QbR Frequently Asked Questions

Disclaimer: These are general answers and may not be applicable to every product. Each ANDA is reviewed individually. This document represents the Office of Generic Drugs's (OGD's) current thinking on these topics.

Format and Submission

How should QbR ANDAs be submitted?

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD) format, a submission format adopted by multiple regulatory bodies including FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate implementation of the QbR. The ANDA Checklist for completeness and acceptability of an application for filing can be found on the OGD web page: http://www.fda.gov/cder/ogd/anda_checklist.pdf .

What is a QOS?

The Quality Overall Summary (QOS) is the part of the CTD format that provides a summary of the CMC aspects of the application. It is an important tool to make the QbR review process more efficient.

How long should a QOS be?

OGD believes the CTD guidance[1] recommendation of 40 pages to be an appropriate compromise between level of detail and concision. The CTD guidance recommendation does not include tables and figures.

The same information should not be included in multiple locations in the QOS. Instead of repeating information, refer to the first location of the original information in the QOS by CTD section number.

Should the QOS be submitted electronically?

All applications should include an electronic QOS. For paper submissions, it is recommended that both an electronic QOS and a paper QOS be included.

What file format should be used for the QOS?

All applications, both eCTD and paper submissions, should have an electronic QOS. The electronic QOS should be contained in one document. Do not provide separate files for each section or question.

The electronic QOS should be provided as both a pdf **and** a Microsoft Word file. Microsoft Word files should be readable by Word 2003.

[1] Guidance for Industry M4Q: The CTD – Quality (August 2001) http://www.fda.gov/cder/guidance/4539Q.htm

What fonts should be used in the QOS?

> Because of FDA's internal data management systems, please use only use these TrueType fonts: Times New Roman, Arial, Courier New. Times New Roman is recommended as the main text font.

Should the applicable QbR question be presented within the body of Module 2 of the relevant section, followed by sponsor's answer?

> Yes, include all the QbR questions without deletion in the QOS.

Can the granularity of module 3 be used in module 2?

> Yes, the granularity can be used for section and subsection headings. However, the QOS should always be submitted as a single file.

Can color be used in the QOS?

> Yes, but sponsors should ensure that the QOS is legible when printed in black and white. Colored text should not be used.

Is the QOS format available on OGD webpage and questions therein mandatory to be followed?

> For an efficient review process, OGD desires all applications to be in a consistent format. See the OGD QbR questions and example QOS:
> http://www.fda.gov/cder/ogd/QbR-Quality_Overall_Summary_Outline.doc
> http://www.fda.gov/cder/ogd/OGD_Model_Quality_Overall_Summary.pdf
> http://www.fda.gov/cder/ogd/OGD_Model_QOS_IR_Product.pdf

For amendments to applications, should the documentation consist of a revision of the QOS? Would new PD reports be required?

> The QOS should not be updated after submission of the original ANDA. Any additional data (including any new PD reports) should be provided as a stand alone amendment. Responses to deficiencies should be provided in electronic format as both a pdf and Microsoft Word file.

After January 2007, what will happen to an application that does not have a QOS or contains an incomplete QOS?

> OGD will contact the sponsor and ask them to provide a QOS. If the sponsor provides the QOS before the application comes up for review, OGD will use the sponsor's QOS.
>
> OGD's QbR questions represent the current thinking about what information is essential to evaluate an ANDA. Reviewers will use deficiency letters to ask ANDA sponsors the questions that are not answered in the sponsor's QOS.
>
> In February 2007, 75% of ANDAs submitted contained a QOS.

If a question is not applicable to a specific formulation or dosage form, should the question be deleted or unanswered?

> Sponsors should never delete a QbR question, but instead answer as not applicable, with a brief justification. Please answer all parts of multi-part questions.

For sterile injectables, to what extent should sterility assurance be covered in QOS?

> The current QbR was not intended to cover data recommendations for Sterility Assurance information. In the future, other summaries will cover other disciplines.
>
> MAPP 5040.1, effective date 5/24/04, specifies location of the microbiology information in the CTD format.

Where in the CTD should an applicant provide comparative dissolution data between the generic and RLD?

> The comparison between the final ANDA formulation and the RLD should be provided in 5.3.1, this comparison should be summarized in the QOS. Comparisons with other formulations conducted during development should be included in 3.P.2.

Is it possible to submit an amendment in CTD format for a product that was already submitted in the old ANDA format?

> No, all amendments to an application under review should use the same format as the original submission.

How is a paper CTD to be paginated?

> "Page numbering in the CTD format should be at the document level and not at the volume or module level. (The entire submission should never be numbered consecutively by page.) In general, all documents should have page numbers. Since the page numbering is at the document level, there should only be one set of page numbers for each document."[2]. For paper submission, tabs locating sections and subsections are useful.

For the ANDA submitted as in paper CTD format, can we submit the bioequivalence study report electronically? Or does the Agency require paper copy only?

> The bioequivalence summary tables should always be provided in electronic format.

Will QbR lead to longer review times?

> Many of the current long review times result from applications that do not completely address all of the review issues and OGD must request additional information through the deficiency process. This iterative process will be reduced with the use of the QbR template.
>
> Sponsors that provide a QOS that clearly and completely addresses all the questions in the QbR should find a reduction in the overall review time.

Will DMFs for the drug substance be required to be in CTD if the ANDA is in CTD format?

> No. CTD format DMFs are recommended.

What should be included in 3.2.R.1.P.2, Information on Components?

> COA's for drug substance, excipients and packaging components used to produce the exhibit batch.

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[2] Submitting Marketing Applications According to the ICH/CTD Format: General Considerations http://www.fda.gov/cder/guidance/4707dft.pdf

How should an ANDA sponsor respond to deficiencies?

OGD requests that sponsors provide a copy of the response to deficiencies in electronic format as both a pdf file and a Microsoft Word file.

QUALITY OVERALL SUMMARY CONTENT QUESTIONS

2.3 Introduction to the Quality Overall Summary

What information should be provided in the introduction?

Proprietary Name of Drug Product:

Non-Proprietary Name of Drug Product:

Non-Proprietary Name of Drug Substance:

Company Name:

Dosage Form:

Strength(s):

Route of Administration:

Proposed Indication(s):

Maximum Daily Dose:

2.3.S DRUG SUBSTANCE

What if an ANDA contains two or more active ingredients?

> Prepare separate 2.3.S sections of the QOS for each API. Label them 2.3.S [API 1] and 2.3.S [API 2].

What if an ANDA contains two or more suppliers of the same active ingredient?

> Provide one 2.3.S section. Information that is common between suppliers should not be repeated. Information that is not common between suppliers (e.g. different manufacturing processes) should have separate sections and be labeled accordingly (drug substance, manufacturer 1) and (drug substance, manufacturer 2).

Can information in this section be provided by reference to a DMF?

> See individual questions for details. As a general overview:
>
> - Information to be referenced to the DMF
> - Drug substance structure elucidation;
> - Drug substance manufacturing process and controls;
> - Container/closure system used for packaging and storage of the drug substance;
> - Drug substance stability.
> - Information requested from ANDA Sponsor
> - Physicochemical properties;
> - Adequate drug substance specification and test methods including structure confirmation;
> - Impurity profile in drug substance (process impurity or degradant);
> - Limits for impurity/residual solvent limits;
> - Method validation/verification;

- Reference standard.

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

What format should be used for this information?

Chemical Name:

CAS #:

USAN:

Molecular Structure:

Molecular Formula:

Molecular Weight:

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting point, and partition coefficient?

What format should be used for this information?

Physical Description:

pKa:

Polymorphism:

Solubility Characteristics:

Hygroscopicity:

Melting Point:

Partition Coefficient:

Should all of these properties be reported? Even if they are not critical?

Report ALL physicochemical properties listed in the question even if they are not critical. If a property is not quantified, explain why, for example: "No pKa because there are no ionizable groups in the chemical structure" or "No melting point because compound degrades on heating".

What solubility data should be provided?

