Guidance for Industry

Drug Product

Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 150 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Upinder Atwal 301-827-5848 or (CBER) Christopher Joneckis 301-435-5681.

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

January 2003
CMC

Guidance for Industry

Drug Product

Chemistry, Manufacturing, and Controls Information

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

and/or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research

Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

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

January 2003
CMC

TABLE OF CONTENTS[1]

I. INTRODUCTION 1

II. BACKGROUND 2

A. The Common Technical Document — Quality (CTD-Q) Format 2

1. Format of Drug Product Information in Multiple Related Applications 3
2. Format of Drug Product Information for Multiple Product Presentations and/or Manufacturing Schemes in One Application 3

B. Content Information Included in an Application 4

C. Additional Guidance 5

D. Drug Master Files 6

E. Environmental Assessments 6

III. DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P.1) 6

A. Description of Dosage Form 6

B. Container Closure System 7

C. Composition Statement 7

IV. PHARMACEUTICAL DEVELOPMENT (P.2) 10

A. Components of the Drug Product (P.2.1) 11

1. Drug Substance (P.2.1.1) 11
2. Excipients (P.2.1.2) 12

B. Drug Product (P.2.2) 13

1. Formulation Development (P.2.2.1) 13
2. Overages (P.2.2.2) 14
3. Physicochemical and Biological Properties (P.2.2.3) 14

C. Manufacturing Process Development (P.2.3) 15

D. Container Closure System (P.2.4) 16

E. Microbiological Attributes (P.2.5) 16

F. Compatibility (P.2.6) 17

V. MANUFACTURE (P.3) 18

A. Manufacturer(s) (P.3.1) 18

B. Batch Formula (P.3.2) 19

C. Description of Manufacturing Process and Process Controls (P.3.3) 21

1. Flow Diagram 21
2. Description of Manufacturing Process and Process Controls 22

[1] Alphanumeric designations in parentheses that follow headings show where information should be placed in applications that are submitted in Common Technical Document (CTD) format.

3. Reprocessing and Reworking *24*
D. Controls of Critical Steps and Intermediates (P.3.4) **25**
E. Process Validation and/or Evaluation (P.3.5) **26**
VI. CONTROL OF EXCIPIENTS (P.4) **27**
A. Specifications (P.4.1) **28**
B. Analytical Procedures (P.4.2) **29**
C. Validation of Analytical Procedures (P.4.3) **29**
D. Justification of Specifications (P.4.4) **30**
E. Excipients of Human or Animal Origin (P.4.5) **31**
F. Novel Excipients (P.4.6) **31**
VII. CONTROL OF DRUG PRODUCT (P.5) **31**
A. Specification(s) (P.5.1) **31**
B. Analytical Procedures (P.5.2) **35**
C. Validation of Analytical Procedures (P.5.3) **36**
D. Batch Analyses (P.5.4) **36**
1. Batch Analysis Reports *37*
2. Collated Batch Analyses Data *37*
E. Characterization of Impurities (P.5.5) **38**
1. List of Expected Impurities *38*
2. Identification of Impurities *38*
F. Justification of Specification(s) (P.5.6) **40**
VIII. REFERENCE STANDARDS OR MATERIALS (P.6) **42**
IX. CONTAINER CLOSURE SYSTEM (P.7) **43**
X. STABILITY (P.8) **44**
A. Stability Summary and Conclusion (P.8.1) **44**
B. Postapproval Stability Protocol and Stability Commitment (P.8.2) **44**
C. Stability Data (P.8.3) **44**
1. Formal Stability Studies *44*
2. Supporting Stability Studies *45*
3. Stress Studies *45*
XI. APPENDICES (A) **46**
A. Facilities and Equipment (A.1) **46**
B. Adventitious Agents Safety Evaluation (A.2) **47**
1. Nonviral Adventitious Agents *48*
2. Viral Adventitious Agents *48*
C. Excipients (A.3) **49**
XII. REGIONAL INFORMATION (R) **50**

A. Executed Production Records (R.1.P) **50**

1. Executed Production Records *50*

2. Information on Components *50*

B. Comparability Protocols (R.2.P) **51**

C. Methods Validation Package (R.3.P) **51**

XIII. LITERATURE REFERENCES (3.3) **51**

ATTACHMENT 1 ..... **52**

GLOSSARY **58**

Guidance for Industry[2]

Drug Product

Chemistry, Manufacturing, and Controls Information

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale and/or justification for the proposed revision.*
- *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*
- *If possible, e-mail an electronic copy (Word) of the comments you have submitted to the docket to* cunninghamp@cder.fda.gov.

I. INTRODUCTION

This guidance provides recommendations on the chemistry, manufacturing, and controls (CMC) information for drug products that should be submitted in original new drug applications (NDAs) and abbreviated new drug applications (ANDAs). The guidance addresses the content of original NDAs and ANDAs. The guidance is structured to facilitate the preparation of applications submitted in Common Technical Document (CTD) format (see section II.A and B). The recommendations apply to all NDAs and ANDAs, although more detailed guidance on the content of an application may be available in separate guidance documents for specific types of drug products or dosage forms (see section II.C).

This guidance addresses the information to be submitted for marketing approval of drug products to ensure continued product quality (i.e., the identity, strength, quality, purity, and potency). Recommendations are provided on the information that should be included for (1) description and composition of the drug product, (2) manufacture, (3) control of excipients, (4) control of drug products, (5) reference standards or materials, (6) container closure systems, and (7)

[2] This guidance has been prepared by the Drug Product Technical Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration in collaboration with the Center for Biologics Evaluations and Research (CBER).

stability. Information is also provided on the type of pharmaceutical development information that should be included in an NDA or ANDA.

This guidance, when finalized, will replace the guidance entitled *Submitting Documentation for the Manufacture of and Controls for Drug Products* (February 1987).

II. BACKGROUND

A. The Common Technical Document — Quality (CTD-Q) Format

In November 2000, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use issued harmonized guidance for the format of drug product applications (i.e., Common Technical Document (CTD)). The CTD describes a format for applications that (supplemented with regional information) can be used for submission to the regulatory authorities in the United States, European Union, and Japan. One focus of this effort was harmonizing the format for quality information (i.e., chemistry, manufacturing, and controls) that will be submitted in an application. FDA's guidance on *M4Q: The CTD — Quality* describes the format for the quality information submitted in Module 3 of an application and provides additional information on formatting aspects of an application. Applicants can submit NDAs and ANDAs using the CTD-Q format. Applicants should review FDA's guidance on *M4Q: The CTD — Quality* and other related CTD guidance documents for detailed formatting recommendations on preparing an application in CTD format.

Module 3 of each application should include the specified CTD sections: Drug Substance (3.2.S), Drug Product (3.2.P), Appendices (3.2.A), Regional Information (3.2.R) and Literature References (3.3). In some cases, the majority of information to address the drug substance sections will be incorporated by reference from a drug master file (DMF). However, an applicant should still provide information to address some of the drug substance subsections. The content of the drug substance section (3.2.S) of Module 3 will be the subject of a forthcoming guidance addressing CMC information for drug substances (drug substance guidance). The Appendices, Regional Information, and Literature References sections include information for both drug substance and drug product, as appropriate.

This *Drug Product* guidance has been organized in a format conforming to Module 3 of the CTD, and it provides CMC content recommendations specific to drug product, including recommendations for the Appendices, Regional Information, and Literature References sections. Alphanumeric designations in parentheses corresponding to the CTD format follow relevant headings and text to show where information is to be placed in the CTD.[3] Recommendations specific to drug substance, including recommendations

[3] Arabic numbers have been assigned to specific sections of the CTD. For example, the designation 3.2 before S, P, A, and R indicates Module 3, Body of Data section 2. Where this guidance discusses Module 3, Body of Data section 2, for brevity, the initial designation 3.2 is not repeated throughout the rest of the guidance (e.g., 3.2.P.3.1 reads P.3.1).

for the Appendices, Regional Information and Literature References sections, will be provided in the drug substance guidance.

1. Format of Drug Product Information in Multiple Related Applications

In general, when separate applications are submitted for drug products, each application should contain stand-alone drug product information even when the applications are related (e.g., tablet and oral solution with the same active ingredient submitted at the same time). In some rare cases, quality information can be incorporated by reference from a related application (e.g., co-marketing agreements). It is recommended that an applicant discuss cross-referencing of drug product quality information with the appropriate review division before submitting an application that uses cross-references. Information on when separate applications should be submitted is available in the following guidances:

- *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*[4]

- *Variations in Drug Products that May Be Included in a Single ANDA*

2. Format of Drug Product Information for Multiple Product Presentations and/or Manufacturing Schemes in One Application

Under certain circumstances (see guidances cited in II.A.1), different product presentations (e.g., strengths, container closure configurations, formulations) and/or manufacturing schemes (e.g., aseptic and terminal sterilization) can be submitted in the same application. In general, when a single application can be submitted, information for each of the product presentations and manufacturing schemes should be combined and presented together in one Drug Product (P) section with information provided in the Appendices, Regional Information, and Literature References sections for each of the product presentations and manufacturing schemes, as warranted. For example, if 100 milligram (mg) tablets will be marketed in a bottle and a unit-dose blister package, the information should be presented in one P section. The majority of the CMC information would be identical for the two products. The information that differs between the two would be presented together in the appropriate subsections (e.g., P.7 — Container Closure System, P.8 — Stability), but would be physically or electronically separated within the subsection.

However, there are cases when it is more appropriate and logical to have information presented separately for product presentations or manufacturing schemes that can be included in a single application. Information presented separately means one complete P

[4] In February 2001 (66 FR 11175), the Agency made available a draft version of this guidance.

section followed by other complete P sections.[5] Information should be presented separately when a single application can be and is submitted for:[6]

- A drug product that consists of two different formulated products. Separate P sections for each of the formulated products should be provided. For example, information on the drug product and reconstitution diluent should be presented in separate P sections for a drug product supplied with a reconstitution diluent.[7] Similarly, separate P sections should be provided for an oral contraceptive with active and placebo tablets.

- Parenteral drug products with different formulations (e.g., lyophilized, liquid, preserved, nonpreserved). Each formulation should be presented in a separate section. However, different strengths, fills, and container closure configurations can be included in the same P sections. For example, if an application includes a nonpreserved formulation packaged in two sizes of unit dose vials and a prefilled syringe and a preserved formulation packaged in a multidose vial, two separate P sections should be provided. One P section will include the information on the nonpreserved formulation and the other P section would include the information on the preserved product.

- Modified release products with different release mechanisms or release rates (e.g., 1-day and 7-day transdermal drug delivery system). Each release mechanism or release rate should be presented separately.

B. Content Information Included in an Application

The application should include information in every P subsection for each of the product presentations (e.g., strengths, container closure configurations, formulations) and manufacturing schemes (e.g., alternative processes, drug substance source, manufacturing site) intended for approval under the application. There may be circumstances in which specific documentation (e.g., batch release data or certificate of analysis, executed production record, stability data) on a presentation or manufacturing scheme need not be included, such as when the intermediate strengths or container sizes are omitted in a bracketed stability study or when site specific stability studies are not needed preapproval. Although specific documentation might not be needed in some circumstances, the application should still include the remaining information on the product presentation or manufacturing scheme.

---

[5] See FDA's guidance on *M4Q: The CTD — Quality* for additional guidance on formatting separate P sections.

[6] An applicant should refer to the guidances cited in section II.A.1 for information on when a single application can be submitted. For NDAs, the Agency may, for administrative reasons, choose to file separate NDAs for a submission that is eligible to be filed in a single NDA. When separate NDAs are filed, the recommendations in II.A.1 apply.

[7] If the diluent is the subject of a Center for Devices and Radiological Health (CDRH) 510k application or premarket approval application (PMA), only a citation to that application need be provided. Citations can be provided to approved applications in other situations when appropriate (e.g., devices).

If information is not provided in a P subsection at all or for a particular product presentation or manufacturing scheme, this should be stated in the application and a reason given. Information should be provided in the Appendices, Regional Information, and Literature References sections for each of the product presentations and manufacturing schemes, as appropriate. If an Appendices or Regional Information subsection or the Literature References section is not applicable, this should be stated in the application.

Before preparing an application, an applicant can discuss with CDER or CBER questions about providing less than full information on each of the product presentation and manufacturing schemes included in an application. This advance discussion can preclude expending time and effort in preparing an application that CDER or CBER might later determine to be incomplete.

C. Additional Guidance

This *Drug Product* guidance and the forthcoming drug substance guidance, when finalized, will be the primary *content* guidances for NDA and ANDA applicants. For quality, the general *format* guidance is *M4Q: The CTD — Quality*. These are the first guidances an applicant should consider when preparing the quality section (i.e., chemistry, manufacturing, and controls) of an NDA or ANDA (Module 3).

This guidance references ICH guidance documents cited in the CTD-Q and FDA's guidances on general technical topics (i.e., stability, container closure systems, analytical procedures and methods validation, sterilization process validation, drug master files, and environmental assessments) rather than incorporating this detailed information. These guidances are referenced in the text and/or listed at the end of a section. An applicant should refer to these guidances for recommendations on the detailed information that should be included in the application to address the general technical topic.

