
Questions and Answers on Quality Related Controlled Correspondence Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**September 2021
Pharmaceutical Quality**

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Questions and Answers on Quality Related Controlled Correspondence Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This questions and answers (Q&A) guidance provides FDA's current thinking on quality-related scientific and regulatory topics that appear frequently in controlled correspondence submissions.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

The Office of Pharmaceutical Quality (OPQ) reviews correspondence from generic drug manufacturers and related industry or their representatives related to generic drug development (i.e., controlled correspondence submissions) requesting information regarding chemistry, manufacturing, and controls, as well as product quality microbiology for generic drugs. OPQ also reviews controlled correspondence inquiries related to Type II drug master files for drug substances submitted in support of generic drug applications. OPQ has observed that the same questions are frequently received in multiple controlled correspondence submissions. These Q&A are intended to proactively respond to those scientific and regulatory topics that appear frequently in controlled correspondence addressed by OPQ, thereby allowing industry to move forward with certain generic drug development activities without the need to submit controlled correspondence to FDA.

¹ This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at <https://www.regulations.gov/docket?D=FDA-2017-D-6821>). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

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III. QUESTIONS & ANSWERS

The Q&A below were derived from numerous controlled correspondence submissions addressed by OPQ. We recommend that these Q&A be reviewed before submitting a controlled correspondence for one of the scientific and regulatory topics denoted below.

1. Bracketing/Matrixing

Question:

Is it acceptable to use a bracketing approach for the manufacture of the exhibit batches of a generic drug product with multiple strengths produced from common bulk granulations (or blends)? Do all of these exhibit batches need to be put into the stability program?

Answer:

A bracketing approach is acceptable for a drug product with multiple strengths, as long as the active and inactive ingredients are in the same proportion between the different strengths (i.e., the strengths are dose proportional). According to the FDA guidance for industry *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (May 2014), for abbreviated new drug applications (ANDAs), three separate intermediate bulk granulations (or blends) should be manufactured. One batch of bulk granulation (or blend) should be used to manufacture all the strengths proposed. The other two bulk granulations (or blends) can be used to manufacture only the lowest and the highest strengths. Three bulk granulations (or blends) should be used to manufacture the strength(s) tested in the bioequivalence (BE) studies.

Stability data should be provided for three batches of the highest strength and three batches of the lowest strength, and three batches of the strength(s) tested in the BE studies if the strength used in the BE study was not the highest or lowest strength. Release data should be provided for all the batches that were manufactured.

Section Reference:

FDA guidance for industry *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (May 2014)

2. Container-Closure Changes

Question 1:

If the reference listed drug (RLD) is a sterile injectable drug product packaged in an ampule, can the generic product be packaged in a vial?

Answer 1:

A proposed generic drug product is not required to have the same container closure system (CCS) as the RLD. However, the ANDA generally must contain information to show that the proposed generic drug product has the same conditions of use and the same labeling, with certain

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permissible differences, as the RLD.² Refer to FDA guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019).

The proposed CCS will be evaluated during the review process.³ In the assessment of an ANDA's proposed CCS, the Agency will, among other things, evaluate any differences in the proposed CCS relative to the RLD CCS and determine whether these differences would result in the proposed generic drug product not having the same conditions of use and the same labeling (with certain permissible differences) as the RLD.

You should follow the recommendations in the FDA guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation* (July 1999) for the chemistry, manufacturing, and controls (CMC) information that should be submitted in the ANDA.

Question 2:

Should a proposed generic ophthalmic drug product have the same cap color as the RLD when that color is not in line with the American Academy of Ophthalmology (AAO) recommendation?

Answer 2:

As described in the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics* (July 1999), the cap color of ophthalmic drug products should follow AAO color codes, or the applicant should provide adequate justification for deviations from the AAO color coding system. For the proposed generic drug product, the Agency recommends that the color be in accordance with AAO recommendations.

Section References:

Section 505(j)(2)(A)(i) and (j)(2)(A)(v) of the FD&C Act

American Academy of Ophthalmology (AAO) recommendations:

<https://www.aaopt.org/about/policies/color-codes-topical-ocular-medications>

FDA guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation* (July 1999)

FDA guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019)

² See section 505(j)(2)(A)(i) and 505(j)(2)(A)(v) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)(21 U.S.C. 355(j)(2)(A)(i) and 21 U.S.C. 355(j)(a)(A)(v)).