The BCS solubility classification[3] of the drug substance should be determined for oral dosage forms.

Report aqueous solubility as a function of pH at 37º C in tabular form. Provide actual values for the solubility and not descriptive phrases such as "slightly soluble".

[3] See BCS guidance http://www.fda.gov/cder/guidance/3618fnl.pdf for definition

Solvent Media and pH	Solubility Form I (mg/ml)	Solubility Form II (mg/ml)

Should pH-solubility profiles be provided for all known polymorphic forms?

> No, it is essential that the pH-solubility profile be provided for the form present in the drug product. The relative solubility (at one pH) should be provided for any other more stable forms.

Physicochemical information such as polymorphic form, pKa, solubility, is usually in the confidential section of DMF. Is reference to a DMF acceptable for this type of information?

> No, knowledge of API physicochemical properties is crucial to the successful development of a robust formulation and manufacturing process. In view of the critical nature of this information, OGD does not consider simple reference to the DMF to be acceptable.

The *Guidance for Industry: M4Q: The CTD-Quality Questions and Answers/ Location Issues* says only the polymorphic form used in the drug product should be described in S.1 and other known polymorphic forms should be described in S.3. OGD's examples placed information about all known polymorphic forms in S.1. Where does OGD want this information?

> This information may be included in either S.1 or in S.3. Wherever presented, list all polymorphic forms reported in literature and provide brief discussion (i.e., which one is the most stable form) and indicate which form is used for this product.
>
> Other polymorph information should be presented by the ANDA applicant as follows:
>
> - 2.3.S.3 Characterization: Studies performed (if any) and methods used to identify the potential polymorphic forms of the drug substance. (x-ray, DSC, and literature)
> - 2.3.S.4 Specification: Justification of whether a polymorph specification is needed and the proposed analytical method
> - 2.3.P.2.1.1 Pharmaceutical Development –Drug Substance: Studies conducted to evaluate if polymorphic form affects drug product properties

Why does OGD need to know the partition coefficient and other physicochemical properties?

> Physical and chemical properties may affect drug product development, manufacture, or performance.

2.3.S.2 Manufacture

Who manufactures the drug substance?

How should this be answered?

> Provide the name, address, and responsibility of each manufacturer, including contractor, and each proposed production site or facility involved in manufacturing and testing. Include the DMF number, refer to the Letter of Authorization in the body of data, and identify the US Agent (if applicable)

How do the manufacturing processes and controls ensure consistent production of the drug substance?

Can this question be answered by reference to a DMF?

Yes. It is preferable to mention the source of the material (synthetic or natural) when both sources are available.

The DMF holder's COA for the batch used to manufacture the exhibit batches should be provided in the body of data at 3.2.S.4.4.

If there is no DMF, what information should be provided?

A complete description of the manufacturing process and controls used to produce the drug substance.

2.3.S.3 Characterization

How was the drug substance structure elucidated and characterized?

Can structure elucidation be answered by reference to a DMF?

Yes.

What information should be provided for chiral drug substances?

When the drug substance contains one or more chiral centers, the applicant should indicate whether it is a racemate or a specific enantiomer.

When the drug substance is a specific enantiomer, then tests to identify and/or quantify that enantiomer should be included. Discussion of chirality should include the potential for interconversion between enantiomers (e.g. racemization/epimerization).

How were potential impurities identified and characterized?

List related compounds potentially present in the drug substance. Identify impurities by names, structures, or RRT/HPLC. Under origin, classify impurities as process impurities and/or degradants.

ID	Chemical Name	Structure	Origin
	[Specified Impurity]		

Is identification of potential impurities needed if there is a USP related substances method?

Yes.

Can this question be answered by reference to a DMF?

The ANDA should include a list of potential impurities and their origins. The methods used to identify and characterize these impurities can be incorporated by reference to the DMF.

According to the CTD guidance, section S.3 should contain a list of potential impurities and the basis for the acceptance criteria for impurities, however in the OGD examples this information was in section S.4. Where should it go?

This information may be included in either S.3 or in S.4.

2.3.S.4 Control of Drug Substance

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

What format should be used for presenting the specification?

Include a table of specifications. Include the results for the batch(es) of drug substance used to produce the exhibit batch(es). Identify impurities in a footnote. Test results and acceptance criteria should be provided as numerical values with proper units when applicable.

Tests	Acceptance criteria	Analytical procedure	Test results for Lot#
Appearance			
Identification A: B:			
Assay			
Residual Solvents			
Specified Impurities RC1 RC2 RC3 Any Unspecified Impurity Total Impurities			
[Additional Specification]			

*RC 1: [impurity identity]
RC 2: [impurity identity]
RC 3: [impurity identity]

What tests should be included in the drug substance specification?

USP drugs must meet the USP monograph requirements, but other tests should be included when appropriate. For USP and non USP drugs, other references (EP, BP, JP, the DMF holder's specifications, and ICH guidances) can be used to help identify appropriate tests.

Only relevant tests should be included in the specification. Justify whether specific tests such as optical rotation, water content, impurities, residual solvents; solid state properties (e.g. polymorphic form, particle size distribution, etc) should be included in the specification of drug substance or not.

Does OGD accept foreign pharmacopeia tests and criteria for drug substances?

There are several examples where a drug substance is covered by a monograph in EP or JP, but not in the USP. ANDA and DMF holders can obtain information regarding physicochemical properties, structure of related impurities, storage conditions, analytical test methods, and reference standards from EP or JP to support their submission to OGD. Although the USP remains our official compendium, we usually accept EP when the drug substance is not in USP (However, a complete validation report for EP methods should be provided in the ANDA).

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

What level of detail does OGD expect for the analytical method justifications and validations?

Provide a summary of each non-USP method. This can be in a tabular or descriptive form. It should include the critical parameters for the method and system suitability criteria if applicable. See an example in section 2.3.P.5 of this document.

For each analytical procedure, provide a page number/link to the location of validation information in Module 3. For quantitative non-compendial analytical methods, provide a summary table for the method validation. See an example in section 2.3.P.5 of this document.

Is validation needed for a USP method?

No, but USP methods should be verified and an ANDA sponsor should ensure that the USP assay method is specific (e.g. main peak can be separated from all process impurities arising from their manufacturing process and from degradation products) and the USP related substance method is specific (e.g. all the process impurities and degradants can be separated from each other and also separated from main peak).

Is validation needed if the USP method is modified or replaced by an in-house method?

Yes. Data supporting the equivalence or superiority of the in-house method should be provided. In case of a dispute, the USP method will be considered the official method.

Is reference to the DMF for drug substance analytical method validations acceptable?

No. ANDA sponsors need to either provide full validation reports from the ANDA holder or reference full validation reports from the DMF holder (provided there is a copy of the method validation report in the ANDA and method verification from the ANDA holder).

Appearance

Identity

Assay

Impurities (Organic impurities)

What format should be used for related substances?

List related compounds potentially present in the drug substance. (Either here or S.3)

Name	Structure	Origin
[Specified Impurity]		

Provide batch results and justifications for the proposed acceptance criteria. See guidance on ANDA DS impurities[4] for acceptable justifications. If the DS is compendial, include the USP limits in the table. If the RLD product is used for justification/qualification, then its results should also be included. If an ICH justification is used, then the calculation of the ICH limits should be explained.

To use the ICH limits, determine the Maximum Daily Dose (MDD) indicated in the label and use it to calculate the ICH Thresholds: Reporting Threshold (RT), Identification Threshold (IT), and Qualification Threshold (QT).

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

1. The amount of drug substance administered per day
2. Higher reporting thresholds should be scientifically justified
3. Lower thresholds can be appropriate if the impurity is unusually toxic

Sponsors can use the ICH limits to ensure the LOQ for the analytical method is equal or below the RT, establish the limit for "Any Unspecified Impurity" to equal or below the IT, and establish limits for each "Specified Identified Impurity" and each "Specified Unidentified Impurity"[5] to equal or below the QT.

