etc., to assure blend homogeneity.

Q. 8. For tablet compression controls, should applicants demonstrate that the product meets its specifications, such as hardness and friability, at the low and high criteria of the proposed ranges?

A. 8. Yes. The proposed range of hardness during compression, release and stability testing can be justified by meeting the specifications at the low and high points of the range. Applicants may also cite studies performed during product development to support the range.
Q. 9. What types of controls are preferred for products manufactured using wet granulation processes?

A. 9. Typically, a quantitative endpoint determination is recommended that relate to process controls. Examples of such controls include changes in power consumption for high shear operations, moisture content for fluid bed process or processing ranges for solvent addition, granulation time, among others. These examples should not be considered all-inclusive but provide ideas for quantitative endpoints. In the case of organic solvents, applicants should follow USP <467> and FDA documents related to identification and control of residual solvents. Likewise, if water is used in the process, controls should be implemented. Studies to evaluate the impact on water content on product quality that are performed in the development phase may be used for justification.

Q. 10. Multi-particulates and pellets are commonly used in capsules. What are some of the general considerations related to these technologies?

A. 10. Applicants should pay particular attention to bead size. FDA recently issued guidance to industry on bead size and it is recommended that industry follow those recommendations. In-process controls should also be developed which establish the final bead size. For bead products that have multiple controlled release designs, in-process controls should be established at the appropriate stage of manufacturing for the beads in order to establish and monitor the release profile of the product.

Q. 11. What is industry expected to provide in regard to the compatibility of equipment process materials and the drug product for parenterals and other liquid formulations?

A. 11. Generally, it is recommended that studies be performed during pharmaceutical development that assess the compatibility of the dosage form with the process materials which have direct contact with the drug product during manufacturing.

Section 2.3.P.7 Container Closure System

Q. 1. Please provide some general considerations regarding common comments related to container closure systems.

A. 1. A common deficiency is that information in section 2.3.P.2.4 and 2.3.P.7 of the QbR-QOS is missing or insufficient. Oftentimes applicants appear to rely on information submitted in previously approved ANDAs. While a reference to approved ANDAs may be acceptable, applicants must take into consideration the characteristics of the proposed product (including drug substance) and whether the container closure system must assure certain properties be maintained (e.g., moisture protection, light production, droplet size, etc.).
When referencing approved products using the same container closure system, a copy of the test results of the components should be included in the ANDA. If necessary, applicants should provide justification that the container closure is appropriate for the drug product.

**Q. 2.** For section 2.3.P.2.4 (development section), it asks “What specific container closure attributes are necessary to assure product performance.” What are some general expectations for this section?

**A. 2.** Firms should include rationale for choosing the proposed container closure system. Applicants should address any studies performed to identify critical suitability attributes such as, protection, compatibility and performance, and safety of the container/closure. Applicants should review FDA’s guidance on container closure systems for additional advice on important aspects related to the dosage form.

**Q. 3.** Is section 2.3.P.7 the appropriate place to answer the QbR question “What container closure system(s) is proposed for packaging and storage of the drug product? Has the container closure system been qualified as safe for use with the dosage form?

**A. 3.** Yes. Applicants should fully describe the container closure system that is being proposed for the drug product. Applicants should also provide assurance that the container closure system has been qualified for use with the designated dosage form in this section.

**Q. 4.** When addressing suitability of the container closure system for the proposed drug product, please describe some “best practices” that should be considered by the applicant.

**A. 4.** Applicants must address both functionality and safety. Adequate testing information should be provided to support the container closure system. There are a number of compendial tests results and controls that should be provided, such as, USP <381>, <87>, <88>, <660>, <661> and <671>, as appropriate. The compendial tests are provided to demonstrate that the container closure system performance, suitability, compatibility and safety. Applicants should also be aware of any other testing or certification that should be included. Pay particular attention to 21 CFR sections 173-186 for a list of materials that are safe for use in direct or indirect food contact.

**Q. 5.** What are some of the common deficiencies for solutions or suspensions as it relates to container closure systems?