³ In this Q&A, the term *review* also means *assessment*, which is the term that CDER's Office of Pharmaceutical Quality and Office of Generic Drugs will generally use in place of review. Assessment means the process of both evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

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3. Dissolution

Question:

If the dissolution method for a proposed generic drug product is not available in the FDA Dissolution Methods Database or in the United States Pharmacopeia (USP), can the Agency provide the dissolution method for the product?

Answer:

When neither the USP dissolution method nor the FDA's Dissolution Methods Database provide a dissolution method for a product, the Agency recommends that applicants develop an appropriate and discriminating dissolution method for the proposed drug product, taking into consideration the method development and validation principles described in the USP General Chapter <711> *Dissolution* or General Chapter <724> *Drug Release*, and USP General Chapter <1092> *The Dissolution Procedure: Development and Validation*.

Please note that the Agency considers that dissolution should be product-specific and therefore the selection of the dissolution method and setting of the acceptance criterion/criteria should be based on the dissolution data generated for the proposed drug product. Therefore, for the in vitro dissolution method to be used for quality control (QC) of your proposed drug product, the Agency recommends that irrespective of the source of the proposed dissolution method (USP, FDA, or in-house), additional dissolution studies be conducted to demonstrate the suitability of the selected method for the proposed drug product. For this purpose, the Agency recommends that the report for the development and validation of an in-house method or verification of a USP method being proposed for dissolution QC testing be provided in the drug product's ANDA submission, specifically in Module 3.2.P.5.⁴ The report should include complete information/data on: i) solubility of the drug substance(s); ii) adequacy of the selected dissolution testing conditions (i.e., apparatus, rotation speed, medium, volume, sampling times, etc.); iii) validation/verification of the robustness of the selected dissolution method; iv) validation/verification of the analytical method used to assay the dissolution samples; and v) demonstration of the discriminating ability of the dissolution method [for modified release products and immediate release drug products containing low soluble drug substance(s)].

Additionally, for generic immediate release solid oral drug products including a highly soluble drug substance (per the Biopharmaceutics Classification System (BCS) definition⁵), the Agency recommends that dissolution QC testing be conducted as described in FDA's guidance for industry *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* (August 2018). The information/data supporting the high solubility of the drug substance(s), as described in the BCS guidance (ICH guidance for industry *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021)) should be included in the ANDA submission (Module 3.2.P.5 or Module 3.2.S.1.3), in addition to the proposed drug product's dissolution data.

⁴ See FDA guidance for industry *ANDA Submissions: Content and Format of Abbreviated New Drug Applications* (June 2019).

⁵ See ICH guidance for industry *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021).

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Please note that the acceptability of the proposed dissolution method and acceptance criterion(a) will be determined during the ANDA review process based on the totality of the provided dissolution data/information and additional data/information may be requested during the submission review process.

Section References:

USP General Chapter <711> *Dissolution*

USP General Chapter <724> *Drug Release*

USP General Chapter <1092> *The Dissolution Procedure: Development and Validation.*

Guidance for industry *ANDA Submissions: Content and Format of Abbreviated New Drug Applications* (June 2019)

Guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997)

Guidance for industry *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* (August 2018)

International Council for Harmonisation (ICH) guidance for industry *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021)

4. Microbiology (Endotoxin testing)

Question 1:

How should a bacterial endotoxins test acceptance criterion be determined for the finished drug product?

Answer 1:

The finished drug product bacterial endotoxins test acceptance criterion should be determined based on the maximum dose that can be delivered within one hour as interpreted from the package insert. Special considerations can include:

- Additional doses that may be administered after the initial dose,
- Maintenance doses administered after an initial bolus dose,
- Incremental dose increases, and
- For anesthetics or other drugs for which repeat doses are administered until a desired clinical outcome is achieved, the maximum number of potential doses at the minimum specified time interval between doses that could be administered in a one-hour period.

The USP General Chapter <85> *Bacterial Endotoxins Test* recommended maximum endotoxin exposure is NMT 5 EU/kg (interpreted as within 1 hour) for most drugs based on an average

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patient weight of 70 kg. For drugs administered to pediatric patients, consult the WHO-CDC growth charts⁶ for average weight at the youngest patient age for the proposed generic drug.