An impurity must be qualified if a limit is established above the QT. Options for qualification include reference to the specific impurity listed in a USP monograph, comparison to the RLD product, identifying the impurity as a significant metabolite of the drug substance, literature references including other compendial monographs (EP, BP, JP), or conducting a toxicity study.

[4] http://www.fda.gov/cder/guidance/6422dft.pdf

[5] The ANDA DS guidance states "For unidentified impurities to be listed in the drug substance specification, we recommend that you clearly state the procedure used and assumptions made in establishing the level of the impurity. It is important that unidentified specified impurities be referred to by an appropriate qualitative analytical descriptive label (e.g., unidentified A, unidentified with relative retention of 0.9)". Q3A(R) states "When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application."

Name	Drug Substance (Lot #)	USP Limit for Drug Substance	RLD Drug Product (Lot #)	Proposed Acceptance criteria	Justification
[Specified Impurity,Identified]	[Batch Results]		[Batch Results]		
[Specified Impurity,Unidentified]					
Any Unspecified Impurity					
Total Impurities					

Include the column for RLD drug product only if that data is used to justify the drug substance limit (example a process impurity that is also found in the RLD).

What is OGD's policy on genotoxic impurities?

FDA is developing a guidance for genotoxic impurities. According to the ICH Q3A lower thresholds are appropriate for impurities that are unusally toxic.

If impurities levels for an approved generic drug are higher than the RLD, can the approved generic drug data be used as justification for a higher impurity specification?

According to ANDA DP and DS Impurity guidances, any approved drug product can be used to qualify an impurity level. However, the guidances qualify this by later stating "This approved human drug product is generally the reference listed drug (RLD). However, you may also compare the profile to a different drug product with the same route of administration and similar characteristics (e.g. tablet versus capsule) if samples of the reference listed drug are unavailable or in the case of an ANDA submitted pursuant to a suitability petition."

What if there are no impurities' tests found in the USP monograph for a USP drug substance? What should the ANDA sponsor do?

Please work with your supplier (DMF Holder) to ensure that potential synthetic process impurities (e.g. isomers (if any), side reaction products), degradation impurities, metal catalysts, and residual solvents are adequately captured by your impurities test method. There may be information available in published literature as well, regarding potential impurities.

Can levels of an impurity found in the RLD and identified by RRT be used for qualification?

Qualification of a specified unidentified impurity by means of comparative RRT, UV spectra, and mass spectrometry with the RLD may be acceptable. However, the ANDA sponsor should make every attempt to identify the impurity.

If levels are higher than in an approved drug product then the sponsor should provide data for qualification of the safety of this impurity at this level.

Can a limit from a USP monograph for "any unspecified impurity" be used to justify a limit for "any unspecified impurity" greater than the ICH Q3 identification threshold?

> No. Any unspecified impurity (any unknown) limit should not exceed ICH Q3A "IT" based on MDD. Non-specific compendial acceptance criteria (e.g. Any Individual Impurity is NMT 0.5%) should not be used for justification of proposed impurity acceptance criteria. However, if the USP limit is less than the ICH threshold, then the USP limit should be used.

Can a limit for an identified impurity in the drug substance be qualified with data obtained from RLD drug product samples treated under the stressed conditions?

> No. Test various samples of marketed drug product over the span of its shelf life (ideally, near the end of shelf-life). Data generated from accelerated or stressed studies of the RLD is considered inappropriate.

Impurities (Residual Solvents)

Will OGD base residual solvent acceptance limits on ICH limits or process capability?

> The ICH guidance on residual solvents[6] provides safety limits for residual solvents but also indicates that "residual solvents should be removed to the extent possible". ANDA residual solvent limits should be within the ICH safety limits, but the review of the ANDA includes both of these considerations.
>
> OGD generally accepts the ICH limits when they are applied to the drug product.

What about solvents that are not listed in Q3C?

> Levels should be qualified for safety.

Impurities (Inorganic impurities)

Polymorphic Form

When is a specification on polymorphic form necessary?

> See ANDA polymorphism guidance[7] for a detailed discussion.

Particle Size

When is a drug substance particle size specification necessary?

> A specification should be included when the particle size is critical to either drug product performance or manufacturing.
>
> For example, in a dry blending process, the particle size distribution of the drug substance and excipients may affect the mixing process. For a low solubility drug, the drug substance particle size may have a critical impact on the dissolution of the drug product. For a high solubility drug, particle size is often not critical to product performance.

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[6] http://www.fda.gov/cder/guidance/Q3Cfnl.pdf

[7] http://www.fda.gov/cder/guidance/6154dft.pdf

What justification is necessary for drug substance particle size specifications?

As for other API properties, the specificity and range of acceptance criteria for particle size, and the justification thereof, could vary from none to very tight limits, depending upon the criticality of this property for that drug product.

Particle size specifications should be justified based on whether a change in particle size will affect the ability to manufacture the product or the final product performance.

In general, a sponsor either should demonstrate through mechanistic understanding or empirical experiments how changes in material characteristics such as particle size affect their product.

In the absence of pharmaceutical development studies, the particle size specification should represent the material used to produce the exhibit batch.

When should the particle size be specified as distribution [d90,d50,d10] and when is a single point limit appropriate?

When critical, a particle size should be specified by the distribution. There may be other situations when a single point limit can be justified by pharmaceutical development studies.

2.3.S.5 Reference Standards

How were the primary reference standards certified?

For non-compendial, in-house reference standards, what type of qualification data is recommended? Will a COA be sufficient?

COA should be included in Module 3, along with details of its preparation, qualification, and characterization. This should be summarized in the QOS.

In terms of the qualification data that may be requested, it is expected that these reference standards be of the highest possible purity (e.g. may necessitate an additional recrystallization beyond those used in the normal manufacturing process of the active ingredient) and be fully characterized (e.g. may necessitate in the qualification report additional characterization information such as proof of structure via NMR) beyond the identification tests that are typically reported in a drug substance COA. Standard Laboratory Practice for preparation of reference standards entails recrystallization to constant physical measurements or to literature values for the pure material.

2.3.S.6 Container Closure System

What container closure is used for packaging and storage of the drug substance?

Can this question be answered by reference to a DMF?

Yes.

2.3.S.7 Stability

What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

Can this question be answered by reference to a DMF?

The ANDA QOS should always include the retest or expiration date. The retest date or expiration is required to be present in the labeling of the drug substance container and to be present on all COAs. Drug substance stability data that supports the retest or expiration date should be included by reference to the DMF.

What is a retest date?

Retest date: The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.[8]

Retest period: The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times (and a different portion of the batch used after each retest), as long as it continues to comply with the specification.

What is an expiration date?

Expiration date: The date placed on the container label of a drug substance designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.[8] For most biotechnological/biological substances known to be labile, it is more appropriate to establish an expiration date than a retest date (period). The same may be true for certain antibiotics.[8]

Should information about the intrinsic stability of the drug substance such as stress testing and identification of degradation pathways go in this section?

No, this information may affect the design, performance or manufacture of the drug product and should be discussed in the QOS at 2.3.P.2.1.1. The data should be included in module 3 of the application.

[8] Q1A(R2) Stability Testing of New Drug Substances and Products http://www.fda.gov/cder/guidance/5635fnl.pdf

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

What are the components and composition of the final product? What is the function of each excipient?

How should the composition be presented?

For each strength, list the quantitative composition and function of each component in the drug product. Include solvents and processing aids removed during processing. Indicate which components are compendial. Excipient grade should be discussed in 2.3.P.4 (Control of Excipients). The total amount of material in exhibit and production batches goes in [2.3.P.3]

For modified release products with multiple processing steps, the composition of the significant intermediates (for example: tablet cores or beads) should be presented, in addition to the composite composition statement.

Ingredient	Function	Weight/tablet	% (w/w)
[Drug Substance]	Active		
[Excipient, NF]			
[Solvent]	Solvent*		
Total Weight			

* Removed during the manufacturing process

Identify and justify any formulation overages or overfills that appear in the final product. Manufacturing overages should be discussed in 2.3.P.3. Overfills are discussed in the appropriate USP sections on Pharmaceutical Dosage Forms.