**A. 5.** Some common deficiencies are the failure to provide extractable and leachable testing for the stopper or other container materials. In some cases, information related to dye or adhesive
migration from labeling should be provided. Firms should carefully assess potential issues that should be evaluated that are unique to the drug product and proposed container closure system.

**Q. 6.** What information does FDA typically expect regarding the analytical methods used for analysis of the extractables and leachables?

**A. 6.** The analytical methods should be appropriate for detection of the extractables and leachables from the container closure system. Applicants should also be mindful that when establishing limits for extractables/leachables, those limits are not addressed by ICH or the ANDA impurity guidance. Therefore, acceptance criteria should be supported by scientific rationale and based on publicly available toxicological information or applicable information in the CFR sections.

**Q. 7.** Is testing per USP <1> expected for multiple dose containers?

**A. 7.** Firms should perform USP<1> testing for multiple-dose containers. It is important to demonstrate withdrawal of the contents without removal or destruction of the closure per USP testing. Applicants should implement suitable controls, for example, for coring, seal-sealing, fragmentation, etc., to assure that the closure is adequate for multiple entries.

**Q. 8.** Does OGD expect moisture permeation studies for products in blister packages?

**A. 8.** Yes. Data from moisture permeation studies should be provided when products are packaged in blisters. There also may be a need for a leak test as an in-process or release and stability analysis test.

**Q. 9.** Does FDA ever request information related to the integrity of tablets during shipping or transportation?

**A. 9.** Applicants should be aware that “shipping” information may be required for low-hardness tablets. ODT and chewable tablets are often produced at a low-hardness range. For these products, FDA should consider the need for ‘shipping’ studies to demonstrate that the stresses of shipping will not result in chipping or breaking of the tablets. Perhaps more importantly, companies should consider the potential impact of shipping when designing low hardness products to assure that the product can withstand the rigors of shipping via commercial channels.
Section 2.3.P.5 Control of the Drug Product and Section 2.3.P.9 Stability

QbR-QOS

Q. 1. Are there particular issues related to the QbR-QOS that are found to reoccur?

A. 1. The P.5 sections of the QbR-QOS and the body of data submitted in ANDAs should include all the proposed controls for routine analysis of the drug product batches including:

- proposed specifications
- analytical methods with associated validations
- batch analysis data for exhibit batches
- justifications for all proposed criteria

Applicants should assure that the information provided in the QOS and the body of data are the same. Reviewers often find that the information is not consistent.

Q. 2. The QbR-QOS identifies two sets of questions. What are the common deficiencies identified for the following questions?

Specifications

Q. 2.a. What is the drug product specification? Does it include all the critical drug product attributes?

A. 2.a. The applicant should provide the specifications for routine release testing of the drug product AND to ensure that all critical quality attributes (CQA) are included in the specifications. The CQAs may be based on compendial specifications and/or the attributes of the reference listed drug and also information associated in the labeling. Development studies may be conducted by the applicant to assure that the drug product meets the attributes of identity, purity, potency, assay and quality. Examples of typical CQAs for solid oral and solution dosage forms are provided in ICH Q6A(3) and QbR-Frequently Asked Questions, June 2007.

Q. 2.b. For each test in the specification, are the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

A. 2.b. Specifications are defined per ICH Q6A as “a list of tests, references to analytical procedures, and appropriate acceptance criteria are numerical limits, ranges, or other criteria for the tests described.” Typically a table or list of proposed tests, acceptance criteria, and analytical

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procedures for the drug product analysis are included. The most common deficiencies cited are inconsistencies in the specifications listed in the QbR-QOS (CTD module 2.3) versus the body of data (CTD module 3.2). These two sets of specifications must match. The QOS should be a summary of the detailed information found in the body of data.

**Impurities/Degradation Products**

**Q. 3.** Applicants continue to receive significant comments related to proposed criteria and justifications for impurities and degradation products. What are the common comments issued to applicants related to impurities/degradation products.

**A. 3.** A common deficiency related to justification of specifications relates to control of process impurities in the drug product. While ICH Q3B(R2) is typically used for the qualification threshold for all specified impurities which may be appropriate for degradation products, it is not acceptable for impurities solely linked to the drug substance synthetic route (process impurities). Drug product limits for a process impurity should be set no higher than that proposed for the drug substance.