Finally, an applicant should consider guidances that are available for specific technical issues, dosage forms, or drug product types when preparing its NDA or ANDA. These guidances provide additional recommendations on unique scientific and technical aspects of the topic. Some references to these types of guidances are included in this guidance. However, the references are given only as examples, and the list is not meant to be all-inclusive. Some examples of these types of guidance are:

- *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products*

- *The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use*

- *ANDAs: Impurities in Drug Products* (under development)

- *Submission of Chemistry, Manufacturing and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use*, CBER/CDER (under development)

CDER and CBER continue to update existing and publish new guidance documents. An applicant should use current guidance when preparing an NDA or ANDA submission. Current guidance documents are available on the Internet at http://www.fda.gov/cder/guidance/index.htm and http://www.fda.gov/cber/guidelines.htm.

D. Drug Master Files

Under FDA's regulations, an application may incorporate by reference all or part of the contents of any drug master file (DMF) to address particular drug product issues if the DMF holder provides written authorization to the applicant and the authorization is included in the application (Module 1). The authorization must describe the incorporated material by name, reference number, volume and page number of the DMF (21 CFR 314.420). See CDER's *Drug Master Files* guidance for more information.

E. Environmental Assessments

All NDAs and ANDAs must include either an environmental assessment (EA) or claim of categorical exclusion from the requirement to provide an environmental assessment (21 CFR 25.15(a)). Although included in Module 1 of the CTD, this information is considered part of the chemistry, manufacturing, and controls documentation in the United States. Applicants should refer to 21 CFR part 25 and the guidance for industry *Environmental Assessment of Human Drug and Biologics Applications* for additional information on environmental assessments.

III. DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P.1)

A brief description of the dosage form and container closure system and a statement of the composition of the drug product should be provided.

A. Description of Dosage Form[8]

A brief description of the dosage form should be provided. For CDER products, the description should use standard dosage form terminology found in the CDER *Data Standards Manual* (http://www.fda.gov/cder/dsm).[9]

[8] Headings that are not followed by alphanumeric designations (i.e., non-CTD-Q headings) are included in this document for ease of providing recommendations on the information that should be included under a CTD-Q heading (in this instance *Description and Composition of the Drug Product (P.1)*). An application submitted in CTD-Q format need not include these non-CTD-Q headings. An applicant can physically or electronically separate information under a CTD-Q heading as it chooses. However, once a particular approach is adopted, the same approach should be used throughout the life of the application.

B. Container Closure System

A brief description of the container closure systems proposed for marketing should be provided. If an overfill (see section IV.B.1) is used, the amount of overfill in each container should be identified. Information on the suitability of the container closure systems should be provided in P.2.4. A full description of the container closure systems and their specifications should be provided in P.7.

C. Composition Statement

The composition statement describes the qualitative and quantitative formulation of the drug product intended for commercial distribution. The composition statement must contain a list of all components used in the manufacture of the drug product regardless of whether or not they appear in the finished drug product (21 CFR 314.50(d)(1)(ii)(a)). Furthermore, the statement should include: (1) reference to the quality standards used, (2) the function of the component, (3) the amount of the component on a per unit basis, (4) the total weight, volume or other appropriate measure of the unit, and (5) any explanatory notes.

In some instances, the composition of distinct subformulations (e.g., cores, coating) of the drug product should be listed separately in the composition statement. For example, some modified release products (1) contain a mixture of immediate release and extended release beads within a capsule shell or (2) are formulated with the drug substance apportioned between a modified release core and an immediate release coating. In these cases, the composition of the immediate release and extended release portions of the drug product should be listed separately.

Additional guidance on each element of the composition statement is provided below. An illustrative example of a composition statement is provided in Table 1.

- Components

Components used in the manufacture of the drug product, regardless of whether or not they appear in the finished drug product, should be identified by the established name. If an established name does not exist for a component, a complete chemical name (i.e., the current Chemical Abstracts Service (CAS) index name) should be used.

Trace amounts of harmless substances added solely as tracers or markers for individual product identification should be included in the composition statement and the batch formula (P.3.2). Suitability of the proposed tracer or marker should be discussed in

[9] CDER's *Data Standards Manual* (DSM) provides standard nomenclature for use in various FDA databases. For the list of dosage form terminology used for approved drug products (e.g., on label), applicants should refer to Appendix C of FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (i.e., the Orange Book). An applicant proposing to use different terminology should contact the appropriate chemistry review team.

P.2.1.2. Tracers and markers need not be disclosed in the drug product labeling except for those used in parenteral drug products (21 CFR 201.100(b)).

For drug product components that are mixtures (e.g., colorants, coatings, flavors, inks), proprietary names can be used in the drug product composition statement if the quantitative and qualitative composition of the mixture is provided or referenced. For ease of review, CDER and CBER prefer that the quantitative and qualitative composition of mixtures be included in the application in a separate table. If it is not possible to include this information in the application, the information can be provided in a drug master file (DMF) when an appropriate letter of authorization from the DMF holder is included in the application (21 CFR 314.420(b)).

Capsule shells should be listed as a component and descriptive information provided in the composition statement (e.g., size, shape, color). The quantitative and qualitative composition of the capsule shell should be provided or referenced.

- References to Quality Standards

For compendial components, the appropriate official compendium should be cited.[10] Compendial components should comply with the monograph standard included in the official compendium, and citation of the official compendium confirms compliance with this standard. The compendium should be cited even if an in-house specification that provides for more testing than that of the compendial monograph is used to evaluate the component. For noncompendial components, the type of standard used to evaluate the component should be listed (e.g., in-house standard, *Code of Federal Regulations* (CFR) citation, DMF holder's standard). The applicant specific numeric code (e.g., SPEC 101.2b) of the specification used to evaluate the quality of the component should not be listed in the composition statement. The actual specification used for the drug substance should be provided in S.4.1. For the excipients, the actual specification should be provided in P.4.1 or P.4.6 and A.3 as appropriate.

- Function(s)

The function (i.e., role) of each component in the formulation should be stated. Components that are used in the manufacture of the drug product and do not appear in the finished drug product except at residual levels (e.g., some solvents) should be identified as processing agents.

- Amount

The target amount of each component by definite weight or other measure should be provided on a per unit basis. The amount of weight per unit volume should be on the per milliliter (mL) basis regardless of the size of the container. The metric system should be used whenever possible.

[10] A compendial component is a component that has a monograph in an official compendium as defined in section 201(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(j)).

In general, a fixed amount for each component should be stated. A quantity sufficient (q.s.) designation can be used when appropriate (e.g., q.s. to pH 5.5, q.s. to 1 mL). For excipients (e.g., coatings, lubricants) where a range has been justified (see section IV.A.2), the target amount should be listed in composition statement. However, the target and range should be included in the batch formula (P.3.2). The following components should be listed in the composition statement, but the amount of each component on a per unit basis need not be provided: (1) processing agents, (2) purposefully added gases that are intended to remain as part of the finished drug product (e.g., nitrogen added to head space), and (3) imprinting inks.

The amount of drug substance in the specified unit, including any overages, should be listed. An explanatory note should identify any justified overages (see section IV.B.2). If the amount of the drug substance in the composition statement and the strength listed in the labeling on the specified unit basis differ (e.g., when label strength is based on active ingredient rather than the salt or hydrate), an explanatory note should be included.

- Total weight, volume, or other appropriate measure

The total weight, volume, or other appropriate measure (e.g., one transdermal patch) of the unit being described should be specified.

- Notes

Explanatory notes should be included as appropriate. For example, explanatory notes should be used to identify drug substance overages, differences in the amount of drug substance on the per unit basis and labeled strength, and the location of the qualitative and quantitative composition statements for mixtures listed in the composition statement.

358

Table 1: Example Target Composition Statement					
Component	Reference to Quality Standard	Function	50 mg tablet	100 mg tablet	150 mg tablet
Core Tablet					
Drug substance	In-house standard	Drug Substance	55 mg[1]	110 mg[1]	165 mg[1]
Excipient X	NF	Diluent	30 mg	60 mg	90 mg
Excipient Y	NF	Disintegrant	22 mg	44 mg	66 mg
Excipient Z	In-house standard	Binding Agent	5 mg	10 mg	15 mg
Magnesium Stearate	NF	Lubricant	1.5 mg	3 mg	4.5 mg
Core Tablet Weight			113.5 mg	227.0 mg	340.5 mg
Film Coat Solution					
Purified Water	USP	Processing Agent	—	—	—
Hydroxypropyl Methylcellulose	USP	Film Coat	4.5 mg	9 mg	13.5 mg
Color Red™[2]	DMF Holder Y standard	Film Coat Color	—	0.2 mg	—
Color Blue™[2]	DMF Holder Y Standard	Film Coat Color	0.05 mg	—	0.45 mg
Titanium Dioxide	USP	Opacifier	0.1 mg	0.1 mg	—
Total Tablet Weight			118.15 mg	236.30 mg	354.45 mg
Print Ink Solution					
Printing Ink Solution[3]	DMF Holder Z Standard	Identification	—	—	—

[1] Equivalent to 50, 100, and 150 mg, respectively, on the anhydrous basis
[2] The qualitative and quantitative composition statements for the two colors are incorporated by reference from DMF 99999. The information is located in the January 21, 2001 amendment to the DMF, Volume 2, page 104 and 105. See the letter of authorization from DMF Holder Y in Module 1.
[3] The qualitative and quantitative composition of the ink is provided in Table XYZ in the application.

359

Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

360
361

362 IV. PHARMACEUTICAL DEVELOPMENT (P.2)

363

364 The Pharmaceutical Development section should contain information on the development studies
365 conducted to establish that the dosage form, formulation, manufacturing process, container
366 closure system, microbiological attributes, and usage instructions are appropriate for the purpose
367 specified in the application. The studies included in this section are distinguished from routine
368 control tests conducted according to specifications (e.g., release testing, stability testing).

Additionally, this section should identify and describe the formulation and process attributes, including critical parameters, that can influence batch reproducibility, product performance, and drug product quality.

Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

A. Components of the Drug Product (P.2.1)

1. Drug Substance (P.2.1.1)

a. Key Physicochemical Characteristics

Key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic form, solvation or hydration state, pH, dissociation constant (pKa)) of the drug substance identified in S.3.1 that can influence the performance or manufacturability of the drug product should be discussed. If the drug substance is structurally modified from an active moiety (e.g., salt, endogenous protein) and the modification affects a key physicochemical (e.g., solubility) and/or biological characteristic, this should be discussed. These discussions should cross-reference any relevant stability data in S.7.3.

To evaluate the potential effect of key drug substance physicochemical characteristics on the performance of the drug product, studies on drug product are sometimes warranted. For example, if particle size is expected to influence the dissolution rate, drug product testing should be conducted to support the appropriateness of the test and acceptance criteria for the drug substance particle size distribution. Data from drug product studies to investigate the potential effect of and the appropriateness of the acceptance criteria for drug substance physicochemical characteristics should be provided in this section of the application. For example, the ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* describes some of the circumstances in which drug product studies are recommended (e.g., Decision Tree #3 and #4 (Part 2)). The data from these studies should be used, as appropriate, to justify the drug substance specification (S.4.5).

b. Compatibility

The compatibility of the drug substance with the excipients used in the drug product should be discussed. For combination drug products, the compatibility of the drug substances with each other should also be discussed.

If there is evidence of chemical or physical incompatibility, justification for using the component should be provided. This justification can include, for example,

stability data to demonstrate that changes observed in development studies do not occur at significant levels in the drug product through shelf life or qualification of impurities that result from an interaction between the drug substance and an excipient or between drug substances.

2. Excipients (P.2.1.2)

The choice of excipients, their concentration, and the characteristics that can influence the drug product performance or manufacturability should be discussed relative to the respective role of each excipient. Any excipient ranges included in the batch formula (P.3.2) should be justified in this section of the application (P.2.1.2). Excipient ranges can often be justified based on the experience gained during the development of the formulation and manufacturing process. The ability of functional excipients (e.g., antioxidants, penetration enhancers) to perform throughout the intended drug product shelf life should also be discussed. The information provided should be used, as appropriate, to justify the excipient (P.4.4) and drug product (P.5.6) specifications.

Additional information should be provided for certain types of excipients, as discussed below. Applicants can refer to the forthcoming guidance on nonclinical studies for development of pharmaceutical excipients, for recommendations on the development of safety profiles that may be warranted for an excipient.

- Novel Excipients

Novel excipients are those that are used in the United States for the first time in a human drug product or by a new route of administration. The manufacturing, chemistry, and controls (CMC) information for a novel excipient should be provided in the same level of detail as that provided for a drug substance. The CMC information or a cross-reference to a DMF that provides the CMC information should be included in A.3. See sections VI and XI.C for additional guidance on the information that should be submitted to support the use of a novel excipient.