Note that, in general, the only acceptable justification for an overage in the final drug product formulation is the demonstration of the same overage in the RLD

Does any excipient exceed the IIG limit for this route of administration?

How should the composition be compared to the IIG limits?

List IIG limits for each excipient in a table.

Ingredient	Amount per unit of Drug Product, Strength	IIG levels (per unit)
[Excipient]		

Please note that the publicly available IIG database http://www.accessdata.fda.gov/scripts/cder/iig/ provides the highest level for a single unit.

In the OGD review of this question, reviewers may compare the maximum daily dose of an excipient to the maximum daily dose of that excipient found in a previously approved drug product with the same route of administration.

If the maximum daily dose of an excipient exceeds the IIG level (for single unit) in the public database, then it is prudent for an ANDA sponsor to identify an example use of this

excipient in an approved drug product at a higher daily dose than in the proposed ANDA product.

What details are expected for an excipient that is not specifically listed in the IIG, especially colors or flavors?

For colors or flavors, indicate the compositions or have the manufacturer fax the composition to OGD if it is not available to the sponsor.

What about elemental iron?

In the QOS, a sponsor should indicate that their product meets the 21 CFR 73.1200 requirement of NMT 5-mg elemental iron/day. We encourage sponsors to include the detailed calculation of iron content/day in Module 3.

Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?

What comparisons does OGD recommend?

The ANDA drug product must be pharmaceutically equivalent to the RLD.

Compare the formulation of the RLD to the proposed generic drug product

Reference Listed Drug	Proposed Generic Drug Product	Function
[Excipient]	[Excipient]	
[Excipient]	[Excipient]	

Can an ANDA product use different excipients than the RLD?

Differences in inactive ingredients are generally acceptable. For more complex dosage forms please provide justifications for differences in inactive ingredients. In addition, note that several specific dosage forms have stricter requirements indicated in the CFR.

- Parenteral, ophthalmic, and otic solutions must have the same inactive ingredients (see 21 CFR 314.127(a)(8) and 21 CFR 314.94(a)(9) for requirements and exceptions)
    - Inactive ingredient changes permitted in drug product [21 CFR 314.94(a)(9)].
        - (iii) - Parenteral use: Should be Q1[9] and Q2[10] except for preservative, buffer or antioxidant
        - (iv) - Ophthalmic & Otic use: Should be Q1 and Q2 except for preservative, buffer, thickening agent or tonicity adjuster.
        - (v) Topical use (including aerosol & nasal solutions): Should contain same inactive ingredients (Q1). However, an abbreviated application may include different inactive ingredients

[9] Q1= the same inactive ingredients

[10] Q2= the same concentration of inactive ingredients

    - The allowable changes described in the CFR are only allowable "provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product." Allowable changes may require justification by additional bioequivalence studies.
- For solutions, differences in inactive ingredients may affect eligibility for biowaivers (see 21 CFR 320.22(b)(3)(iii)) and thus the differences should be justified here. Examples
    - Amount of sorbitol or mannitol in an oral solution
    - Amount of penetration enhancer in a topical product
    - Any Q1 or Q2 difference in an ophthalmic solution
    - Any Q1 or Q2 difference in inhalation and nasal spray products[11]
- For suspensions please always justify differences in inactive ingredients especially with respect to their effect on viscosity and resuspendability

Can an ANDA product use a different release mechanism than the RLD?

An ANDA product may have a different mechanism as long as the product performance and safety will be equivalent to the RLD. OGD can reject an application with a passing bioequivalence study if the difference in mechanism poses a safety or efficacy risk to the public (see 21 CFR 314.127(a)(8)(ii)(A)(5)).

For modified release products, please explain any difference in release mechanism from the RLD. It is recommended that comparative dissolution between the RLD and ANDA products in multiple dissolution media be provided. If there are differences, please explain the differences in terms of the release mechanism.

Will OGD fail to approve a product that is bioequivalent to the RLD and meets specifications based on the answer to this question?

If the differences between RLD and ANDA product can affect safety or efficacy when used according to the label, then OGD has the authority under the CFR to not approve the ANDA product.

For modified release products, it is possible for two products with very different plasma concentration profiles (such as different shape or different Tmax) to have equivalent AUC and Cmax. In such cases, the sponsor should identify the formulation and/or release mechanism attributes that are responsible for this difference in profiles and provide a justification as to why the difference in plasma concentration profiles does not affect therapeutic equivalence.

2.3.P.2 Pharmaceutical Development

How long should the development report be?

A complete development report should be included in Module 3. It should include development from the initial planning for an ANDA for this RLD. It should tell the

[11] Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action http://www.fda.gov/cder/guidance/5383DFT.pdf

development story that led to the final formulation and include the identification of critical formulation and process variables for this product. See ICH Q8 for details.

The Module 3 development report should summarize the development process and should not include raw study reports. It should present the results of the development pathway using summary charts and tables. The reader should be able to see how the formulation evolved in development and what the sponsor learned from each change.

How long should the summary of the development report in the QOS be?

The QOS of the development report should be guided by the questions provided by OGD.

How far back should development history go?

To the initial planning for an ANDA for this RLD.

What if the dissolution method used in development process is different from the FDA recommended dissolution method?

Any appropriate dissolution method can be used in the development process.

Can development lots be non-GMP produced?

Yes.

What should a sponsor do if legal advice is not to share motivations for choices made in development that involve working around formulation or process patents.

If a justification is not provided in the development report, a reviewer may ask the firm by telephone for an explanation.

Why is OGD asking questions about Product Development?

The goal of a generic sponsor is to design a product that is equivalent to the RLD. As FDA is moving toward quality by design and away from quality by testing, reviewers are expected to evaluate the design of a potential generic product. Once the design of a product is understood then it is possible to set specifications and other requirements to verify that the sponsor is consistently manufacturing product that performs as intended.

The questions on the product development report are intended to guide the reviewer to find useful information about the design of the product and for the sponsor to explain what they did and why.

If a development process reflects a fundamental understanding of the drug product and how its design focused on achieving the critical performance goals, OGD considers that this product is a lower risk than a similar product whose quality is not supported by a development report.

Pharmaceutical development studies can also aid in setting specifications with acceptance criteria that are relevant to critical product performance attributes.

Will OGD find deficiencies in a sponsor’s development process?

No, sponsors are free to do whatever development studies they decide are appropriate.

Reviewers will not write deficiencies based on their evaluation of the sponsors’ research and development program. Reviewers may make comments regarding the conclusions of

the applicant, and a reviewer's evaluation of the pharmaceutical development information supplied may affect the risk assessment of the application.

2.3.P.2.1 Components of the Drug Product

2.3.P.2.1.1 Drug Substance

Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

What does OGD want to know?

The answer should include drug substance properties that affect stability, manufacturing, or biopharmaceutics. The knowledge about drug substance properties drives decisions about formulation and manufacturing.

The intrinsic stability of the drug may affect the design, performance or manufacture of the drug product, thus the characterization of the intrinsic stability of the drug substance (as observed in stress testing or through knowledge of the potential degradation pathways) should be discussed here.

Studies conducted to support the conclusions should be summarized; for example dissolution as a function of drug substance particle size. These studies may provide a basis for setting specifications and acceptance limits or removing tests from the drug substance specification.

2.3.P.2.1.2 Excipients

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

When firms have historical experience and stability data, are excipient compatibility studies needed?

OGD agrees with the ICH Q8 recommendation that compatibility of drug substance with excipients be evaluated as part of pharmaceutical development. However, in some circumstances, experience may suffice. When the ANDA is Q1 and Q2 the same as the RLD, in the absence of known stability problems, historical data may be acceptable in lieu of compatibility studies. However, ANDA sponsors should be cautioned that there might be incompatibilities between drug substance and excipients used in the RLD.