Lack of adequate justification for the proposed degradation product is frequently cited as a deficiency. The following examples of ways to justify specified degradation product criteria may be helpful for applicants:

**Examples: Specified Impurities**

- Specified impurity limits are aligned with USP monograph criteria
- Acceptance criteria are aligned with the qualification threshold recommended in ICH Q3B(R2) and ANDA Guidance: Impurities in Drug Products (ref 5,6) as long as there are no safety concerns. When calculating the qualification threshold using recommended percentage or total daily intake of specified impurities, the lower value should be followed
- Qualification of proposed criterion may be based on the following:
  - Level of impurity observed in the RLD. Data from multiple batches of the RLD at or near expiry may be provide for qualification
  - Significant human metabolite of drug substance. Literature references should be provided to verify that the compound is a significant human metabolite
  - Scientific literature provided that there are no concerns related to its intended use

Impurities that are structural alerts for genotoxicity should be controlled at the Threshold of Toxicological Concern of 1.5 mcg/day, as cited by EMA and draft FDA guidance (EMA, Guideline on the Limits of Genotoxic Impurities, Committee for Medicinal Products for Human Use (CHMP)(Doc. Ref EMEA/CHMP/QWP/251344/2006), Jan. 1, 2007/ FDA, Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products:
Recommended Approaches (draft), December 2008). A higher limit may be proposed based on safety studies demonstrating that the proposed limit does not pose a safety concern.

**Examples: Unspecified Impurities**

The proposed limit should be equal to or below the recommended ICH Q3B(R2) identification threshold based on maximum daily dose. Note that when a USP monograph includes a limit for “any impurity” or “any other impurity” for unidentified impurities, it is recommended that the identification threshold be used for the criterion rather than the USP monograph limit.

**Examples: Other Impurity Considerations**

Applicants often set the same criteria for both release and stability specifications for a degradation product when there is an increasing trend during stability studies. When a trend is observed, FDA recommends that the criteria in the release specifications be set tighter in order to provide better assurance that all batches meet the regulatory criteria throughout shelf life.

**Stereoisomeric Issues**

Q. 4. Over the last several years, stereoisomeric drug products have increased in prevalence and FDA has provided some guidance. While some guidance exists for such products, please address some of the commonly cited deficiencies related to such compounds?

A. 4. The following recommendations are example of issues that should be considered when addressing these products.

Applicants should pay particular attention to FDA’s guidance, Development of New Stereoisomeric Drugs and ICH Q6A and in particular the Decision Tree 5 in the ICH document as it pertains to requirements for chiral drug substances and drug products.

For chiral impurities it is recommended to include controls for the enantiomer and diastereomers in the drug product as permitted by the sensitivity of the analytical methods. The exception to this recommendation may be in cases where adequate pharmaceutical development studies demonstrate racemization or epimerization is NOT a possibility during manufacturing or storage of the drug. The limits for chiral impurities may be justified by comparison with the RLD, published literature or safety studies.

**Chiral Assay**

Q. 5. When is a chiral assay recommended?

A. 5. If the API is prone to racemization or formation of other diasteromers during the manufacturing or storage of the drug product, FDA typically expects a chiral assay. When racemization is insignificant or a very small amount of chiral impurities are expected to be present, a non-chiral assay may be considered as a sufficient control.
Enantiomers

Q. 6. What ‘identity’ information should be provided by the applicant for enantiomers?

A. 6. FDA’s guidance, Development of New Steroisomeric Drugs recommends that products containing enantiomers should have a discriminating identification test. FDA advises that such a test is especially important when a racemate of the API is present in an approved drug product. In such cases, a stereospecific ID test is expected. Likewise, the agency typically expects a stereospecific ID test when the drug substance is prone to racemization under the manufacturing process and storage conditions.

Enantiomers - Additional Testing

Q. 7. What are common examples of when additional identification testing is required?

A. 7. If a proposed identity test is nonspecific, FDA is likely to request a specific identity test, especially when there is a likelihood of conversion of the active ingredient into another form (e.g., salt, polymorph, stereoisomer) based on the process or during storage.