- Noncompendial–Non-novel Excipients

Depending on the functionality (e.g., complexing agent) and the route of administration of the drug product, additional information, up to and including the level of information recommended for novel excipients, can be warranted. An applicant is encouraged to discuss the use of noncompendial–non-novel excipients with the appropriate review division prior to submitting its application to ascertain the level of information that would be warranted to support the use of the excipient. The additional CMC information or a cross-reference to a DMF that provides the additional CMC information should be included in A.3. See sections VI and XI.C for additional guidance on the information that should be submitted to support the use of this type of excipient.

- Excipients used at higher levels than in previously approved products with the same route of administration, or components used as tracers or markers

Information to support the safety of these materials should be referenced in this section of the application. This information could include citations to FDA's regulations, Food Chemical Codex citations, or citations to supporting toxicology data provided elsewhere in the application (include study number).

- Excipients that can impart their own pharmacological activity

Information should be provided in this section of the application (P.2.1.2) when using any excipient (e.g., docusate sodium, caffeine, methionine) that has the potential to impart its own pharmacological effect. Data or cross-reference to data that support the lack of pharmacological activity of the excipient at the levels used in the drug product should be provided. If studies have been included elsewhere in the application, the study number should be provided in the cross-reference.

When a component that is usually identified as an excipient contributes to the intrinsic pharmacological activity of the drug substance (e.g., levonordefrin or epinephrine for local anesthesia), CMC information for the component should be provided in the application or incorporated by reference from a DMF. The information should be provided in the same level of detail as that for a drug substance. The CMC information or a cross-reference to a DMF that provides the CMC information should be included in A.3.

B. Drug Product (P.2.2)

1. Formulation Development (P.2.2.1)

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. For modified release drug products, a detailed description of the release mechanism (e.g., erodible matrix system, barrier erosion, diffusion) and a summary of the development of the release mechanism should be included.

A summary of all formulations used in clinical trials should be provided. The differences between clinical formulations and the proposed commercial formulation described in P.1 (i.e., composition statement) should be discussed. Any changes between the proposed commercial formulation and those formulations used in clinical batches and primary stability batches should be clearly described and the rationale for the changes provided. Results from comparative in vitro studies (e.g., dissolution), or comparative in vivo studies (e.g., bioequivalence), that link clinical formulations to the proposed commercial formulation described in P.1 should be summarized[11] and a cross-reference to the studies

[11] Here and elsewhere in the guidance when a summary of clinical or nonclinical information is recommended, the summary information or a cross-reference to the appropriate summary information in Module 2 of a CTD formatted application can be provided in the specified Module 3 section.

(with study numbers) should be provided. A summary of the development of an in vitro/in vivo correlation and a cross-reference to the studies (with study numbers) should be provided.

Any special features of the drug product (e.g., scoring of immediate release tablets, multilayer tablet) should be identified and a rationale provided for their use. Data to support the appropriateness of such features should also be provided. For example, use of a tablet score could be justified if the product labeling indicates that the split tablet is a valid dose (i.e., efficacy established). Data to support scoring should include content uniformity and dissolution studies comparing split versus whole tablet.[12]

Some dosage forms (e.g., liquids and semisolids) normally include an overfill of the formulation in the product container. Overfill is the volume or weight of the formulation filled in each container in slight excess of the labeled content. The amount of overfill is dependent on the physical properties of the finished dosage form (e.g., viscosity, surface tension) and the container closure system (e.g., design). In determining the amount of overfill, the applicant should consider the labeled dose to be delivered and how the dose will be administered (e.g., metered dose, syringe void volumes). The rationale for the amount of overfill should be provided. The amount of overfill should be sufficient to ensure that the finished dosage form meets appropriate pharmacopeial tests (e.g., *United States Pharmacopeia* (USP) *General Chapters* <1> *Injections*, <698> *Deliverable Volume*, <755> *Minimum Fill*).

For drug products supplied with a reconstitution diluent, the development and choice of any co-packaged diluents should be discussed.

2. Overages (P.2.2.2)[13]

An overage is a fixed amount of the drug substance in the dosage form that is added in excess of the label claim. Any overages included in the formulations described in P.1 should be justified. Information should be provided on the: (1) amount of overage, (2) reason for overage (e.g., compensate for expected and documented manufacturing losses, ensure proper dose delivery), and (3) justification for the amount of the overage. The overage should be included in the amount of drug substance listed in the composition statement (P.1) and the representative batch formula (P.3.2). In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend the expiration dating period, is not appropriate.

3. Physicochemical and Biological Properties (P.2.2.3)

[12] CDER's Manual of Policies and Procedures (MAPP 5223.2*) Scoring Configuration of Generic Drug Products.* explains the Center's policy on this topic. CDER MAPPs are available at http://www.fda.gov/cder/mapp.htm.

[13] Justified ranges, rather than overages, can be used for excipients. The justification for a proposed excipient range should be included in section P.2.1.2.

Parameters relevant to the performance or manufacturability (e.g., powder flow characteristics) of the drug product should be addressed. Physicochemical and biological properties such as pH, osmolarity, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity can be relevant. The discussion should cross-reference any relevant stability data in P.8.3. A summary of the development of a dissolution or drug release test and a cross-reference to the studies (with study numbers) should be provided.

For solutions, the concentration of the drug substance in the drug product should be compared to the solubility of the least soluble solid state form. When the drug load is close to saturation, the solid state forms of the drug substance that can crystallize from the drug product vehicle should be discussed. The discussion should cross-reference any relevant data in S.3.1.

Development studies to investigate the potential effect of and the appropriateness of drug product acceptance criteria for physicochemical and biological properties of the drug product should be summarized in this section of the application (P.2.2.3). For example, information would be provided from studies to investigate whether acceptance criteria for polymorphism should be included in the drug product specification or to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution versus disintegration testing (ICH *Q6A Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances*; Decision Tree #4 (Part 3) and Decision Tree #7 (Part 1)). The data from these studies should be used, as appropriate, to justify the drug product specification (P.5.6).

C. Manufacturing Process Development (P.2.3)

The selection and optimization of the manufacturing process described in P.3.3 (i.e., intended for production batches), in particular the critical aspects of the process, should be explained. During the development phase, the process should be well documented so differences between the manufacturing processes used to produce the clinical safety and efficacy, bioavailability, bioequivalence, or primary stability batches and the process described in P.3.3 can be identified. The differences that can influence the performance or manufacturability of the product should be discussed.

A table should be provided that compares the equipment used to produce clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for production batches. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (P.5.4). The table should identify (1) the identity (e.g., batch number) and use of the batches produced using the specified equipment (e.g., bioequivalence study batch # 1234), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment differences (e.g., different design, operating principle, size).

D. Container Closure System (P.2.4)

Container closure system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

A brief description of the container closure systems listed in P.7 and the container closure system used for storage and transportation of protein drug products should be provided. The suitability of the container closure systems should be discussed. The discussion should consider, for example, choice of materials, protection from moisture and light,[14] compatibility of the materials of construction with the dosage form (including sorption to container and leaching),[15] safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product). Other information to support the appropriateness of the container closure system or its use (e.g., cleaning instructions for a metered dose inhaler) should be provided as warranted. The studies performed to assess the suitability of the container closure system should be provided in this section of the application (P.2.4).

If an NDA is submitted for a new plastic that will be used for blood component storage, adequate information on the plastic should be submitted, including the identification of the leachables such as plasticizers since plasticizers are more readily leached into a lipid such as blood than an aqueous solution.

The results of suitability studies can form the basis for inclusion, or omission, of specific tests on the finished product, container closure system, or individual packaging components. For example, when suitability studies and stability data demonstrate that leachables from the container closure systems used for products such as ophthalmic solutions or large volume parenterals (LVPs) are consistently below agreed upon levels, routine testing of the finished product for leachables would not be necessary.

Additional guidance is available in:
- FDA: *Container Closure Systems for Packaging Human Drugs and Biologics*

E. Microbiological Attributes (P.2.5)

Where appropriate, the microbiological attributes of the drug product, drug substance, and excipients should be discussed in this section (P.2.5). The discussion should include, for example:

[14] Data, such as light transmission data, would be provided in P.2.4. Results from photostability studies, when warranted, should be provided in P.8.3 and cross-referenced in this section (P.2.4).
[15] The level of di-2-ethylhexyl phthalate (DEHP) leaching from polyvinyl chloride containers should be assessed, and appropriate reference to DEHP leaching should be included in the product labeling.

- the rationale for not performing microbial limits testing for nonsterile products (e.g., Decision Tree #8 in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances)*

- the rationale for not performing microbial limits testing for nonsterile drug substances and excipients (e.g., Decision Tree #6 in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances)*

- the selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial

- for sterile products, the integrity of the container closure system as it relates to preventing microbial contamination

Although chemical testing for preservative content is the attribute normally included in the drug product specification, antimicrobial preservative effectiveness should be demonstrated during development. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using an antimicrobial preservative effectiveness test (e.g., USP <51> *Antimicrobial Effectiveness Testing*).

Tests and acceptance criteria for microbiological attributes should be included in the specifications, as appropriate (e.g., drug substance, S.4.1; excipients, P.4.1, P.4.6; drug product, P.5.1).

Additional guidance is available in:

- FDA: *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

F. Compatibility (P.2.6)

The compatibility of the drug product with any diluents (i.e., constitution, dilution of concentrates, admixing),[16] or dosage devices specified in the drug product labeling and the compatibility of the drug product with likely coadministered drug products should be addressed to provide appropriate and supportive information for the labeling. The information should be used to identify in the labeling diluents and other drug products

[16] *Admixing* refers to the removal of a parenteral drug product from its immediate container and its subsequent addition to IV fluids.

that are compatible with the drug product as well as those that are found to be incompatible. Compatibility studies should assess, for example, precipitation, sorption onto injection vessels or devices, leachables[17] from containers and administration sets, and stability. The design and extent of the compatibility studies depend on the type of drug product and its anticipated usage. Recommendations on stability studies to assess compatibility will be provided in the forthcoming guidance *Stability Testing of Drug Substances and Drug Products.*[18]

In addition to assessing the compatibility of drug products admixed with diluents identified in the labeling, compatibility studies should also be performed with commonly used diluents even if they are not identified in the drug product labeling. These studies should be performed because it is likely that the diluents will be used whether or not they are specifically discussed in the labeling. At a minimum, admixing with Lactated Ringer's Injection, 5% weight/volume (w/v) Dextrose Injection, and 0.9% w/v Sodium Chloride Injection should be studied.

Constitution or dilution studies performed as part of formal stability studies to confirm product quality through shelf life should be reported in P.8.3.

Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

V. MANUFACTURE (P.3)

A. Manufacturer(s) (P.3.1)

The name, address, and manufacturing responsibility should be provided for each firm (including contract manufacturers, packagers, and testing laboratories) and each site (i.e., facility) that will be involved in the manufacturing, packaging, or testing of the drug product. Each site should be identified by the street address, city, state, and, when available, the drug establishment registration number.[19] The addresses should be for the

[17] The level of di-2-ethylhexyl phthalate (DEHP) leaching from polyvinyl chloride containers should be assessed, and appropriate reference to DEHP leaching should be included in the product labeling.

[18] In June 1998 (63 FR 31224), the Agency made available a draft revision of this guidance. When finalized, this revision will be the primary reference source on stability testing of drug substances and drug products.

[19] See 21 CFR part 207 for registration requirements for producers of drugs. The registration number is the seven-digit central file number (CFN) or ten-digit FDA Establishment Identifier (FEI).

location where the relevant manufacturing, packaging, or testing operation will be performed. Addresses for corporate headquarters or offices need not be provided. Building numbers or other specific identifying information should be provided for multifacility campuses. For sites processing sterile drug substances, drug products, or packaging components, the sterile processing area (e.g., room, filling line) should also be included. Addresses for foreign sites should be provided in comparable detail, and the name, address, and phone number of the U.S. agent for each foreign drug establishment, as required under 21 CFR 207.40(c), should be included.

The information should be provided for:

- Manufacturers of the drug product and in-process materials (e.g., controlled release beads)
- Packagers and labelers[20]
- Laboratories that perform quality control tests on bulk drug substance(s), components, intermediates, container closure systems, and finished drug product, including stability testing
- Facilities other than the drug product manufacturing site that perform sterilization operations (e.g., gamma irradiation of packaging components)

To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail address of a contact person be provided for each site listed in the application. Facilities should be ready for inspection when the application is submitted to FDA.

B. Batch Formula (P.3.2)

A batch formula should be provided that includes a list of all components used in the manufacturing process, their amounts on a per batch basis, including overages, a reference to their quality standards, and any explanatory notes. Batch formulas should be provided for the intended validation batch sizes of each formulation. If a common formulation is used to produce multiple products (e.g., strengths), a single batch formula can be provided.

In some instances, separately blended or formulated materials that are later combined during manufacturing should be listed separately in the batch formula. For example, some modified release products contain a mixture of immediate release and extended release beads within a capsule shell. In this case, separate batch formulas for the individual subcomponents of the dosage unit should be provided.

Additional guidance on each element of the batch formula is provided below. An illustrative example of a batch formula is provided in Table 2.

- List of All Components

[20] Only those required to register under 21 CFR part 207.