Would acceptable drug product stability be accepted as evidence of excipient-drug substance compatibility?

Acceptable drug product stability is the goal and is necessary for ANDA approval, but this question asks how that goal was reached. End product testing confirms that the goal was reached for the samples tested. Quality by design requires that the mechanistic and formulation factors that affect stability be identified. Relying only on end-product testing is not quality by design and is considered higher risk.

What types of compatibility studies does OGD recommend?

Simple visual inspections of mixed components are NOT acceptable. See Serajuddin et al., J Pharm Sci, 88 696-704 (1999) for an example of a binary compatibility study.

Preparation of trial formulations for accelerated stability testing can be used with DOE to identify interactions that are correlated with reduction of stability.

2.3.P.2.2 Drug Product

How should the drug product development be divided into the OGD questions? It seems like there is overlap among questions.

Here is a high level overview of what OGD is looking for. There are more details in the individual questions.

- What attributes should the drug product possess?
  Answer: What was the goal?
- How was the drug product designed to have these attributes?
  Answer: How did you plan to get there? What variables were adjusted to reach the goal?
- Were alternative formulations or mechanisms investigated?
- How were the excipients and their grades selected?
- How was the final formulation optimized?
  Answer: What studies were conducted during pharmaceutical development? What was learned from them?

What attributes should the drug product possess?

What does OGD mean by attributes in this question?

The answer to this question should describe the Target Product Profile (TPP) that the sponsor is trying to produce.

What is a Target Product Profile?

From R. C. Hwang and D. L. Kowalski, *Design of experiments for formulation development*, Pharmaceutical Technology (Dec 2005)

"A good formulation must be manufacturable, chemically and physically stable throughout the manufacturing process and product shelf life, and bioavailable (i.e., it must contain the exact amount of API in each dose that can be readily absorbed by the human body). In addition, many quality standards and special requirements must be met to ensure the efficacy and safety of the product

All of these formulation goals can be described as the target product profile (TPP). It is important to establish the TPP so that the formulation effort will be effective and focused. The TPP usually includes the route of administration, dosage form and size, special-delivery requirement, maximum and minimum doses, and aspects of pharmaceutical elegance (appearance). The TPP guides formulation scientists to establish formulation strategies and keep formulation effort focused and efficient. Many aspects of the TPP are determined based on factors such as competing drugs on the market or the target patient population (e.g. pediatric formulations may require chewable tablets or a suspension)."

For all ANDA products, bioequivalence with the RLD would be part of the TPP. The TPP might also include the desired drug release profile.

Any characterization of the RLD (dissolution, impurities, lot-to-lot variability) should be discussed under this question.

The TPP should consider the RLD dosage form, drug release mechanism, and labeling (dosage & administration, how supplied).

How was the product designed to have these attributes?

How should a sponsor answer this question?

For most ANDA products, this question would address how the ANDA sponsor designed their product to be bioequivalent to the RLD and meet other aspects of the TPP. It would usually include a discussion of the intended dissolution or drug release profile, the choice of release mechanism, and identification of critical formulation and manufacturing variables that were adjusted to yield a bioequivalent product. A formulation may also be designed to overcome limitations of the drug substance such as poor solubility, poor dissolution, poor permeability, poor stability, or short plasma duration.

If a DOE was used to identify which variables were critical, then it should be described in this question. If a DOE was used to adjust formulation or manufacturing variables to obtain a bioequivalent product, it should be described under the formulation alternatives question. If a DOE was used to improve, establish robustness of, or establish a design space around an acceptable formulation, it should be discussed under the formulation optimization question.

Explain the level of detail needed about the mechanism?

For release profiles, the sponsor should describe how the product achieves the desired profile. For example, does it use an enteric coating or slow release matrix.

Were alternative formulations or mechanisms investigated?

What studies should be discussed under this question?

Studies used to adjust formulation or manufacturing variables to obtain a bioequivalent product should be presented here. These could use a DOE to adjust several variables at once and find an optimal formulation. The studies could also be the result of a trial and error process.

The study summary should describe each formulation and clearly indicate what properties were used to evaluate each formulation. Formulations can be evaluated for their effect on dissolution, in vivo bioavailability, stability or other attributes depending on the development process.

What is the value of describing alternative formulations to the FDA?

OGD is interested in changes to the composition that altered product performance. The development report should cover the knowledge gained from all formulations attempted.

Information on alternative formulations could be used for purposes such as

- assessing post-approval formulation changes
- establishing dissolution test conditions that can detect formulation differences
- setting acceptance limits on raw material or drug substance properties

- establishing that varying the level of an excipient does not alter product performance

Which alternative formulation should be described?

The module 3 development report should include all formulations investigated in the development process. The summary in the QOS should point out to the reviewer which of these formulations were most important and indicate what the sponsor learned about what components are critical or non-critical to product performance.

If an ANDA sponsor, were to develop an IVIVC, then the formulations used in that development should be described here.

Is there a design space for formulation, what will be benefits of design space in postapproval changes?

A design space for composition can be established. This is determined by an individual sponsor's development program. It is not an ANDA requirement to establish a design space.

Changes within an established design space will not require prior approval. Other advantages of a design space are covered in the answer about advantages of providing information about alternative formulations.

If one biostudy failed and the formulation was changed as a result, should the complete report of the failed study be submitted?

With respect to the formulation development program, only the summary results (AUC, Cmax, Tmax) of failed studies should be included in the development report along with the formulations (and applicable dissolution data) used in each study.

Complete biostudy reports should be submitted only for failed biostudies on the marketed formulation.

Will reporting of failed experiments damage the applicant?

Failed experiments will not be damaging to the applicant, they will help the reviewer identify critical formulation attributes.

How were the excipients and their grades selected?

How is selection of excipients different from the design of the formulation?

There is overlap between the questions. The design of the formulation would identify the desired excipient functionality. In this question, the selection of the particular excipient and grade that provides that functionality is described. It is important to indicate when a grade of excipient has been discovered to be critical.

To what extent is it necessary to characterize the different grades of excipient?

The exhibit batch should be produced using the same grade of excipient to be used in commercial production.

If the excipient is the subject of a USP/NF monograph, it should comply with that monograph's provisions. Justification should be provided for the particular grade of excipient chosen and the assessment of criticality of the excipient grade. If multiple grades

of excipients were evaluated, that information should appear in the PD report. Information on multiple grades may be used as supporting evidence to justify applicable specifications limits, or possibly their exclusion altogether (e.g. viscosity).

How was the final formulation optimized?

What does OGD mean by formulation optimization?

An optimization study evaluates relatively small variations around a target formulation. It could also include studies of formulation robustness. Thus, it is distinguished from screening studies that may be conducted earlier in development that explore a large range of space and seek a formulation that meets the Target Product Profile.

What is the benefit to an ANDA sponsor of performing a formulation optimization?

A formulation optimization will establish the robustness of the formulation and may support a design space for the formulation composition. Formulation optimization may also be conducted to optimize the manufacturing process (example determine the optimal lubricant level).

2.3.P.2.3 Manufacturing Process Development

Why is OGD asking questions about Process Development?

An OGD reviewer is trying to evaluate two main questions about the manufacturing process:

- Will the sponsor be able to scale up the exhibit batch to production scale and still produce product consistent with the exhibit batch?
- Will the sponsor be able to manufacture the product consistently over time?

The process development report is where the sponsor demonstrates process understanding that can convince the reviewer that they will be able to scale up the process and execute it consistently. Failure to identify critical process parameters and the critical process steps is an indication that a process may not be well understood. Unidentified critical steps or process parameters may be indicative of a poorly controlled manufacturing process and considered higher risk. .

How should process development information be divided up among the questions?

A high level view of the questions is as follows:

- Why was the manufacturing process described in 3.2.P.3 selected for this drug product?
  - *Connect the process choices to DS properties.*
- How are the manufacturing steps (unit operations) related to the drug product quality?
  - *Connect the process to the product and identify critical steps.*
- How were the critical process parameters identified, monitored, and/or controlled?