For drug products administered topically on a body surface area basis, the recommended maximum endotoxins exposure is 100 EU per square meter.

For drug products administered intrathecally (or epidurally due to risk of inadvertent intrathecal administration), the maximum recommended exposure is 0.2 EU/kg (in 1 hour).

Please note that USP monographs may contain historical bacterial endotoxins test acceptance criteria that may not reflect the maximum dose that can be interpreted from the current drug package insert of the RLD. The proposed endotoxin limit for a proposed generic product should be based on dosing in the current RLD package insert. If the calculated limit is higher than the USP monograph limit, we recommend that applicants submit a controlled correspondence to confirm acceptability with the Agency prior to submission of the ANDA.

Question 2:

Is it acceptable to omit bacterial endotoxin limits in the proposed specification for a topical ophthalmic drug product?

Answer 2:

Topical ophthalmic drug products are generally not required to be tested for bacterial endotoxins. Therefore, the finished product release and stability specifications for topical ophthalmic products are not required to include testing for bacterial endotoxins unless the labeling indicates that the product is nonpyrogenic. However, if the labeling for a topical ophthalmic product includes directions for use on an abraded eye and/or use during surgery, a bacterial endotoxin specification for the drug product may be appropriate.⁷

Please note that this answer is specific to this question and does not address other ophthalmic drug products, dosage forms, or combination products that include an ophthalmic drug product component.

Section References:

Centers for Disease Control and Prevention (CDC) growth charts:
https://www.cdc.gov/growthcharts/who_charts.htm

USP General Chapter <85> *Bacterial Endotoxins Test*

USP <771> *Ophthalmic Products — Quality Tests*

FDA guidance for industry *Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012)

⁶ See https://www.cdc.gov/growthcharts/who_charts.htm for growth charts.

⁷ See FDA guidance for industry *Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012).

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5. Number of Batches

Question 1:

If an applicant intends to have more than one drug product manufacturing site in an abbreviated new drug application (ANDA), how many exhibit batches should be provided for each site?

Answer 1:

Stability data from three exhibit batches manufactured at each drug product manufacturing site for each strength should be submitted in the ANDA, or a bracketing approach as described in Section 2 above should be used. The applicant should submit data from at least three batches of drug product that can include any one of the following batch sizes:

- Three pilot scale batches, three batches that meet the minimum dosage form batch recommendations, whichever is larger, or three commercial scale batches
- Two pilot scale batches or two batches that meet the minimum dosage form batch recommendations, whichever is larger, and one small scale batch
- Two commercial scale batches and one small scale batch

This data should be submitted from each drug product manufacturing site.

Section References:

FDA guidance for industry ANDAs: *Stability Testing of Drug Substances and Products* (June 2013)

FDA guidance for industry ANDAs: *Stability Testing of Drug Substances and Products Questions and Answers* (May 2014)

FDA guidance for industry on *Q1A(R2): Stability Testing of New Drug Substances and Products* (November 2003)

6. Orientation

Question 1:

If the generic drug product is a “for injection” (sterile lyophilized powder), can stability data for exhibit batches be generated using only one orientation?

Answer 1:

According to the FDA guidance for industry ANDAs: *Stability Testing of Drug Substances and Products Questions and Answers* (May 2014), “For primary batches of liquids, solutions, semi-solids, and suspensions, the product should be placed into an inverted (or horizontal) position and an upright (or vertical) position.” Since lyophilized powders do not fall under one of these categories, exhibit batches for drug products that are sterile lyophilized powders may be placed on stability in one orientation alone, provided that the ANDA submission includes an adequate justification for the orientation selected.

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Question 2:

If a product is packaged using blow-fill-seal technology and the container is composed of a single material, can stability data for exhibit batches be generated using only horizontal or upright orientation?

Answer 2:

For products packaged using blow-fill-seal technology, stability studies on exhibit batches may be performed in one orientation alone, as long as the orientation provides maximal contact for the drug product with container closure system components, including the seal and neck. See guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation* (July 2002).

Therefore, stability testing conducted in the horizontal position would be acceptable if adequate justification is provided in the submission to demonstrate that the position selected represents the maximum contact of the drug product and container closure system components. Stability testing conducted only in the upright or vertical position would generally be unacceptable due to the lack of exposure of the drug product to the seal and the twist-off neck area.