All components should be included in the batch formula. Processing agents (such as water, solvents, and nitrogen or other gases) that do not remain in the finished product should be included in the batch formula. Any gases used during manufacture should be listed and their purpose identified (e.g., blanket formulation, fill vial headspace) in an explanatory note.

- Amounts

The definite weight or measure for each component of the batch formula should be listed. The amount of drug substance listed should include any justified overage (see section IV.B.2). For excipients where a range has been justified (see section IV.A.2), the target amount and range should be included in the batch formula.

- Reference to Quality Standards

For compendial components, the appropriate official compendium should be cited.[21] Compendial components should comply with the monograph standard included in the official compendium, and citation of the official compendium confirms compliance with this standard. The compendium should be cited even if an in-house specification that provides for more testing than that of the compendial monograph is used to evaluate the component. For noncompendial components, the type of standard used to evaluate the component should be listed (e.g., in-house standard, CFR citation, DMF holder's standard). The applicant specific numeric code (e.g., SPEC 101.2b) of the specification used to evaluate the quality of the component should not be listed in the composition statement. The actual specification used for the drug substance should be provided in S.4.1. For the excipients, the actual specification should be provided in P.4.1 or P.4.6 and A.3 as appropriate.

- Notes

Explanatory notes should be included as appropriate. For example, explanatory notes should be used to identify components that are removed during processing or the purpose of inert gases used during the manufacturing process.

[21] A compendial component is a component that has a monograph in an official compendium as defined in the Federal Food, Drug, and Cosmetic Act.

Table 2: Proposed Batch Formula[1] — 250 mg Trademark™ Tablets		
Core Tablet		
Component	Reference to Quality Standard	Amount (kg) per batch
Drug Substance	In-house Standard	500
Excipient X	NF	310
Excipient Y	NF	280
Excipient Z	In-house standard	50
Magnesium Stearate	NF	15 (range 14.5 to 15.5)
Purified Water	USP	(200)[2]
Total Batch Size		X
Film Coat Solution[3]		
Component	Reference to Quality Standard	Amount (kg) per batch
Hydroxypropyl Methylcellulose	USP	10
Purified Water	USP	(200)[2]
Color Red™	DMF Holder Y Standard	10
Color White™	DMF Holder Y Standard	1.5
Total Batch Size		Y
Print Ink Solution		
Component	Reference to Quality Standard	Amount (kg) per batch
Colorant™	DMF Holder Z Standard	0.15
Solvent	NF	10
Total Batch Size		Z

[1] Theoretical yield is 2,000,000 tablets.
[2] Water is removed during processing.
[3] Film coat weight may vary between 80% – 120% of target coating weight.

C. Description of Manufacturing Process and Process Controls (P.3.3)

The description of the manufacturing process and process controls should include a flow diagram of the manufacturing process and a detailed description of the manufacturing process and process controls. If alternative processes are to be used, the information should be provided for each alternative. Differences in the manufacturing process described in this section and the manufacturing processes used to produce the batches used for clinical efficacy, bioavailability, bioequivalence, or primary stability studies that can influence the performance of the product should be discussed in P.2.3.

1. Flow Diagram

A flow diagram should be provided giving the steps of the process and showing where materials enter the process. The entire manufacturing process should be depicted (e.g., weighing of components through finished product release). The flow diagram can be

supplemented with information presented in tabular form, if appropriate. The flow diagram should include:

- each manufacturing step with identification of the critical steps and any manufacturing step where, once the step is completed, the material might be held for a period of time (i.e., noncontinuous process) before the next processing step is performed
- the material being processed
- critical process controls and the points at which they are conducted
- the type of equipment used (equipment model number is not needed)

2. Description of Manufacturing Process and Process Controls

A description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should be provided. This description provides more detail than that provided in the flow diagram. The complete manufacturing process intended for the validation batches should be described for each drug product (e.g., strength, packaging configuration). However, segments of the manufacturing process common to multiple products need only be described once. For example, the formulation of a solution that is used to produce vials and prefilled syringes can be described once, but a separate description of the filling/packaging operations would be expected. Equipment should, at least, be identified by type (e.g., tumble blender, in line homogenizer) and working capacity where relevant. Novel processes or technologies and packaging operations that directly affect product quality should be described in greater detail. The description should identify all process controls and the associated numeric ranges, limits, or acceptance criteria. Furthermore, any process controls that are considered critical process controls should be highlighted. See below for additional information on process controls.

For NDAs, the description of the manufacturing process can be either a detailed narrative description or a proposed master production record (MPR).[22] However, CDER and CBER prefer that a detailed narrative be provided for an NDA. For ANDAs, the proposed MPR should be submitted. A narrative description should be submitted to supplement a MPR when appropriate, for example, when novel processes or technologies warrant description in greater level of detail. Executed Production Records should be provided in R.1.P

A statement should be provided that ruminant-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the same facility. Submission of additional facility information could be warranted for multi-use facilities where there is a potential for cross-contamination with adventitious agents (see XI.A and XI.B). Additional facilities information for biotechnology-derived drug products should be included in A.1, when appropriate.

[22] A master production record is sometimes referred to as a master production and control record.

- **Process Controls**

Process controls is an all-inclusive term used to describe the controls used during production to monitor and, if appropriate, adjust the process and/or to ensure an in-process material with an established specification or the finished drug product will conform to its respective specification. The term includes:

- Operating parameters — conditions that can be adjusted to control the manufacturing process (e.g., temperature, pH, time, mixing speed)
- Environmental controls — conditions associated with the manufacturing facility (e.g., temperature, humidity, clean room classification)
- Process tests — measures used to monitor and assess the performance of the process
- In-process material tests — measures used to assess the quality attributes of an in-process material and ultimately lead to a decision to accept or reject the in-process material or drug product

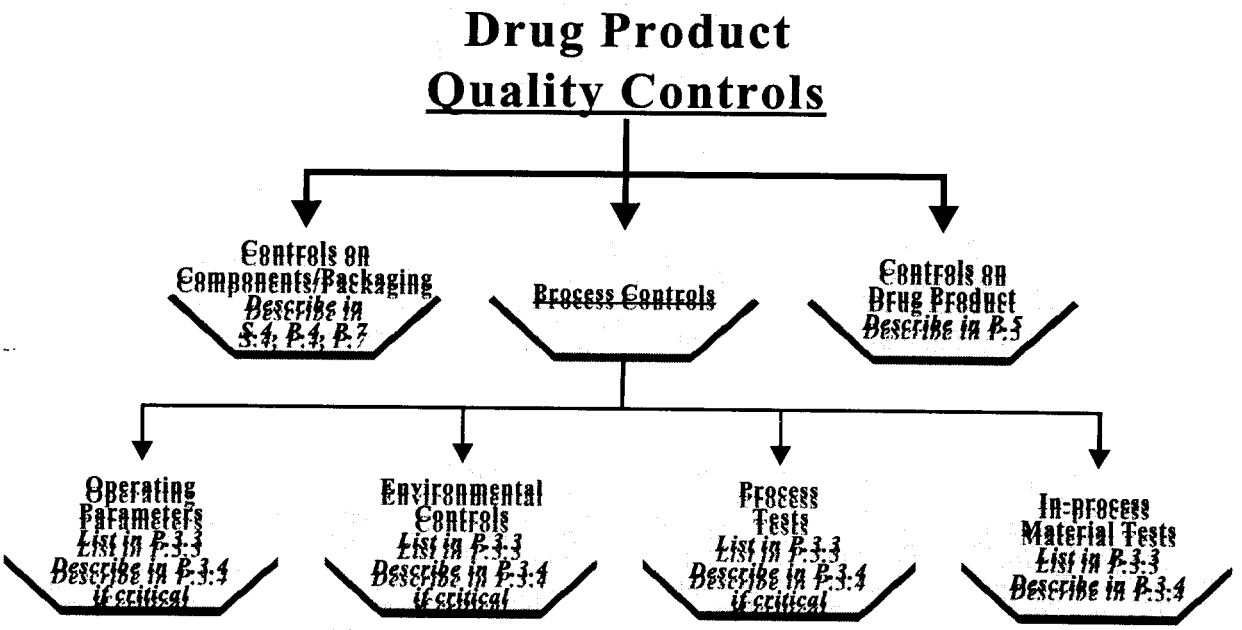
Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All process controls, critical or otherwise, should be included in the description of the manufacturing process (MPR or narrative).

Depending on the drug product and the manufacturing process, a particular process control may or may not be critical as illustrated in the following examples:

- A mixing speed range can be critical for forming an emulsion, but may not be critical for mixing a chemical solution.
- The humidity in the manufacturing facility can be critical for an effervescent tablet but may not be critical for an ointment.
- The clean room classification, while critical for a sterile product, may not be critical for a nonsterile product.
- Time frames for certain unit operations or overall drug product production can be critical for some products (e.g., lagering time for metered dose inhalers, hold times during sterile processing).

All in-process material tests and any of the operating parameters, environmental conditions, and process tests that ensure each critical manufacturing step is properly controlled should be specifically identified as critical in the flow diagram and description of the manufacturing process in this section of the application (P.3.3) and in P.3.4. All in-process material tests are considered critical process controls by definition because they directly assess the quality attributes of an in-process material and ultimately lead to a decision to accept or reject the in-process material or drug product. A summary of where information on drug product quality controls should be located in applications submitted in CTD-Q format is provided in Figure 1.

877
878
879 **Figure 1**
880
881



882
883
884
885 *3. Reprocessing and Reworking*
886
887 Reprocessing is the introduction of an in-process material or drug product, including one
888 that does not conform to a standard or specification, back into the process and repeating
889 steps that are part of the approved manufacturing process. Continuation of a process step
890 after a process test has shown that the step is incomplete is considered to be part of the
891 normal process and is not reprocessing. For most drug products, reprocessing need not
892 be described in the application. In general, the documentation of and data to support the
893 reprocessing of a production batch should be retained by the manufacturer and be
894 available for review by FDA upon request. However, if there is a significant potential for
895 the reprocessing operation to adversely affect the identity, strength, quality, purity, or
896 potency of the drug product, the reprocessing operations should be described and justified
897 in this section (P.3.3) of the application. For example, reprocessing of proteins would be
898 considered a reprocessing operation that should be described in the application. Any data
899 to support a justification should be either referenced or submitted in P.3.3. However,
900 validation data, when warranted to support the reprocessing operation, should be
901 provided in P.3.5.
902
903 Reworking is subjecting an in-process material or drug product that does not conform to a
904 standard or specification to one or more processing steps that are different from the

manufacturing process described in the application to obtain acceptable quality in-process material or drug product. In general, reworking operations are developed postapproval, and the application is updated through submission of a prior approval supplement. However, if reworking operations are anticipated at the time of the original submission, they should be described in this section of the application (P.3.3) with justification for the reworking operation and any data (or references to data) to support the justification. Validation data, when warranted to support the reworking operation, should be provided in P.3.5.

Both reprocessing and reworking are considered nonroutine events. If reprocessing or reworking are expected to be used for the majority of batches, the procedures should be included as part of the manufacturing process described in the application.

D. Controls of Critical Steps and Intermediates (P.3.4)

In this section of the application, all critical process controls (see section V.C.2) and their associated numeric ranges, limits, or acceptance criteria should be identified and justified and a brief description of the test provided. Any experimental data to support the justification should be included in this section (P.3.4) as well. For critical operating parameters and environmental controls, numeric ranges, limits, or acceptance criteria typically can be based on the experience gained during the development of the manufacturing process. (See section V.E for possible exceptions when process validation information is warranted.) Critical process control values from relevant batches (i.e., those for which batch analyses have been provided in P.5.4) should be provided as part of the justification. Additional information should be provided in this section (P.3.4) under the following circumstances.

- **Biological Tests**

Analytical procedures and associated validation information should be provided for biological tests.[23]

- **In-Process Tests Used In Lieu of Finished Product Tests**

In some cases, results from in-process tests (e.g., process tests, in-process material tests) during the manufacturing process can be used in lieu of testing the finished product to satisfy a test listed in the finished product specification. For example, testing the pH of a solution during the manufacturing process may be sufficient to satisfy a test listed in the finished product specification provided in P.5.1. This approach, however, should be supported with data that demonstrate test results or product performance characteristics do not change from the in-process stage to finished product. These data, along with the analytical procedure and associated validation information, should be provided in P.3.4.

[23] The term biological tests includes biological (i.e., using animal or cells), biochemical (e.g., enzyme reaction rates), and immunochemical procedures. Information on procedures from an official compendium to assess pyrogen, bacterial endotoxin, sterility, and microbial levels does not need to be provided, but the test procedure should be referenced.

Information should be included in the method validation package (R.3.P), as appropriate. When the same analytical procedure is used for both the in-process test and the finished product test, the acceptance criterion for the in-process test should be identical to or tighter than the acceptance criterion in the finished product specification.

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*[24]
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

E. Process Validation and/or Evaluation (P.3.5)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical tests used in the manufacturing process, where appropriate. Validation information relating to the adequacy and efficacy of any sterilization process (e.g., drug product, packaging components) should be submitted in this section of the application. However, submission of other manufacturing process validation information in the application is not necessary for most drug products.[25] When applicable, validation information should be provided for processes used to control adventitious agents. This information should be included in A.2.