- *Summarize the critical parameters and the process development studies used to do this.*

- What is the scale-up experience with the unit operations in this process?
  - *Summarize the scale up plan and the process development studies that support it.*

More details are discussed under the individual questions.

Why was the manufacturing process described in 2.3.P.3 selected for this drug product?

What level of detail should a sponsor provide?

The sponsor should first describe the choice of manufacture process at a high level. For example, for a solid oral dosage form the sponsor should explain the choice between direct compression or wet granulation or some other approach. The sponsor should indicate the factors that were considered including the properties of the drug substance, the desired properties of the drug product, and the complexity and robustness of the process.

Once the process train was selected, a sponsor should focus on particular steps for which there are alternatives available (for example rationale for the selection of high shear granulation versus fluid bed granulation) and explain the motivation for each choice.

Why does OGD want to know this?

This is an opportunity for the sponsor to demonstrate the process understanding used to develop the manufacturing process. If there is process understanding, the manufacturing process is better controlled and considered lower risk.

Is it necessary to investigate alternative unit operations?

It is not required for development studies to evaluate alternative unit operations. However if such studies were conducted to support a process choice, it would aid the reviewer to describe them.

Is it acceptable for a sponsor to indicate that the need to use existing equipment was part of the selection process?

Yes

How are the manufacturing steps (unit operations) related to the drug product quality?

What type of information does OGD want to see to connect process steps to product quality?

The answer to this question the sponsor should indicate the critical steps in the manufacturing process, and establish a link between unit operations and the target product profile, through pilot scale studies or prior knowledge. A sponsor should know which unit operations are critical to which drug product properties. It may be useful to present this information in the form of a matrix between unit operations and quality attributes. Once a step is identified as being critical then the sponsor must design their process to ensure that this step succeeds or have tests in place to detect if the step fails.

	Raw Material	Drug Layering	CR Coating	Encapsulation
Purity	**Critical**			
Assay/Content Uniformity		**Critical**		**Critical**
Release Profile			**Critical**	**Critical**
Stability	**Critical**		**Critical**	

How were the critical process parameters identified, monitored, and/or controlled?

What is a critical process parameter?

A critical process parameter (CPP) is any measurable input (input material attribute or operating parameter) or output (process condition or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency.

Scale independent CPPs, such as material attributes, are the most valuable, because they can be directly used for scale up. For example, a material attribute CPP, such as moisture content, should have the same target value in the exhibit batch process and the commercial scale process. An operating parameter CPP, such as air flow rate, would be expected to change as the process scale changes.

How should critical process parameters be identified?

Prior experience or knowledge can identify key process parameters. A key process parameter is a designation for a potentially critical process parameter. For example, in a blending process, the mixing speed can clearly be identified as a key process parameter because if mixing speed were zero the process step would not be successful. However, this does not mean that mixing speed is always a critical parameter. If development studies demonstrated the blending was not affected by realistic changes in mixing speed, it would not be identified as critical. Without development studies, a sponsor may have a large number of key parameters they need to constrain at fixed values because they might be critical. Classification of key parameters as critical or not critical is an important step toward a flexible manufacturing process.

Risk assessment tools can prioritize the key parameters for further investigation to determine if they are critical.

Critical process parameters should be identified by scientific investigations and controlled variations of operating parameters. The focus in the process development report is on the additional studies that build this knowledge. These studies can be conducted on pilot or lab scale and do not need to be conducted under cGMP. When the sensitivity of critical process parameters is established, this can be used to design appropriate control strategies.

How much data is needed?

In order to provide flexibility for future process optimization, when describing the development of the manufacturing process, it is useful to describe any measurement systems that allow monitoring of critical attributes or process end-points. Collection of process monitoring data during the development of the manufacturing process can provide useful information to enhance process understanding. The process controls that provide

process adjustment capabilities to ensure control of all critical attributes should be described. These provide a means for a risk control strategy.

How can previous experience be used?

When supported by documented examples, prior experience can be used to classify a key parameter as not critical. For example, an ANDA sponsor that used the same blender for multiple products with similar formulations might use that information to support a claim that the key process parameter mixing speed was not critical.

Prior experience may also be used to develop process models and thus reduce the number of experiments needed to establish the critical process parameters for the current product.

Prior experience can serve as the basis for a proposed design space. However, a design space may need to be supported by some data on the current product.

Is it necessary to establish a design space?

No. A design space provides a clear path to regulatory flexibility but it is not required. A sponsor may choose to establish a design space after approval.

What is the scale-up experience with the unit operations in this process?

What type of experience should be included?

Valuable experience includes experience with other products using the same unit operations, literature references/vendor scale-up factors, the lab scale to exhibit batch process transfer for this product, exhibit batch production, as well as modeling and dimensional analysis.

The result should be a plan to scale up the process to commercial scale that includes identification of operating parameters that may be scale dependent and process monitoring (in excess of meeting regulatory specifications) that ensures the commercial scale process will be equivalent to the process that produced the exhibit batch.

In the answer to this question, the sponsor should describe how the scale-up plan was developed.

How can previous experience be used?

Prior experience with the unit operations should be included in the process development report to support a scale up plan.

How should sponsors decide when it is appropriate to reference previously approved ANDAs and which ones (all?) to reference?

Sponsors should consider referring to more recent ANDAs, if relevant. The most relevant ANDAs are those in which the same unit operations were scaled up. Other important criteria are similarity of equipment and change of scale, physical properties of the drug, similarity of dosage form, and similarity of the excipients.

2.3.P.2.4 Container Closure System

What specific container closure attributes are necessary to ensure product quality?

What container closure information should be provided here and what should go in section P.7?

2.3.P.2.4 should discuss studies conducted to identify what are the needed attributes including identity, suitability (protection, compatibility, and performance), and safety. We further recommend information from 'Guidance to Industry –Container Closure Systems for Packaging Human Drugs and Biologics'. For solid oral products, the need for container closure development studies is generally driven by identified stability issues. For drug products that incorporate delivery devices (nasal sprays, MDI/DPI), pharmaceutical development studies conducted to design the device should be discussed in this section.

For example, 2.3.P.2.4 can discuss:

- Stability concerns for drug product requiring special storage
  - Light resistant
  - Moisture protection
  - Inert atmosphere
- Suitability of proposed system
  - Dosage form compatibility (e.g. extractables, leachables, dye from labeling)
  - Performance of C/C system (e.g. dropper consistency, calibration of delivery device)

2.3.P.7 should reference applicable quality control test results in the body of data that demonstrate that the proposed system has these attributes.

2.3.P.3 Manufacture

Who manufactures the drug product?

What information is requested here?

Include the location(s) of drug product manufacturing, testing and packaging. Information for responsibilities must be specific (type of test and name of material tested for should be clearly described).

Name and Address	Detailed Responsibilities	cGMP Certification
ABCD Inc. Street City, State CFN #	▪ Manufacturing, Packaging, and Testing for release and stability of drug product	Provided on page #
EFGH Labs. Street City, State CFN #	▪ Particle size test for drug substance ▪ Microbial limit test for Water	Provided on page #

What are the unit operations in the drug product manufacturing process?

Process Flow Diagram and Narrative Summary

What should be in the diagram?

Include a process flow diagram for the proposed commercial process and a brief (< 1 page) narrative summary of the manufacturing process. Indicate the location of any in-process tests. Include points of material entry and process conditions.

Reprocessing statement:

Should the QOS include a reprocessing statement?

In the QOS, indicate if there is reprocessing and include the text of the reprocessing statement from 3.2.P.3.3 in the QOS.

What is the reconciliation of the exhibit batch?

What information is requested?

In the QOS, a table for reconciliation should be provided. Yield should be cumulative and all losses accounted for. Include a reference to any applicable investigation of losses. Tables on batch reconciliation summaries in the QOS should not exceed 1/2-1 page.