Quantitative Color Tests

Q. 8. When is a quantitative color test expected to be included as a control?

A. 8. A color control should be considered for solutions. A quantitative control for color utilizing a color-based comparison with the RLD is recommended. Frequently, FDA requests a quantitative color control where degradation of the API may occur over the shelf life of the product or where there is an effect on the product based on interactions with the API and excipients, manufacturing equipment or among excipient that can cause a change in color of the drug product. If pharmaceutical development reports demonstrate the absence of such interaction, it may be possible to justify not including a quantitative color control for solutions.

Reconstitution Time Criterion

Q. 9. What are the agency’s expectations for reconstitution time criterion?

A. 9. For products that require reconstitution prior to administration to the patient, applicants should propose a limit for reconstitution based on observed data, the RLD, or in some cases, the intended use, such as emergency administration. Typically the limit is based on a comparison to the RLD. If an applicant does not propose a limit (see ICH Q6A), the applicant should provide reference to development studies in P.5. that support an omission of a criterion.
Post-Filing ANDA Updates

Not only are complete ANDAs necessary at the time of filing to promote an efficient review process, it is also necessary for industry to update ANDAs during pendency at the Agency in order to avoid undue delays. While the universe of such submissions is limited, it is important to note examples of information that must be included in ANDAs prior to approval.

Applications subject to paragraph IV patent certifications require submission of documentation to confirm that the RLD holder and patent holder have been notified of the patent challenge. Additionally, when patent issues are “closed” (settled, court decision, etc.) during the pendency of the ANDA, the application should be updated at that time to allow FDA to determine whether there any patent related barriers that continue to exist.

Additionally, RLD holders may list new patents or may be granted new periods of exclusivity while ANDAs are pending with the Agency. In those cases, ANDA holders should monitor the Orange Book and submit updates to their ANDAs on a timely basis to assure completeness of the application. Similarly, RLD holders may update the RLD labeling necessitating the ANDA applicant to update the labeling accordingly.

FDA may request other administrative information or ANDA applicants may identify administrative updates that are necessary in order for FDA to make an approval determination. The examples above are not an exhaustive list but rather some issues that can result in potential delays. ANDAs lacking this information diverts FDA resources from reviewing activities and may delay final action on pending ANDAs.
Helpful References

5. FDA, OGD, *Guidance for Industry, ANDAs: Impurities in Drug Substances (R1)* (Rockville, MD, June 2009).
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23. FDA, “Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).”
25. FDA, “21 CFR 73 Listing of Color Additives Exempt from Certification”, [Synthetic Iron Oxide, Sec.73.1200].
29. FDA, “21 CFR 170 Food Additives–21 CFR 180 Food Additives Permitted in Food or in Contact with Food on an Interim Basis Pending Additional Study.”
30. Food and Chemicals Codex 6 (USP, Rockville, MD, 2010).
32. FDA, “21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceutical,” [Testing and Approval or Rejection of Components, Drug Product Containers, and Closures, Sec. 211.84 (d) (2)].
36. FDA, QbR Frequently Asked Questions (June 4, 2007).
37. ICH, Q3B *Impurities in New Drug Products (R2)* (Geneva, July 2006).
41. FDA, Development of New Stereoisomeric Drugs (Rockville, MD, 1992).
42. FDA, “21 CFR 211 cGMPs for Finished Pharmaceuticals” [Testing and Release for Distribution, Sec. 211.165 (a)], revised Apr. 1, 2010.
44. FDA, *MAPP 5223.2, Scoring Configuration of Generic Drug Products* (Rockville, MD, Nov. 1, 1995).
49. A. Gupta, V.A. Sayeed, and M.A. Khan, “The Science and Regulatory Perspectives of Pharmaceutical Suspensions,” in *Pharmaceutical Suspensions, From Formulation Development*


54. ICH, Q1A(R2) *Stability Testing of New Drug Substances/Products* (2003).

55. ICH, Q1B *Photostability of New Drug Substances and Products* (1996),(2010).


58. FDA, QbR Frequently Asked Questions (June 4, 2007).


64. ICH, Q3B, *Impurities in New Drug Products (R2)* (Geneva, July 2006)