Submission of validation information for reprocessing and reworking operations usually is not warranted. However, it can be warranted when the reprocessing or reworking operation is of the type for which process validation information is submitted when routinely performed or when the reprocessing or reworking operations have a significant potential to affect the identity, strength, quality, purity, or potency of the product (e.g., protein drug products).

[24] In August 2000 (65 FR 52776), the Agency made available a draft revision of this guidance entitled *Analytical Procedures and Methods Validation*. When finalized, this revision will be the primary reference source on this topic for NDA and ANDA applicants.

[25] All manufacturing processes should be validated. However, in most cases, the validation information is reviewed during facility audits under current good manufacturing practices (CGMP) regulations (21 CFR part 211).

Additional guidance is available in:

- FDA: *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

VI. CONTROL OF EXCIPIENTS (P.4)

Information on the control of excipients is included in P.4 and, when warranted, A.3 of the application. The location of the excipient information in the application is described below. Additional information on excipients should be included in P.2.1.2, as appropriate.

- **Compendial–Non-novel Excipients**:[26] When a compendial excipient is tested according to the monograph standard with no additional testing and the applicant intends to perform full testing on each batch received, the excipient (e.g., Sodium Chloride, USP) can be listed under P.4 with no detailed information provided in P.4.1 through P.4.4. In any other circumstance, information should be included in P.4.1 through P.4.4 of the application. The P.4.1 to P.4.4 information for each individual excipient should be grouped together in the application.
- **Noncompendial–Non-novel Excipients**: Information should be included in P.4.1 through P.4.4 of the application. The P.4.1 to P.4.4 information for each individual excipient should be grouped together in the application. Furthermore, depending on the circumstances, additional CMC information for the excipient can be warranted. When warranted, the additional CMC information or a cross-reference to a DMF that provides the additional CMC information should be included in A.3. See sections IV.B.2 and XI.C for additional guidance on the information that should be submitted to support the use of this type of excipient.
- **Novel Excipients**: Information on novel excipients should be included in P.4.6 and A.3.
- **Excipients of Human or Animal Origin**: Any excipient of human or animal origin should be identified in P.4.5.

In general, the above information relates to excipients that are materials (i.e., chemicals) combined with the drug substance. However, information on other components of the drug product should also be included in section P.4, as appropriate. For example, information on the components of a transdermal patch drug delivery system and the patch itself should be included in P.4.1 through P.4.4. The development of the delivery system should be discussed in P.2.2.1.

[26] A compendial excipient is an excipient that has a monograph in an official compendium as defined in the Federal Food, Drug, and Cosmetic Act. Inclusion of an excipient in an official compendium does not ensure that the excipient has ever been used in an FDA-approved human drug product. Therefore, a compendial excipient can be a novel excipient.

1005
1006 **A. Specifications (P.4.1)**
1007
1008 A specification for each excipient used in the manufacture of the drug product should be
1009 provided, regardless of whether or not the excipient appears in the finished drug product
1010 (e.g., processing agent). The specifications should be provided in this section of the
1011 application (P.4.1.), except specifications for novel excipients should be provided in P.4.6
1012 and A.3.
1013
1014 The specification should confirm the quality of the excipient and should focus on those
1015 characteristics found to be useful in assessing its function, suitability, and safety. The
1016 specification sheet should list all tests to which the excipient will conform and the
1017 associated acceptance criteria and should also include a reference to the analytical
1018 procedures that will be used to perform each test. Acceptance criteria are numerical
1019 limits, ranges, or other criteria for the tests described. Presentation of information in a
1020 tabular format is recommended.
1021
1022 In addition to listing all the tests for an excipient, the specification should identify the
1023 tests that the drug product manufacturer will routinely perform and the test results that
1024 will be accepted from the excipient manufacturer's certificate of analysis (COA).[27] At a
1025 minimum, the drug product manufacturer must perform an appropriate identification test
1026 (21 CFR 211.84(d)(1)). However, when there are specific safety concerns relating to an
1027 excipient, testing in addition to an identity test would be warranted. For example,
1028 diethylene glycol contamination of polyols such as glycerin and propylene glycol has
1029 caused numerous fatalities, and the specification should include testing for potential
1030 impurities and contaminants for each batch received by the drug product manufacturer.
1031
1032 A compendial excipient should conform to the monograph standard. Only a citation to
1033 the appropriate official compendium need be provided when the excipient specification is
1034 identical to the compendial monograph and full monograph testing will be performed on
1035 each batch of excipient.[28] When the specification for a compendial excipient differs from
1036 the compendial monograph (e.g., additional tests, tighter acceptance criteria than in the
1037 monograph, different analytical procedures) or test results will be accepted from the
1038 excipient manufacturer's COA, the in-house specification should be provided. If the
1039 specification for an excipient is based on a compendium other than an official
1040 compendium, the excipient should still conform to the monograph in an official
1041 compendium if there is such a monograph.
1042

---

[27] The drug product manufacturer must establish the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)). The reliability of the analyses need not be established at the time the application is submitted. However, the specification should indicate the tests that will be performed once the reliability of the supplier's results has been established in accordance with current good manufacturing practices.

[28] A compendial excipient is expected to comply with the monograph in the current revision of the official compendium cited. Therefore, when citing an official compendium, the version of the compendium should not be included in the citation. For example, the *National Formulary (NF)* should be cited rather than *NF 20*.

Certain *General Chapters* in the USP contain a statement that the text of the USP is harmonized with the corresponding texts of the *European Phamacopoeia* (EP) and the *Japanese Pharmacopoeia* (JP). However, where a difference appears, or in the event of dispute, the result obtained from the USP procedure is conclusive.

Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

B. Analytical Procedures (P.4.2)

The analytical procedures used by the applicant for testing the excipients, excluding those for novel excipients, should be provided in P.4.2. The analytical procedures for novel excipients should be included in A.3. When the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, a statement indicating the analytical procedure and reference can be provided rather than the analytical procedure itself.

Additional guidance is available in:

- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

C. Validation of Analytical Procedures (P.4.3)

All analytical procedures for excipients should be validated. When analytical procedures from the current revision of an official compendium or other FDA recognized standard references (e.g., AOAC International Book of Methods, analytical procedures from EP or JP that are interchangeable with a USP *General Chapter*) are used, they should be verified to be suitable under actual conditions of use. Submission of validation information in the application is normally not needed for excipients. Validation information should be submitted if there are special circumstances. For example, submission of validation information for an excipient can be appropriate if a characteristic of the excipient or the excipient itself is critical to product quality (e.g., adjunct, carrier) but the critical nature of the excipient cannot be or is not assessed as part of the drug product testing.

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*[29]
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

1074
1075
1076 **D. Justification of Specifications (P.4.4)**
1077
1078 Justifications for the proposed excipient specifications should be provided where
1079 appropriate. For compendial excipients, justification of the acceptance criteria for tests
1080 beyond those included in the monographs is recommended (e.g., particle size, flow
1081 properties, impurities). The specifications for noncompendial excipients should be
1082 justified as recommended for the drug substance (guidance will be provided in the
1083 discussion of section S.4.5 of the forthcoming drug substance guidance). The
1084 justification should be based on relevant development data (P.2.1.2), batch analyses
1085 (P.5.4, R.1.P), and any other relevant data, such as data from drug product stability
1086 studies (P.8). The discussion in this section should unify, either by reference or in
1087 summary, data and information that are located in other sections of the application.
1088
1089 A certificate of analysis (COA) from the manufacturer and the test results for the same
1090 batch from the drug product manufacturer should be provided for the components
1091 described in P.4. The information should be for the materials used to produce the batch
1092 described in the executed production record (R.1.P). Test results should be expressed
1093 numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms
1094 such as *conforms* or *meets specification* is discouraged.
1095
1096

Additional guidance is available in:

- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

[29] In August 2000 (65 FR 52776), the Agency made available a draft revision of this guidance entitled *Analytical Procedures and Methods Validation*. When finalized this revision will be the primary reference source on this topic for NDA and ANDA applicants. Although excipients are not included within the scope of the guidance, applicants can refer to this guidance for general principles on validation of analytical procedures.

E. Excipients of Human or Animal Origin (P.4.5)

Excipients of human or animal origin should be identified. The genus, species, country of origin, source (e.g., pancreas), and manufacturer or supplier should be clearly indicated. Furthermore, for excipients derived from ruminant materials, the application should state whether the materials are from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11). Guidance is available from FDA on *The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use.*

The potential adventitious agents should be identified, and general information regarding control of these adventitious agents (e.g., specifications, description of the testing performed, and viral safety data) should be provided in this section. Details of the control strategy and the rationale for the controls should be provided in A.2.

Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

F. Novel Excipients (P.4.6)

Novel excipients are excipients used for the first time in a human drug product in the United States or by a new route of administration. Any novel excipient should be identified and its specification included in this section of the application (P.4.6).

Additionally, full details of manufacture, characterization, and controls, with cross-references to supporting safety (nonclinical and/or clinical) data, should be provided. The information should provide the same level of detail as that provided for a drug substance, and according to the drug substance format (guidance will be provided in the forthcoming drug substance guidance). This detailed information should be provided in A.3 unless the information is provided in an appropriately referenced DMF.

VII. CONTROL OF DRUG PRODUCT (P.5)

A. Specification(s) (P.5.1)

The proposed specification for the drug product should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered

acceptable for its intended use. *Conformance to specification* means that the drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. A specification is one part of the strategy to control drug product quality. They are proposed and justified by the manufacturer and approved by the Agency. Specifications are established to confirm the quality of drug products rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring product quality as it relates to safety and efficacy. Information on periodic quality indicator tests is provided below.

The specification sheet should list all tests to which each batch of a drug product will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VII.F). Presentation of information in a tabular format is suggested. The specification sheet should also identify:

- tests that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))
- all analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[30]
- acceptance criteria for the test using the regulatory analytical procedure and alternative analytical procedures when the criteria are different (e.g., conformance to a spectrum for near infrared (NIR) or retention time for HPLC).
- release and shelf-life acceptance criteria when both are used

The ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides recommendations on tests that should be included in the specification for solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there are sufficient data and justification. Recommendations on tests for other dosage forms are included in Attachment 1.

An illustrative example of a specification sheet is provided in Table 3.

[30] See section VI.B for guidance on USP *General Chapters* that are interchangeable with EP or JP analytical procedures.

1173
1174

Table 3: Specification for Trademark™ Tablets (100 mg)			
Tests	Acceptance Criteria	Regulatory Analytical Procedure	Alternative Analytical Procedure
Description	White, biconvex, 11 mm diameter, 4 mm thick, film coated tablet, with "identifier code XYZ" on one side.	Visual	
Identification Test #1	Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation obtained as specified in the assay.	HPLC, AP[1] # EFG	
Identification Test #2	Responds to the tests for sulfate	USP <191>	
Core Weight[2]	440 mg ± 5%	AP # MOP	
Dissolution	NLT[3] 80% (Q) in 30 minutes	AP # BCD	
Uniformity of Dosage Units	As per USP	HPLC; AP # EFG	
Assay	95.0% to 105.0% LC[4] (release) 90.0% to 110.0% LC (shelf-life)	HPLC, AP # EFG	
Water Content	NMT[5] 1.0%	USP <921>; Method Ic	AP # PQR
Degradation Products Specified Degradation Products • Degradant A • Degradant B • Degradant at RRT[6] XX Unspecified Degradation Product • Individual Unspecified Total Degradation Products	 NMT 0.5% NMT 0.6% NMT 0.3% NMT 0.1% NMT 1.2%	HPLC; AP # EFG	
Residual Solvent A	NMT 200 ppm	GC; AP # XYZ	

[1] AP = Analytical Procedure
[2] Test will be performed on tablet cores in-process.
[3] NLT = not less than
[4] LC = label claim
[5] NMT = not more than
[6] RRT = relative retention time

1175
1176 • **Periodic Quality Indicator Tests**
1177
1178 The CGMP regulations require that for each batch of drug product, there will be
1179 appropriate laboratory determination of satisfactory conformance to the drug product
1180 specification. Drug product failing to meet established standards or its specification and
1181 any other relevant quality control criteria must be rejected (21 CFR 211.165).
1182 Occasionally and when justified, other tests and associated acceptance criteria and
1183 analytical procedures that assess product quality can be included in the application and
1184 not be listed in the drug product specification. These tests, referred to as periodic quality
1185 indicator tests (PQITs), augment the drug product specification. A PQIT is performed at
1186 release on preselected batches and/or at predetermined intervals, rather than on a batch-

to-batch basis. A PQIT can be warranted when a test, performed and reported as part of the batch analyses, has value as an indicator of product quality, but information indicates that the test need not to be performed on each batch of drug product. PQITs can include, for example, osmolality and microbiological testing for solid oral dosage forms. Designation of certain tests such as for description, identification, assay, impurities (unless otherwise justified), dissolution or drug release, or content uniformity as PQITs would not be considered appropriate. The appropriateness of a PQIT can depend on the type of product. For example, justification for a PQIT would be likely for an oral dosage form product than for a biological/biotechnology-derived parenteral drug product. Each request will be considered on a case-by-case basis. PQITs, along with the drug product specification, form a basis for approving the application (see, for example, section 505(b)(1)(D) and 505(d)(3) of the Federal Food, Drug, and Cosmetic Act).[31]

Sufficient data should be available to support a proposal to designate a test as a PQIT. If sufficient data (e.g., data from multiple batches, all proposed manufacturing sites and processes) are available, a PQIT proposal can be included in the original application. A proposal for a PQIT should include:

- the reason the PQIT is being proposed
- justification and data to support the periodic testing
- the protocol (e.g., frequency) for performing the test, including when postapproval changes are implemented
- a commitment

The commitment should state that:

- the PQIT will be performed according to the protocol approved in the application
- failure to meet the acceptance criteria for the PQIT will be handled (e.g., investigation, batch rejection decision) in the same manner as a failure of a test included in the drug product specification and the PQIT will be performed on each subsequent batch until the failure is resolved
- any investigation will assess the effect on all batches produced, in particular, the batches between the last batch tested with a passing test result and the batch that failed
- if the result of the investigation confirms a batch failure or is inconclusive, a changes-being-effected supplement will be submitted to include the test in the drug product specification

A list of PQITs, with associated acceptance criteria and reference to analytical procedures, should be included in P.5.1 of the application. The protocol and commitment should also be included in P.5.1. Data and justification to support the designation of a PQIT should be included in P.5.4 and P.5.6, as appropriate. The recommendations on CMC information that should be provided in P.5.2, P.5.3, and P.5.5 also apply to PQITs.