Process Step	Exhibit Batch Result	Target	Limit
[Step]			
Yield			
[Step]			
Yield			
Units Produced			
[Package Configuration]			
Units Packaged			
Accountability			

Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?

What format should be used?

Batch Formula

List all components (each inactive or processing aid) that contact drug substance or product during any stage of manufacture. Indicate and justify any overages or adjustments that are used.

Component	Pivotal ANDA Batch [# of Units]	Commercial Batch [# of Units]	% (w/w)
[Drug Substance]			
[Excipient]			
[Solvent]			
Total Weight			

Batch records

Should batch records be in the QOS?

No. Include batch records for the ANDA batch and proposed commercial batches in section 3.2.R.1.P.1 or 3.2.P.3.3 . The ANDA checklist of 10/10/2006 recommends 3.2.P.3.3, but according to the 2001 Guidance for Industry M4Q: The CTD - Quality[12] the batch record is regional information and should be in 3.2.R.1.P.1.

What are the in-process tests and controls that ensure each step is successful?

What format should be used?

Provide a table of unit operations and the associated in-process tests for the proposed commercial process. Indicate any differences between the proposed commercial process and the in-process tests for the exhibit batch.

In-Process Test	Acceptance Criteria	Analytical Procedure	Results Exhibit Batch #
[Process Step] [Test Description]			

Justifications for acceptance limits should be supported by pharmaceutical development studies. Example: Hardness range justified with dissolution and friability testing at extremes.

How are the in-process tests related to pharmaceutical development studies?

Question in 2.3.P.2.3: *How are the manufacturing steps (unit operations) related to the drug product quality?*

The critical attributes that were identified in the pharmaceutical development and linked to specific unit operation should be identified in the in-process test or alternatively, controlled in some other way (e.g. via process control or identified through end product release testing).

Question in 2.3.P.2.3: *How were the critical process parameters identified, monitored and controlled?*

[12] http://www.fda.gov/cder/guidance/4539Q.htm

Control of critical process parameters ensures that in-process and release tests will succeed. Well understood critical process parameters may reduce the need for in-process tests and, potentially reduce release tests.

What is the difference in size between commercial scale and exhibit batches? Does the equipment use the same design and operating principles?

How should this information be presented?

Summarize the equipment used on each scale. Indicate any differences in operating principles. The equipment size used for development studies that were smaller than the exhibit batch should also be included when the sponsor used studies on that scale to justify any limits or identify any critical parameters.

Unit Operation	Equipment	Development Studies	ANDA batch	Commercial batch	Rationale for change
		[kg /batch] [units/batch]	[kg /batch] [units/batch]	[kg /batch] [units/batch]	
[Process Step]	[Equipment Class]	[Brand and Size]	[Brand and Size]	[Brand and Size]	
[Process Step]	[Equipment Class]	[Brand and Size]	[Brand and Size]	[Brand and Size]	

Identify changes in equipment, critical or quality related steps and controls, and include rationale for changes. The rationale may be as simple as due to larger batch size (larger bin blender) or may need supportive development data referencing the development report (major change in operating parameters).

In the proposed scale-up plan, what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?

How should this information be presented?

OGD expects the in-process tests, release specifications, and process description to be fixed. The ANDA sponsor has flexibility in adjusting operating parameters (time, flow rate, temperature, etc) to meet these constraints during scale-up. For commercial scale-up, an ANDA sponsor may either propose fixed ranges for these operating parameters in a proposed master batch record or indicate that an operating parameter will be adjusted to reach a desired end-point.

Operating Parameter	Pivotal Batch	Proposed Commercial Scale	Rationale
Unit Operation #1			
Parameter 1	Value or range	Value or range	Adjusted to meet end-point
Parameter 2	Value or range	Value or range	Scale-independent variable
Parameter 2	Value or	Value or range	Linear scale-up rule established

	range		in PD
Unit Operation #2			
Parameter 1	Value or range	Value or range	

The scale-up rationale should be provided and should focus on critical steps in the manufacturing process. This rationale should build on the experience (including problems that were identified and resolved) obtained during development and/or the production of the exhibit batch(es).

What evidence supports the plan to scale up the process to commercial scale?

What is the difference between this question and the scale up question in the pharmaceutical development section?

The answer to this question may be provided by reference to the pharmaceutical development section. It is placed here to indicate that if the OGD reviewer does not believe that the sponsor has an appropriate scale up plan in place, deficiencies may be issued.

Can non cGMP data support scale up?

Yes.

2.3.P.4 Control of Excipients

What are the specifications for the inactive ingredients and are they suitable for their intended function?

Compendial Excipients

What format should be used for presenting the excipient specifications?

For compendial excipients a table indicating the grade is requested

Ingredient	**Manufacturer**	**Grade**	**Lot Numbers***		**Complies with USP/NF Tests**
			Supplier	Applicant	
[Excipient]					

* Lot numbers used in production of the exhibit batch

Where should a sponsor indicate that they have specifications in excess of compendial standards?

In this question, a sponsor should include a table for each excipient that has additional specifications. These additional specifications should be justified in Section 2.3.P.2.2 (Product Development).

Tests	Acceptance Criteria	Analytical Procedure	Batch #
[Extra Test]			[Results from Excipient Batch]

Non-Compendial Excipients

What additional information is requested for non-compendial excipients?

The specifications for the non-compendial excipient should be included in the QOS in a tabular form and indicate method validation if applicable. The grade used should also be indicated.

Excipients from Animal Origin

Reference the location of BSE/TSE certification, country of origin, as applicable.

Novel Excipients

Novel excipients not previous used in may require more details including manufacture, characterization, controls, etc. or a DMF reference and qualification for safety[13]. Novel excipients are almost never used in an ANDA product.

How do I show that an excipient is suitable for its intended function?

For non-critical excipients, the known functions of common excipients are sufficient to determine suitability.

If an excipient is critical, then reference can be made to the pharmaceutical development studies that identify the critical attributes of that excipient. For example, in the development of a modified release product, it is common to pay particular attention to the properties of release controlling excipients.

[13] Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients http://www.fda.gov/cder/guidance/5544fnl.pdf

2.3.P.5 Control of Drug Product

What is the drug product specification? Does it include all the critical drug product attributes?

What format should be used for presenting the specification?

Tests	Acceptance Criteria	Analytical Procedure	Batch #
Appearance			[Results from Exhibit Batch]
Identification A.			
Assay			
Content Uniformity			
Degradation Products [Specified Degradation Product] Any Unspecified Degradation Product Total Degradation Products			
Dissolution			
[Other Specifications]			

For Batch results:

- Results for all strengths should be included. They may be tabulated separately or included in the specification table
- Quantitative results should be presented numerically, not in general terms such as "complies" or "meets limit".
- For Content Uniformity either all the individual results or range and %RSD can be reported for 10 samples. If 30 samples were tested, all the individual results should be reported along with %RSD.
- For Dissolution, either all the individual results or range can be reported for S1. For S2 or S3 all the individual results should be reported.
- For specified degradation products, all results that are equal to or greater than LOQ should be reported. Lower results should be reported as "Below LOQ" or "Not detected".

What tests should be included in the drug product specification?

USP drug products must meet the USP monograph requirements. Any proposed monograph in the PF should be acknowledged or discussed.

In addition to the USP, ICH Q6A can be used to help identify appropriate tests. The following tests are considered generally applicable to all drug products (ICH Q6A):

- Description
- Identification
- Assay
- Degradation products

Other dosage form specific tests should be included as appropriate (e.g. dissolution, uniformity of dosage units, water content, microbial limits, etc.) and their inclusion justified.

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

What level of detail does OGD expect for the analytical method justification and validation?

Provide a summary of each non-USP method. This can be in a tabular or descriptive form. It should include the critical parameters for the method and system suitability criteria, if applicable. For impurity methods, state if impurities are quantified using impurity standards. If not, list the Relative Response Factors for impurities.