Section References:

FDA guidance for industry ANDAs: *Stability Testing of Drug substances and Products – Questions and Answers* (May 2014)

FDA guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation* (July 2002)

7. Packaging

Question 1:

Should the three exhibit batches for a generic product be fully packaged in the proposed marketed packaging?

Answer 1:

In accordance with FDA guidances for industry on *Q1A(R2): Stability Testing of New Drug Substances and Products* (November 2003) and *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (May 2014), one of the three exhibit batches should be completely packaged using all the proposed marketed configurations. This batch could be either a pilot scale or a small scale batch. The other two exhibit batches should be packaged in sufficient quantity to comply with 21 CFR 211.166(a)(1-5) and 211.166(b). All batches, including the small scale batch, should be packaged using commercial packaging equipment or similar equipment. Different batches of packaging material should be used where the packaging material could affect drug product performance and/or delivery.

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Question 2:

For a combination product consisting of a pen injector device with an injectable drug product filled in a cartridge, is it acceptable to package only the amount required for stability into the cartridges and pen injector device for the three exhibit batches submitted in the ANDA?

Answer 2:

For a pen injector device used with an injectable drug product filled in a cartridge and other similar products, we recommend that all three of the exhibit batches be completely filled into cartridges. As described in FDA guidances for industry *Q1A(R2): Stability Testing of New Drug Substances and Products* (November 2003) and *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (May 2014), one of the three batches should be entirely assembled into the pen injector devices. The other two primary stability batches should have a sufficient number of samples packaged and assembled into the pen injector devices for stability and reserve samples, in accordance with 21 CFR 211.166(a)(1-5), 211.166(b), and 211.170.

Section References:

FDA guidance for industry on *Q1A(R2): Stability Testing of New Drug Substances and Products* (November 2003)

FDA guidance for industry *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (May 2014)

21 CFR 211.166(a)(1-5), 211.166(b), and 211.170

8. Scoring and Split Tablet Testing

Question 1:

Is the reference listed drug (RLD) considered to have functional scoring when it is not mentioned in the labeling and half the tablet does not match the lowest labeled dose?

Answer 1:

Any scoring on the RLD should be considered functional scoring, and therefore, the generic product should have similar scoring. According to FDA guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013), “scoring configuration of generic drug products should be the same as the RLD.” We recommend that split tablet testing be performed and the data submitted in the ANDA; otherwise, the Agency may refuse to receive the ANDA due to inconsistent scoring configuration between the RLD and the test product. (FDA guidance for industry *ANDA Submissions – Refuse-to-Receive Standards, Rev. 2* (December 2016)).

Question 2:

If the RLD has partial score lines, can the proposed generic product have a full score line(s)?

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Answer 2:

When the RLD has partial score lines, the generic can have a full score line(s) to produce partial doses equivalent to that of the RLD as indicated in the approved labeling. Scoring between the RLD and generic products should be consistent to ensure that the patient is able to adjust the dose by breaking the tablet in the same manner, such that the patient can switch from the RLD to the generic product without encountering problems related to the dose. Additionally, consistent scoring assures that neither the generic product nor the RLD has an advantage in the marketplace because one is scored and one is not. For additional information, see FDA guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013).

Section References:

FDA guidance for industry *ANDA Submissions – Refuse-to-Receive Standards, Rev. 2* (December 2016)

FDA guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

9. Size and Shape of Generic Solid Oral Dosage Forms

Question:

If the reference listed drug (RLD) has been discontinued and there is no information on its shape and size, is it acceptable to use the shape and size of the FDA designated reference standard to design the generic product?

Answer:

In cases where the RLD is not available because it has been discontinued for reasons not associated with safety and efficacy, FDA may have designated a reference standard. The FDA designated reference standard is recommended to be used in in-vivo bioequivalence studies as well as comparative in-vitro studies. In this situation, if information on the size and shape of the RLD are not available, it is acceptable to use the size and shape of the FDA designated reference standard to develop the generic product provided it meets the recommendations in the size and shape guidance.

Section References:

FDA guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (Oct 2020)

FDA guidance for industry *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (June 2015)