[31] 21 U.S.C. 355 (b)(1) and 355 (d)(3).

It is recognized that only limited data may be available at the time of submission of an application. Therefore, this concept would generally be implemented postapproval once sufficient data are available and after approval of a prior approval supplement.

Additional guidance is available in:

- ICH: *Q3B Impurities in New Drug Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

B. Analytical Procedures (P.5.2)

The analytical procedures used for testing the drug product should be provided. Recommendations on the content and format of analytical procedures will be provided in a forthcoming FDA guidance on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. Information should be provided for all analytical procedures listed in the specification (P.5.1). The following additional guidance is provided on submitting analytical procedure information from published sources.

- **Analytical Procedures from an Official Compendium or Another FDA-Recognized Standard Reference**

If the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, the analytical procedure need not be provided. A specific citation to the analytical procedure is sufficient.[32] When a general chapter or monograph included in an official compendium or other FDA recognized standard reference allows for the use of more than one analytical procedure for a test, the specific analytical procedure that will be used should be cited here (P.5.2) and in the specification (P.5.1). For example, when using USP <921> *Water Determination,* the method should be specified (e.g., Method Ia). If an analytical procedure is based on one of these sources but has been modified, the analytical procedure should be provided.

[32] The current revision of an analytical procedure in a compendial monograph or general chapter should be used. Therefore, when citing an official compendium, the version of the compendium should not be included in the citation. For example, the *USP* should be cited rather than *USP 25*.

- **Analytical Procedures from Other Published Sources**

Analytical procedures from any other published source (e.g., another country's compendium, scientific journal) should be provided.

Additional guidance is available in:

- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

C. Validation of Analytical Procedures (P.5.3)

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product should be provided. Validation of an analytical procedure is the process of demonstrating that analytical procedures are suitable for their intended use. This information should be provided for all analytical procedures listed in the specification (P.5.1). Stability data (S.7.3, P.8.3), including data from stress studies, should be used to support the validation of the analytical procedures. Recommendations on the analytical validation information that should be submitted will be provided in a forthcoming FDA guidance on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. The methods validation package should be provided in R.3.P.

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

D. Batch Analyses (P.5.4)

Batch analysis data should be provided for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies. Batch analysis data should also be provided for any other batches that are being used to establish or justify specifications and/or evaluate consistency in manufacturing. The batch analysis reports

(e.g., COAs) and collated batch analyses data should include a description of the batches. This information can be presented (1) with the batch data as space permits or (2) in a separate table with only the batch identity being included with the batch data. The description should include:

- Batch identity (i.e., batch number), strength, and size
- Date of manufacture
- Site of manufacture
- Manufacturing process, where applicable
- Container closure system
- Use of batch (e.g., bioavailablility, stability)
- Batch number of the drug substance used in the drug product
- Batch number of novel excipients or any excipients that are critical to product performance (e.g., excipients used to form liposomes)

Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *conforms* or *meets specification* is discouraged.

1. Batch Analysis Reports

The batch analysis reports should include results from all tests performed on the batch, including tests that are not part of the proposed specification. References to analytical procedures should be provided.

A summary of any changes in the analytical procedures should be provided if the analytical procedures (1) changed over the course of generating the batch analyses data and/or (2) are different from the analytical procedure included in P.5.2. The summary should identify when an analytical procedure changed, the differences between the analytical procedures, and the impact of the differences with respect to the data being reported. For example, a summary could state that the solvent system for the assay was changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately. If there are significant differences in the analytical procedures (e.g., different fundamental principles such as titration and HPLC), a more detailed summary describing the changes may be warranted

2. Collated Batch Analyses Data

Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria. Collated batch analyses data are not warranted for all tests. However, collated data should be provided for assay and impurities (e.g., degradation products, residual solvents) and should be considered for other tests such as water content.

Additional guidance is available in:

- ICH: *Q3B Impurities in New Drug Products*
- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products; Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

E. Characterization of Impurities (P.5.5)

Information on the drug product impurities should be provided.

1. List of Expected Impurities

All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, excipient degradants, leachables from the container closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification. For example, drug substance process impurities that could carry over to the drug product should be listed here even if they are normally controlled during drug substance testing and will not be included in the drug product specification. When qualified, the qualified level of an expected impurity with a cross reference to the appropriate studies (include study numbers) should be provided.

The list of expected impurities should be based on information from batch release data (P.5.4), stability studies, including stress studies (S.7.3, P.8.3), development data (e.g., container closure system suitability studies (P.2.4)), knowledge of the manufacturing process (e.g., use of organic solvents), and published literature (e.g., known excipient degradants). The rationale for not including an expected impurity in the drug product specification should be provided in P.5.6.

2. Identification of Impurities

Information on the characterization (i.e., structural characterization) of impurities should be provided if not previously provided in S.3.2. An applicant is encouraged to discuss any questions about the identification of impurities with the appropriate review divisions.

- **Degradation Products**

Active ingredient related impurities not covered in S.3.2 can include, for example, degradation products of the active ingredient arising during drug product manufacture or reaction products of the active ingredient with an excipient and/or immediate container

closure system. Attempts should be made to identify all degradation products found at significant levels in the drug product. CDER and CBER regulates a variety of drug products; no single recommendation applies to all drug products for the level of a degradation product that would warrant identification. Recommendations on identification levels may be provided for specific situations. For example, the ICH guidance *Q3B Impurities in New Drug Products* provides recommended identification levels for certain types of impurities in various classes of drug products.

When identification is warranted, the recommendations in S.3.2 of the forthcoming drug substance guidance on approaches for identifying impurities are applicable. A summary of attempts made to identify an impurity should be provided, if it has not been possible to identify it.

- **Residual Solvents**

An applicant is aware of the solvents used in the manufacture of the drug product and, in most cases, those being introduced from other sources (e.g., drug substance, excipients). Because these are known, the identity and presence of residual solvents in the finished drug product can usually be confirmed by using routine analytical techniques. In some cases, structural characterization of an unknown impurity can determine that the impurity is a residual solvent.

- **Miscellaneous Drug Product Impurities**

For purposes of this guidance, a miscellaneous drug product impurity is a drug product impurity other than (1) a degradation product, (2) a residual solvent, or (3) an extraneous contaminant that is more appropriately addressed as a good manufacturing practices issue (e.g., metal shavings). Miscellaneous drug product impurities include, for example, container closure system leachables, excipient degradants, heavy metals, aluminum, and ethylene oxide residuals.

Whether identification of a miscellaneous drug product impurity is warranted depends on the circumstances associated with a specific drug product. In general, the factors that contribute to the decision of whether structural characterization of such impurities is warranted are the (1) observed levels, (2) potential for safety issues to arise from exposure to the impurity (e.g., route of administration, patient population), (3) duration of product use (acute or chronic), and (4) historical knowledge. For example, structure characterization would more likely be requested for a container closure system leachable found in a metered dose inhalation product than for a leachable found in an oral solution.

Additional guidance is available in:

- ICH: *Q1B Photostability Testing of New Drug Substances and Products*
- ICH: *Q3B Impurities in New Drug Products*
- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

F. Justification of Specification(s) (P.5.6)

Justification for the proposed drug product specification should be provided. The justification should be based on relevant development data (P.2), standards in an official compendium, batch analyses (P.5.4), characterization of impurities (P.5.5), stability studies (P.8), toxicology data, and any other relevant data. The discussion in this section should unify data and information that are located in other sections of the application, either by reference or in summary. Data from the clinical efficacy and safety, bioavailability, bioequivalence, and primary stability batches and, when available and relevant, development and process validation batches should be considered in justifying the specification. If multiple manufacturing sites are planned, it can be valuable to consider data from these sites in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug product at any particular site. Justification for an in-process test that is used in lieu of a finished product test should be included in P.3.4.

- **Tests**

Inclusion of a test in the drug product specification need not be justified. However, exclusion of a test that is normally performed on a type of drug product, one that is recommended in a relevant FDA guidance, or one that was reported in the batch analyses (P.5.4) should be justified. For example, the ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* recommends that a test for redispersibility be included in the specification for an injectable suspension. Data generated during product development can be sufficient to justify eliminating this attribute from the specification, and such justification should be included in this section of the application (P.5.6). Similarly, justification for excluding the expected impurities listed in P.5.5 from the drug product specification provided in P.5.1 should be provided in this section of the application (P.5.6).

Justification for the designation of a test as a periodic quality indicator test should be provided.

Occasionally, it may appear that a test performed and reported as part of the batch analyses may not be necessary. For example, the available test results for heavy metals may be very low or below the limit of detection of the analytical procedure or osmolarity results are very consistent for the batches produced in support of the application indicating that there may be no need to perform the test. However, it is not certain if the same type of results will continue to be observed for production batches because (1) limited data are available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment, site) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized. In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria.[33] The proposal should include the (1) reason why the sunset provision is being proposed, (2) number of consecutive production batches that will be produced and tested before inclusion of the test in the drug product specification is reevaluated, (3) criteria that would be achieved, including data analysis plan, for the test to be dropped, and (4) postapproval reporting mechanism for notifying CDER of the test results when the criteria have been achieved. A *sunset test protocol* could also be considered when FDA requests that a test be added to the specification.

- **Acceptance Criteria**

Justification should be provided for all proposed acceptance criteria included in the drug product specification. Results from nonclinical, clinical, and stability studies and manufacturing and analytical capability should be considered when proposing acceptance criteria. Proposed acceptance criteria can include a reasonable allowance for analytical and manufacturing variability. The justification should discuss the basis of the proposed acceptance criteria from the perspectives of available data and analytical and manufacturing capability and variability. Furthermore, any statistical approaches that are used to establish the acceptance criteria should be described. In some cases, data generated from testing samples of the reference listed drug can be used to support acceptance criteria proposed in the application.

Occasionally, an applicant may wish to propose *interim acceptance criteria* for a specific test because there is some uncertainty whether the same type of results will continue to be observed for production batches. This uncertainty often occurs when (1) there are limited data available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment, site) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized. The proposal should include the (1) reason why

[33] A proposal to drop a test, based on historical data, can also be submitted postapproval in a prior approval supplement.

the interim acceptance criteria are being proposed, (2) number of consecutive production batches that will be produced and tested and/or the time frame before the acceptance criteria will be finalized, (3) data analysis plan, and (4) proposed reporting mechanisms for finalizing the acceptance criteria when the proposed final acceptance criteria are tighter, broader, or the same as the interim acceptance criteria. An applicant should not propose using interim acceptance criteria as a substitute for providing recommended or agreed upon (e.g., at pre-NDA meetings) information in an application. For example, proposing interim acceptance criteria would not be appropriate when the stability data package recommended in the ICH guidance *Q1A: Stability Testing of New Drug Substances and Products* has not been provided.[34] For NDAs, finalization of interim acceptance criteria will be a Phase 4 commitment.

- **Analytical Procedures**

The analytical procedures listed in the drug product specification normally need not be justified because the appropriateness of the procedure is supported by information in P.5.2, P.5.3, and R.3.P. In some instances, however, justification for the type of analytical procedure used would be warranted. For example, justification should be provided for the use of a non-stability-indicating assay procedure. The justification should explain the scientific reasons why a stability indicating procedure is not viable and which analytical procedures complement the assay procedure by qualitatively and/or quantitatively monitoring impurities, including degradants.