Example summary for HPLC method:

Mobile Phase	Acetonitrile: Buffer = 30 : 70 Buffer: Dissolve 6.8 g of KH_2PO_4 in 1000 mL of water and adjust pH to 7.4 ± 0.05 with triethylamine
Column	Symtrex C_8, 5 µm, 150 mm × 4.6 mm
Flow Rate	1.5 mL/minute
Temperature	40°C
Detector	UV at 272 nm
Injection Volume	20 µL
Run Time	15 minutes
Retention Time	About 8 minutes
Sample Preparation	Standard and sample solutions contain 0.1 mg/mL of MK
System Suitability	The column efficiency as determined from the MK peak is NLT 5000 theoretical plates. Tailing factor of the same peak is NMT 2.0. RSD of five replicated injections of the standard solution is NMT 1.0%.

For each analytical procedure, provide a page number/link to the location of validation information in Module 3. For quantitative non-compendial analytical methods, provide a summary table for the method validation as in this example:

	Impurities					
	A	**B**	**C**	**D**	**E**	**F[1]**
Specificity	No interference from placebo and known impurities (refer to chromatogram below) MK Peak purity (PDA) > 0.99					
Linearity	0.05-2.5%, $r^2 = 0.99$	0.05-1.0% $r^2 = 0.99$	0.05-1.0% $r^2 = 0.99$	0.05-1.0% $r^2 = 0.99$	0.05-1.0%, $r^2 = 0.99$	0.05-1.0% $r^2 = 0.99$
Precision	RSD 6.7%	RSD 4.5%	RSD 6.8%	RSD 5.2%	RSD 3.2%	RSD 4.5%

Intermediate Precision[2]	RSD 8.2%	RSD 9.2%	RSD 10.4%	RSD 9.6%	RSD 8.2%	RSD 9.8
Accuracy[3]	95-104%	80-97%;	88-105%	92-112%	80-101%	82-115%
LOQ	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
LOD	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%

See section 2.3.S.4 for questions on validation of USP methods and modifications to USP methods.

Appearance

Identification

OGD generally recommends including one specific test.

Assay

Content Uniformity

Impurities (Degradants)

What format should be used for degradation products?

Name	Chemical name/ Identification	Chemical Structure
[Degradation Product]	[Chemical Name]	[Chemical Stucture]

Impurities that are monitored are those classified as degradation products of the drug substance or reaction products with an excipient and/or immediate container-closure. Do not duplicate structures found in drug substance sections 2.3.S.3 or 2.3.S.4.

Generally, process impurities present in the drug substance need not be monitored or specified in the drug product unless they are also degradation products. If ANDA sponsors want to report synthesis precursors or other process impurities of drug substances in the drug product (due to their presence in chromatograms or as markers in chromatograms), they should be limited to the same levels as in the drug substance.

Impurity	Proposed Acceptance Criteria	Justification	ANDA Drug Product (Lot #)	RLD Drug Product (Lot #)
[Specified Degradation Product]			[Results from Exhibit Batch]	
Any Unspecified Degradation Product				
Total Degradation Products				

If the RLD product is used to justify the limits, then the batch analysis of the RLD should be included in the table.

How should acceptance criteria for degradation products be established?

Justification of the impurity specifications can be based on:

- Compendial specifications (Note: unspecified impurities cannot be justified based on USP specifications)
- ICH Q3B(R2)[14] and ANDA Guidance: Impurities in Drug Products[15]
    - Follow the guidance for calculation of the QT and IT
    - Limit for Any Unspecified Degradation Product should be equal to or below the IT
    - Limit for a specified impurity should be equal to or below the QT or qualified

Qualification can be based on

- Level of impurity observed in a FDA-approved human drug product (generally data from a batch of the RLD at or near expiration date)
- Significant metabolite of drug substance
- Scientific literature including EP, BP, and JP.
- Toxicology studies

Should stress testing of the drug product be included in the QOS?

Yes, summarize the results of stress testing of the drug product analytical methods. Include peak purity and peak purity angle.

Stress conditions	**Assay Method**		**Impurity Method**	
	% Assay	Peak Purity	Observed Degradants	Peak Purity
Untreated				
[Condition]				

Stress studies should target 10-30% degradation[16]. For very stable molecules that are difficult to degrade, a justification should be provided along with a summary of forced degradation results (i.e stress conditions that go beyond the usual).

[14] http://www.fda.gov/cder/guidance/4164fnl.htm

[15] http://www.fda.gov/cder/guidance/6423dftrev1.htm

[16] "Conducting Forced Degradation Studies," D W. Reynolds et. al *Pharm Tech* Feb 2002, "Stress Tests to Determine Inherent Stability of Drugs" Singh, et.al *Pharm Tech* April 2000

Dissolution

What format should be used for the dissolution method?

Parameter	Value
Medium	
Volume	
Temperature	
Apparatus	
Rotational Speed	
Specification	

Also include the description and validation of the analytical method used in the dissolution test, if it is not a compendial method.

2.3.P.6 Reference Standards and Materials

How were the primary reference standards certified?

If the same reference standard was used for the drug substance, reference Section 2.2.S.5. If a compendial standard is used, minimal information (generally lot number) is needed. If an in-house standard is used, indicate lot numbers used, source(s) and location of COA(s) and/or qualification information in the body of data.

The answer should also discuss reference standards for impurities, if used.

2.3.P.7 Container Closure System

What container closures are proposed for packaging and storage of the drug product?

How should the container closure system be presented?

In tabular form, provide a summary of the container/closure systems used. Include the different packaging configurations, size of container and closure for each configuration, the manufacturer/supplier and DMF numbers.

Type	Description (Packaging Configuration)	Supplier	DMF
[component]	[Description] (Packaging that uses this)		
Bottle	60 ml white square HDPE (60,100 tablets)		

Has the container closure system been qualified as safe for use with this dosage form?

What information can support this?

Indicate the testing that has been performed to qualify the container/closure system as safe such as: USP <661> and USP <671> or USP <381>, USP <87> and USP <88> for elastomeric closures.

Any other testing or certification such as 21 CFR references (Federal Regulations under 21 CFR sections 174-186 provide a list of materials that are safe for use in direct or indirect food contact).

A statement may be provided referencing products that have been approved using the same packaging system. However, a copy of the test results should also be provided in the body of data.

2.3.P.8 Drug Product Stability

What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?

How should the stability specification be presented?

Tests	Acceptance Criteria	Analytical Procedure
Appearance		
Assay		
Degradation Products		
Dissolution		
[Other Specifications]		

Any tests or criteria that are different from release should be noted and justified.

What drug product stability studies support the proposed shelf life and storage conditions?

Stability protocol

How should the stability protocol be presented?

Strength	Container/Closure	Conditions	Test Schedule	Batches

Conditions should include container/closure orientation if relevant for this dosage form.

Summary of stability test results

How should the stability results be presented?

Always include the results of the stability studies (accelerated and real time) in tabular form. If retained samples were retested (for example, if a dissolution specification is revised), this should be indicated.

	Accelerated (40^{o}C/75% RH) 0, 4, 8, 12 weeks	**Room Temperature (25^{o}C/60% RH) 0, 3, 6, 9, 12 months**
[Test (Limit)]	[Indicate Trend] [Report range of values observed]	[Indicate Trend] [Report range of values observed]

Indicate any special studies conducted to support stability specifications such as: inclusion of stability data/specifications for drug products after constitution, combination with admixtures and/or under other conditions that occur when the drug product is administered according to the labeling instructions. Also summarize cycling studies (freeze-thaw and heat-cool studies) that were conducted.

What is the post-approval stability protocol?

The post-approval stability protocol and commitment should be provided here. The stability protocol should include:

- Storage conditions of stability samples
- Samples that will be placed on stability (packaging configurations)
- Testing intervals
- Tests to be performed and testing schedule

The stability commitment should indicate:

- Validation batches to be placed on stability.
- Subsequent batches to be added to the stability program on a yearly basis.
- Commitment to submit stability data in annual reports and a description of how changes or deterioration in the distributed drug product will be handled as per 21 CFR 314.70 (b) (1) (ii).