Additional guidance is available in:

- ICH: *Q3B Impurities in New Drug Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

VIII. REFERENCE STANDARDS OR MATERIALS (P.6)

Information on the reference standard or reference materials used in testing the drug product should be provided if not previously provided in S.5. Information on the reference standards for drug substance and drug substance impurities should be provided in S.5. A list of available reference standards should be provided in this section (P.6) for any impurities that are unique to the drug product.[35] The reference standards could be for impurities from drug substance and excipient interactions, impurities formed during drug product manufacturing, or an excipient

[34] For those applications that fall within the scope of Q1A.

[35] Whether or not information is included in the application, complete records must be maintained of any testing and standardization of laboratory reference standards (21 CFR 211.194(c)).

impurity or leachable from the container closure system that is included in the drug product specification.

Information on other drug product related reference standards, such as those used in the testing of excipients and packaging need not be included in the application.

> Additional guidance is available in:
>
> - ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
> - ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

IX. CONTAINER CLOSURE SYSTEM (P.7)

A description of the container closure system for the drug product should be provided, including the identity of materials of construction of each primary packaging component and its specification. The same type of information should be provided for functional secondary packaging components as is provided for primary packaging components. For nonfunctional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. Information about the suitability of a container closure system should be provided in P 2.4.

If an NDA is submitted for a new plastic that will be used for blood component storage, adequate information on the plastic should be submitted, including the composition of the plastic.

> Additional guidance is available in:
>
> - FDA: *Container Closure Systems for Packaging Human Drugs and Biologics*

X. STABILITY (P.8)

Information relating to the stability of the drug product should be provided in P.8.

A. Stability Summary and Conclusion (P.8.1)

The types of studies conducted, protocols used, and results of the studies should be summarized. The discussion should include, for example, (1) a summary of stability batches tested, storage conditions used, product attributes tested, shelf-life acceptance criteria, test schedule, amount of data available, and analysis of data (including a summary of the statistical analysis if performed), (2) conclusions regarding the labeled storage conditions and the proposed shelf life, and (3) conclusions regarding in-use storage conditions and shelf life, if applicable.

B. Postapproval Stability Protocol and Stability Commitment (P.8.2)

The postapproval stability protocol and stability commitment should be provided.

C. Stability Data (P.8.3)

Results of stability studies, including statistical analysis if performed, should be presented in an appropriate format (e.g. tabular, graphical, narrative).

1. Formal Stability Studies

The results from long-term, accelerated and, when performed, intermediate studies undertaken on primary stability batches should be provided. Stability study reports should also be included.

The analytical procedures used to generate the data should be identified. Information on the analytical procedures used to generate the data should be included in this section of the application as follows:

- If the analytical procedure listed in the stability protocol is different from the analytical procedure described in P.5 for the corresponding test (i.e., batch release verses stability analytical procedure) or a test included in the stability protocol is not described in P.5 (e.g., weight loss), the analytical procedure, validation of analytical procedures, and justification of acceptance criteria, as appropriate, should be included.

- A summary of any changes in the analytical procedures should be provided if the analytical procedure was changed over the course of generating the stability data. The summary should identify when an analytical procedure changed, the differences between the analytical procedures, and the impact of the differences with respect to the data being reported. For example, a summary could state that the solvent system

for the assay was changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately. If there are significant differences in the analytical procedures (e.g., different fundamental principles such as titration and HPLC), a more detailed summary describing the changes may be warranted

Constitution or dilution studies performed as part of formal stability studies to confirm product quality through shelf life should be reported in this section of the application. Information regarding the compatibility of the drug product with any diluents (i.e., constitution, dilution of concentrates, admixing), dosage devices, or coadministered drug products should be provided in P.2.6.

2. Supporting Stability Studies

Data, other than those from formal stability studies, that support the analytical procedures, the proposed shelf life, and label storage statements can be provided. Such data can include, for example, stability data on small scale batches of drug product, investigational formulations not proposed for marketing, related formulations, or product presented in container closure systems other than those proposed for marketing. Stability data to support holding in-process materials for longer than 30 days should also be provided in this section. Information on the type of container closure system in which the in-process material is held should be included with the stability data. The analytical procedures should be identified, and when analytical procedures are different from those described elsewhere in the application, information should be provided on the analytical procedures to the extent warranted to support the use of the data.

3. Stress Studies

Any results from drug product stress testing and thermal cycling studies should be provided in this section of the application. The design of the stress studies should be discussed briefly. The information should be used, as appropriate, to support the validation of analytical procedures (P.5.3), the impurities acceptance criteria and/or characterization of expected impurities (P.5.1, P.5.5), justification of the drug product specification (P.5.6), and stability summary and conclusions (P.8.1).

Additional guidance is available in:

- FDA: *Submitting Documentation for the Stability of Human Drugs and Biologics*[36]
- ICH: *Q1A Stability Testing of New Drug Substances and Products*
- ICH: *Q1B Photostability Testing of New Drug Substances and Products*
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q3B Impurities in New Drug Products*
- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

XI. APPENDICES (A)

Information relating to both drug substances and drug products should be included in the Appendices (section A) of the application, when appropriate. If drug substance and drug product information is provided in an appendix, the preferred presentation is drug substance information followed by drug product information (e.g., A.1 drug substance then drug product, followed by A.2). The recommendations provided below relate to drug products. Recommendations on the information to include in the Appendices for drug substances will be provided in the forthcoming drug substance guidance.

A. Facilities and Equipment (A.1)

Information on facilities and equipment, in addition to the information provided in other sections of the application (e.g., P.3.1, P.3.3), is usually not needed. However, when contamination with viral adventitious agents or transmissible spongiform encephalopathy (TSE) agents is a concern or for protein products, additional information can be warranted and should be included in this section of the application.

- **Viral Adventitious Agents and TSE Agents**

All developmental or approved products manufactured or processed in the same areas as the applicant's products should be identified when there is potential for cross-contamination with TSE agents. For nonoral, nontopical products, this information should also be provided when there is potential for cross-contamination with viral adventitious agents. Information should be included on the design features of the facility and procedures to prevent cross-contamination of areas and equipment.

[36] In June 1998 (63 FR 31224), the Agency made available a draft revision of this guidance entitled *Stability Testing of Drug Substances and Drug Products*. When finalized, this revision will be the primary reference source on stability testing of drug substances and drug products

1652
1653 If ruminant-derived materials from BSE countries as defined by the U.S. Department of
1654 Agriculture (9 CFR 94.11) are used or manipulated in the same facility, additional
1655 information should be provided, such as whether dedicated equipment is used.
1656
1657 • **For Protein Products**
1658
1659 A diagram should be provided illustrating the manufacturing flow, including movement
1660 of raw materials, personnel, waste, and intermediates in and out of the manufacturing
1661 areas. Information should be presented with respect to adjacent areas or rooms that may
1662 be of concern for maintaining integrity of the product.
1663
1664 Information on all development or approved products manufactured or manipulated in the
1665 same areas as the applicant's product should be included.
1666
1667 A summary description of the product-contact equipment and its use (dedicated or multi-
1668 use) should be provided. Information on preparation, cleaning, sterilization, and storage
1669 of specified equipment and materials should be included, as appropriate.
1670
1671 Information should be included on procedures (e.g., cleaning and production scheduling)
1672 and design features of the facility (e.g., classifications) to prevent contamination or cross-
1673 contamination of areas and equipment where operations for the preparation of cell banks
1674 and product manufacturing are performed.
1675
1676 For biotechnology derived protein products, additional recommendations will be
1677 provided in the forthcoming guidance on the submission of CMC information for a
1678 therapeutic recombinant DNA-derived product or a monoclonal antibody for in vivo use.
1679
1680 **B. Adventitious Agents Safety Evaluation (A.2)**
1681
1682 Information assessing the risk with respect to potential contamination with adventitious
1683 agents should be provided. The recommendations provided below relate to the drug
1684 product. Recommendations on the information to include in A.2 for drug substance will
1685 be provided in the forthcoming drug substance guidance. For example, an applicant
1686 should refer to the drug product guidance for recommendations on viral safety evaluation
1687 studies when they are performed as part of the drug product manufacturing (e.g.,
1688 assessment of a biotechnology-derived excipient). However, if studies are performed as
1689 part of the drug substance manufacturing (e.g., evaluation of a cell line), the applicant
1690 should refer to the forthcoming drug substance guidance. Furthermore, for
1691 biotechnology derived products, additional recommendations will be provided in the
1692 forthcoming guidance on the submission of CMC information for a therapeutic
1693 recombinant DNA-derived product or a monoclonal antibody for in vivo use.
1694
1695 In certain instances, reduced testing of excipients or drug product and/or validation of
1696 removal and/or inactivation of adventitious agents can be appropriate, with justification.
1697 Such instances can include drug products that are terminally sterilized when it has been

demonstrated that terminal sterilization inactivates the adventitious agent. Early dialog with FDA is encouraged in these circumstances.

1. Nonviral Adventitious Agents

Detailed information should be provided on the avoidance and control of nonviral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process, and agent. In general, information provided elsewhere in the application will address these issues (e.g., P.2.5, P.3.5). However, if additional information is warranted to address the issue of nonviral adventitious agents, the information should be included here. For example, information would be included here on the capability of a production process to inactivate or remove TSE agents.

Certifications and/or certificates relating to use of ruminant-derived materials and sourcing of materials from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) should be provided, as appropriate.

2. Viral Adventitious Agents

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable.

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in section VI.E).

The selection of virological tests that are conducted during manufacturing (e.g., post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in section V.D).

The rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in section V.E).

Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

C. Excipients (A.3)

- **Novel Excipients**

Novel excipients are excipients used in the United States for the first time in a human drug product or by a new route of administration. The chemistry, manufacturing, and controls information for a novel excipient should be provided in the same level of detail and in the same format as the information provided for a drug substance (see the forthcoming drug substance guidance).

The suitability of the novel excipient for the intended route of administration should be discussed. Cross-references to supporting safety (nonclinical and/or clinical) data should be provided. Information to support safety can include, for example, references to FDA's regulations, Food Chemical Codex, citations or supporting toxicology data provided in the application (include study numbers).

- **Other Excipients**

Information in addition to that provided in P.4.1 through P.4.4 can be warranted for certain excipients. See sections IV.B.2 and VI for additional guidance on the information that should be submitted to support the use of excipients.

Depending on the functionality (e.g., complexing agent) and the route of administration of the drug product, additional information, up to and including the level of information recommended for novel excipients, can be warranted for noncompendial–non-novel excipients. The additional CMC information or a cross-reference to a DMF that provides the additional CMC information should be included in A.3. An applicant is encouraged to discuss the use of noncompendial–non-novel excipients with the appropriate review division prior to submitting its application to ascertain the level of information that would be warranted to support the use of the excipient.

When a component that is usually identified as an excipient contributes to the intrinsic pharmacological activity of the drug substance (e.g., levonordefrin or epinephrine for local anesthesia), CMC information for the component should be provided in the application or incorporated by reference from a DMF. The information should be provided in the same level of detail as that for a drug substance. The CMC information or a cross-reference to a DMF that provides the CMC information should be included in A.3.

XII. REGIONAL INFORMATION (R)

Information relating to both drug substances and drug products should be included in the Regional Information section (section R) of the application, when appropriate. The recommendations provided below relate to drug products. Recommendations on the information to include in the Regional Information section for drug substances will be provided in the forthcoming drug substance guidance.

A. Executed Production Records (R.1.P)

Executed Production Records (EPRs) for representative batches used in Phase III clinical, bioavailability, bioequivalence, or primary stability studies and supporting production information must be provided (21 CFR 314.50(d)(1)(ii)(*b*)).

1. Executed Production Records

For NDA submissions, an EPR for a batch manufactured on at least a pilot scale should be submitted. In cases where clinical batches used in Phase III trials were less than pilot scale, submission of the EPR for the largest scale clinical batch is also recommended. Discussion of which EPRs should be included in the NDA can be a topic at pre-NDA meetings. For ANDA submissions, EPRs should be submitted for the batches produced in support of the application.

2. Information on Components

The following information must be provided for the components used to produce the drug product batches for which the EPRs are provided (21 CFR 314.50(d)(1)(ii)(*b*)):

- The name and address of the drug substance manufacturer
- The names and addresses of sources of noncompendial excipients
- Names and addresses of sources of the container closure system for the drug product
- The name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility
- Results of any test performed on the components. This should include a certificate of analysis (COA) from the component manufacturer and the test results for the same batch from the drug product manufacturer. Test results should be expressed

numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *conforms* or *meets specification* is discouraged. For excipients, cross-reference to section P.4.4 can be provided if the information has been included there.

B. Comparability Protocols (R.2.P)

A comparability protocol is a protocol describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of postapproval manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety and effectiveness of the drug product. Comparability protocols are optional. If a comparability protocol is proposed, it should be included in this section (R.2.P). Approval of a comparability protocol can justify a reduced reporting category for the particular postapproval change described in the protocol.

C. Methods Validation Package (R.3.P)

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. Part of the methods validation process can include FDA laboratory analysis to demonstrate that an analytical procedure is reproducible by laboratory testing. A methods validation package (multiple copies for paper applications) must be submitted in the application (21 CFR 314.50(e)(2)(i) and 314.94(a)(10)) and should be included in R.3.P.

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*

XIII. LITERATURE REFERENCES (3.3)

References to the scientific literature relating to both drug substances and drug products should be included in the Literature References (3.3) section of the application, when appropriate.

The full bibliographic reference should be cited close to where the reference appears in the text of the application (e.g. in a footnote or section endnote). The full text of the literature cited (e.g., journal article) should be included in the Literature References section, except when otherwise indicated. For example, as previously stated in this guidance, monographs from an official compendium need not be included in the application.

ATTACHMENT 1

Drug Product Specification[37]
Test Recommendations for Specific Dosage Forms

The ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides recommendations on tests that should be included in the specification for solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Recommendations on tests for some other dosage forms are provided below. Tests other than those listed below can be warranted in particular situations or as new information becomes available. Moreover, test recommendations may be available in dosage form specific guidances such as the FDA's guidance on *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products* or guidances for a type of product such as ICH guidance *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.*

The tests recommended below are in addition to the universal tests recommended in Q6A. The universal tests are (1) description, (2) identification, (3) assay, and (4) impurities.

Semisolids (e.g., Creams, Ointments, and Gels)

Semisolids include a variety of dosage forms with different routes of administration (e.g., topical, ophthalmic). The drug products, depending on their use, can be sterile or nonsterile. In general, the following tests are applicable to semisolid drug products. However, depending on the specific dosage form and route of administration, some of the tests listed below may not be applicable or additional tests could be warranted in the specification. For example, although not listed in the tests below, the specification for an ophthalmic ointment should include a test for metal particles (e.g., USP <751> *Metal Particles in Ophthalmic Ointments*).

- Homogeneity

Assay of the product at the top, middle, and bottom of the container should be performed to ensure that the product is homogeneous. If the size of the container is too small to allow sampling of all of these locations, sampling at top and bottom can be performed.

- Uniformity of Dosage Units

A test for the uniformity of dosage units should be included.

- Rheology

Testing of rheological characteristics should be included in the specification. In many cases, a viscosity procedure described in USP <911> *Viscosity* can be used. However, the

[37] Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there is sufficient data and justification (see section VII.A).

suitability of the specified viscosity procedure should be evaluated based on the specific drug product (e.g., non-Newtonian fluids) being tested.

- Minimum Fill

A test for minimum fill should be specified, such as USP <755> *Minimum Fill.*

- pH

Acceptance criteria for pH should be provided where applicable and the proposed range justified.

- Sterility and Microbial Limits

If the product is sterile (e.g., ophthalmics, drug products for open wounds), sterility should be part of the product specification.

In general, it is advisable to perform microbial limit testing of a nonsterile drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation. A proposal to exclude microbial limit testing from the specification should be scientifically justified (rationale provided in P.2.5 and justification, as appropriate, in P.5.6). Acceptance criteria should be provided for total aerobic microbial count, for total combined molds and yeasts count, and for absence of designated microbial species (e.g., Staphlococcus aureus, Escherichia coli, Salmonella species, Pseudomonas aeruginosa). These criteria should be determined by suitable procedures such as those specified in USP <61> *Microbial Limit Tests.*

- Antimicrobial Preservative and Antioxidant Content

If antimicrobial preservatives or antioxidants are used in the product, tests for their content should be included in the specification. Acceptance criteria for the content should be based upon the level that will maintain product quality throughout shelf life.

- Particle Size Distribution (for dispersions)

Particle size, if known to influence bioavailability or bioequivalence, is normally controlled as part of the drug substance specification. However, if formulation and process development studies indicate the possibility for changes in particle size or aggregation of particles during manufacture or storage of the drug product, appropriate controls should be included in the specification.

- Performance Testing

Characterization of product performance can be appropriate depending on the drug product and/or container closure system.

Solutions and Suspensions

Solutions and suspensions include a wide variety of drug products with different routes of administration (e.g., topical, ophthalmic, inhalation). The drug products, depending on their use, can be sterile or nonsterile. ICH *Q6A* provides recommendations on tests for solutions and suspensions as part of its discussion of oral liquids and parenteral drug products. In general, the recommendations in ICH *Q6A* are applicable to any solution or suspension. The applicant should consider the relevance of any individual test recommended in ICH *Q6A* and whether additional tests are warranted based on the specific drug product and its use. Moreover, FDA may provide recommendations on tests for a specific type of solution or suspension in a separate guidance such as *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products.*

Transdermal Drug Delivery Systems

Transdermal drug delivery systems are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver drug through the skin to the systemic circulation. The following tests can be applicable to transdermal systems.

- Uniformity of Dosage Units

A test for the uniformity of dosage units should be included, such as USP <905> *Uniformity of Dosage Units.* Content uniformity should be determined for the active ingredient and penetration enhancers, when used.

- Drug Release

A drug release test should be included that assesses the release of the drug substance at a number of time points spanning the total dosing time. General drug release standards for transdermal delivery systems are included in USP <724> *Drug Release.* The test procedure and test time points used should be demonstrated as suitable for the specific drug product. Drug release should be assessed at a minimum of three time points, including an early time point to demonstrate the absence of dose dumping, one or more intermediate time points to define the release rate profile, and a final time point to show the total delivered dose. More time points can be appropriate depending on the length of time the system will be used or if the delivery rate is not constant. The results should be reported as percent of label claim dissolved per unit of time.

- Residual Monomers

Residual monomers are generally from the pressure sensitive adhesive component of the drug product. A test for residual monomers should be included in the specification unless the omission of the test has been justified in P.5.6.

- Enhancer

Any component used to increase the partitioning of drug substance to the skin and to enhance percutaneous absorption should be defined as an enhancer and identified as such in P.1 and P.2.1.2 of the application. An assay for the enhancer should be included in the specification. Furthermore, inclusion of a release rate test for the enhancer should be considered.

- Functionality Tests (Peel Force and Adhesion Strength)

Tests should be proposed to assess the peel force necessary to remove the protective liner and the adhesion shear strength of the transdermal system (force necessary to remove the transdermal system from a substrate).

- Pouch Integrity Test

A test to assess the seal integrity of the pouch used for packaging the transdermal drug delivery system should be included in the specification.

- Microbial Limits

See information provided under semisolids.

Suppositories

Suppositories are solid bodies of various weights and shapes for introduction into the rectal, vaginal, or urethral orifice.

- Homogeneity

For suppositories in which the drug substance is suspended in a suppository base, homogeneous distribution should be demonstrated.

- Uniformity of Dosage Units

A test for the uniformity of dosage units should be included, such as USP <905> *Uniformity of Dosage Units.*

- Particle Size Distribution

Particle size, if known to influence bioavailability or bioequivalence, is normally controlled as part of the drug substance specification. If formulation and process development studies indicate the possibility for changes in particle size or aggregation of particles during manufacture or storage of the drug product, appropriate controls should be included in the specification.

- Morphology

For suppositories in which the drug substance is suspended in the suppository base and there is evidence the morphic form can change during drug product manufacture or storage, appropriate controls of the drug product should be established to assess the morphic form.

- Softening Point or Melting Range

The softening or dropping point of the suppository, its melting range, or the time required for complete melting should be included in the specification. The studies are usually performed at 37°C.

- Dissolution or Drug Release

The specification for suppositories should include an appropriate test to measure dissolution or drug release. The test design should be appropriate for the specific product and conditions of use.

- Sterility and Microbial Limits

For vaginal and rectal suppositories, see information provided under semisolids for microbial limits. Urethral suppositories should be sterile, and sterility should be part of the product specification.

- Antimicrobial Preservative and Antioxidant Effectiveness Testing

If antimicrobial preservatives or antioxidants are used in the product, tests for their content should be included in the specification. Acceptance criteria for the content should be based upon the level that will maintain product quality throughout shelf life.

Implantable Drug Delivery Systems

Implantable drug delivery systems are reservoirs or matrices containing drug substance, with or without excipients. Implants are inserted into the body (e.g., subdermal, vaginal, intrauterine), where the drug substance is very slowly absorbed over a specified period of time. The drug delivery system can be either biodegraded and subsequently absorbed or removed after the specified period of time

- Particle Size Distribution

The particle size of the drug substance in implants can affect the rate of absorption. The particle size is normally controlled as part of the drug substance specification. However, if formulation and process development studies indicate the possibility for changes in particle size or aggregation of particles during manufacture or storage of the implant, appropriate controls should be included in the specification. If the implant is in the form of

biodegradable microspheres, there should be a test procedure and acceptance criteria for particle size of the microspheres.

- Morphology

If there is evidence the morphic form of the drug substance can change during drug product manufacture or storage, appropriate controls of the drug product should be established to assess the morphic form.

- Physical Characteristics of Delivery System

If polymers are used as a drug delivery system, appropriate controls for their physical properties (such as tensile strength, elongation, thickness, diameter) should be established.

- Uniformity of Dosage Units

A test for uniformity of dosage units should be included.

- Drug Release

The specification should include a test for in vitro drug release. The test should be performed over a sufficient period of time and include a number of time points sufficient to simulate the in vivo use of the drug delivery system. The test design should be appropriate for the specific product and conditions of use and should be designed to assess the variability of the release rate of individual implants. The results should be reported as percent of label claim dissolved per unit of time.

- Sterility

Implants, except vaginal implants, should be sterile, and sterility should be part of the product specification.

- Antimicrobial Preservative and Antioxidant Content

If antimicrobial preservatives or antioxidants are used in the product, tests for their content should be included in the specification. Acceptance criteria for the content should be based upon the level that will maintain product quality throughout shelf life.

GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of results of analytical procedures (ICH Q6A)

Batch: A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified acceptance criteria, and is produced according to a single manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2))

Bioavailability Batch: Batch used in determining the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action

Bioequivalence Batch: Batch used to determine the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study

Clinical Batch: Batch used to support the efficacy, safety, bioavailability, or bioequivalence of the drug product

Combination Product: A drug product that contains more than one drug substance (ICH Q6A)

Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3))

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Degradation Product: A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product (ICH Q6A).

Dosage Form: The physical form (e.g., tablet, capsule, solution) of the drug product. Standard dosage form terminology can be found in the CDER Data Standards Manual (http://www.fda.gov/cder/dsm).

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b))

Drug Product: A finished dosage form (e.g., tablet, capsule, solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b))

Enantiomeric Impurity: A compound with the same molecular formula as the drug substance that differs in the spatial arrangement of atoms within the molecule and is a non-superimposable mirror image (ICH Q3A)

Established Name: The designated FDA official name, the compendial name, the USAN Council name, or the common or usual name (section 502(e)(3) of the Act and 21 CFR 299.4). Ordinarily, the established name of a drug will be the compendial name. However, FDA may designate an established name in cases where a monograph does not exist (CDER Data Standards Manual).

Executed Production Records: The manufacturing record prepared from the master production record for each batch of drug product produced. This is sometimes called the batch production and control record.

Extended Release: Products that are formulated to make the drug available over an extended period after ingestion (ICH Q6A)

Excipient: Any intended component other than the drug substances in the dosage form. This is sometimes called an inactive ingredient.

Formulation: The qualitative and quantitative composition of the drug product. This is often called the composition statement.

Immediate Release: For oral products, a drug product that allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug (ICH Q6A)

Impurity: Any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product (ICH Q6A)

In-process Material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9))

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified acceptance criteria. In the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified acceptance criteria (21 CFR 210.3(b)(10)).

Master Production Record: A record containing the method of manufacture of the drug product, including, in part, the master formula of defined size, complete manufacturing and control instructions, in-process tests and acceptance criteria, equipment and operating parameters, yield and yield reconciliation calculations, and provisions for packaging and labeling (see 21 CFR 211.186(b))

Miscellaneous Drug Product Impurity: For purposes of this guidance, a drug product impurity other than a (1) degradation product, (2) residual solvent, or (3) extraneous contaminant that is more appropriately addressed as good manufacturing practices issues

Modified Release: Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products (ICH Q6A).

Pilot Scale: The manufacture of a drug product by a procedure fully representative of and simulating that to be applied to a production scale batch. For solid oral dosage forms, a pilot scale is generally a minimum one-tenth of full production scale or 100,000 tablets or capsules, whichever is the larger.

Primary Stability Batch: Batch used to generate primary stability data

Primary Stability Data: Data on the drug product stored in the proposed container/closure for marketing under storage conditions that support the proposed shelf life

Production Batch: A batch of drug product manufactured at production scale by using production equipment in a production facility as specified in the application (ICH Q1A)

Quality: The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, purity, and potency (ICH Q6A)

Specific Test: A test that is considered to be applicable to particular drug substances or particular drug products depending on their specific properties and/or intended use (ICH Q6A)

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents and other components including container closure system, and in-process materials. A specification sheet includes the list of tests, references to analytical procedures, and acceptance criteria.

Specified Degradation Product: An identified or unidentified degradation product that is selected for inclusion in the drug product specification and is individually listed and limited in order to ensure the safety and quality of the drug product (Q3B)

Universal Test: A test that is considered to be potentially applicable to all drug substances, or all drug products (e.g., appearance, identification, assay, impurity tests) (ICH Q6A)

Unspecified Degradation Product: A degradation product that is not included in the list of specified degradation products (ICH Q3B)