Guidance for Industry: Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs

Day 2/Session 6:
Ensuring Efficient and Consistent
High Quality Generic Drug Development

Greg Huang

OPQAII/Office of Pharmaceutical Quality, CDER | US FDA

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Learning Objectives

- Describe content & format in Composition Statement of drug product
- Describe what to include in Statement of Ingredients in Labeling
- Understand requirement for consistency in composition information in NDA and ANDA submissions

Introduction

- FD&C Act and 21 CFR 314 require NDA and ANDA to provide:
  - Full list of components in drug product manufacturing
  - Statement of composition of drug product
- The Guidance recommends accurate and complete **composition statement** of drug product and **statement of ingredients** in Labeling.

Definitions

- What is **Composition Statement**?

Qualitative and quantitative information of ingredients of Drug Product (in eCTD 3.2.P.1)

- What is **Statement of Ingredients**?

Information on ingredients listed in Description/Labeling (in eCTD 1.14), and other types of FDA-approved labeling

What to Include in Composition Statement?

- **Name** of all active and inactive ingredients with clear identification (such as grade, type)
- **Reference Quality Standard** – (USP/NF or In-House)
- **Primary Function** of inactive ingredients (refer to USP <1059>)
- **Quantity/Proportion** of all ingredients (in same units)

Example of Composition Statement

Name	Ref. Quality Standard	Function	mg/mL	Quantity mg/vial	% (w/v)
Sodium Drugozide	USP	API	27.3	136.5	2.73
Sodium Chloride	USP	Tonicity	2.5	12.5	0.25
Trisodium Citrate Dihydrate	USP	Buffer	1	5	0.10
Citric Acid Monohydrate	USP	Buffer	1	5	0.10
Edetate Disodium Dihydrate	USP	Preserva-tive	0.554	2.77	0.060

Example (Cont'd)

Name	Ref. Quality Standard	Function	mg/mL	Quantity mg/vial	% (w/v)
Sodium Metabisulfate	In-House	Antioxi-dant	5	25	0.50
Povidone K-17	USP	Stabilizer	1	1	0.10
Sodium Hydroxide	NF	pH adjustor	q.s.	q.s.	q.s.
Hydrochloric Acid (1M)	In-house	pH adjustor	q.s.	q.s.	q.s.
Water for Injection	USP	Solvent	q.s. to 1 mL	q.s. to 5 mL	q.s. to 100 (%)
Nitrogen	NF	Processing Aid	NA	NA	NA

Specifics to Identify Ingredients in Composition Statement

- **Active Ingredients**:
  - Salt Form vs. Free Base
  - If API is a mixture: Components & Composition
- **Inactive ingredients**
  - Hydration form
  - Grade (e.g. composition)
  - Type (e.g. polymer type, MW)
  - Purity

Examples of Identifying API in eCTD 3.2.P.1

- **Salt Form vs. Free Base:**

Include in Composition Statement:

Sodium Drugozide is a salt of Drugozide converted by reacting with sodium hydroxide, each mL of the drug product contains 27.3 mg sodium drugozide, which is equivalent to drugozide 25 mg".

- **Components & Composition if API is a mixture**

Include in Composition Statement:

Drugozide is a mixture of Drugozide-A and Drugozide- B in a ratio of 3 to 1".

Examples of Identifying Inactive Ingredients in eCTD 3.2.P.1

Identification of Ingredient	Ingredient Name	Differentiation
Hydration Form	Trisodium citrate citric acid edetate disodium	Anhydrous, monohydrate, other hydration state
Polymer Type	Povidone	Nominal K-value 18, 19-95, >95
	Hypromellose	1828, 2208, 2906, 2910 by substitution type of methoxy% and hydroxypropoxy%
	Hydroxyethyl Cellulose	30.0%–70.0% of hydroxyethoxy group
	Carbomer	934, 934P, 941, 940 type by cross-linking / copolymer composition

Examples of Identifying Inactive Ingredients in eCTD 3.2.P.1

Identification of Ingredient	Ingredient Name	Differentiation
Composition	Stearic Acid	Stearic Acid (50, 70, 95) by % stearic acid & % palmitic acid
Purity/Content	Acetic Acid Glacial Acetic Acid	Differentiated by content
	Alcohol, Dehydrated Alcohol	

Specifics in Statement of Ingredients in Labeling

- List of Ingredients in 1.14 is consistent with Statement of Composition in 3.2.P.1
- Qualitative info for all active and inactive ingredients
- Quantitative info of API (for all drug products)
- Quantitative info of inactive ingredients (for parenteral injection)

Example of Statement of Ingredients in Labeling in eCTD 1.14

In DESCRIPTION of Labeling:

Each milliliter (mL) contains drugozide 25 mg (equivalent to sodium drugozide 27.3 mg), and the following inactive ingredients:

- Citric acid monohydrate 1 mg, edetate disodium dihydrate 0.554 mg, povidone K-17 1 mg, sodium chloride 2.5 mg, sodium citrate anhydrous 0.877 mg, sodium metabisulfate 5 mg, and

- water for injection, hydrochloric acid and sodium hydroxide added to adjust pH.

Commonly Observed Issues In Composition Statement and Labeling

Common Observation	Examples of Clarification
Compendial Reference not identified	USP/NF, or In-House
Hydration form not identified	Edetate Disodium Dihydrate, Sodium Carbonate Monohydrate
pH adjusting agents not listed or clarified	Hydrochloric acid / sodium hydroxide are used as pH adjusting agents
Inconsistent units of concentration for inactive ingredients in 3.2.P.1	Polysorbate 80 unit in "%v/v" is corrected to "%w/v" , using the same unit as other ingredients.

Commonly Observed Issues In Composition Statement and Labeling (cont'd)

Common Observation	Examples of Clarification
Composition of inactive ingredients deviated from USP monograph	Polysorbate 80 USP is corrected to Pre-acidified Polysorbate 80 In-House.
Grades of USP/NF inactive ingredients not clarified	Povidone K17, Hypromellose 1828 are specified.

Consistency in CMC Submissions

- Qualitative and quantitative info in **batch formula** (3.2.P.3.2), **Master Batch** and **Executed batch records** (3.2.R., 3.2.P.3.3) should be consistent with Composition Statement (3.2.P.1)
- For multiple manufacturing facilities, include all possible ingredients and levels in composition statement; consistent in labeling

Examples of Inconsistency in NDA/ANDA submissions

Examples of Inconsistency	Acceptable Submission
Acid/base as pH adjusters are omitted in either 3.2.P.1 composition table and 3.2.P.3.2 batch formula	Both 3.2.P.1 composition table and 3.2.P.3.2 batch formula include acid/base as pH adjustors consistently.
Composition Table lists an ingredient in fixed amount, but batch formula lists "q.s." for the same ingredient	3.2.P.1 Composition table and 3.2.P.3.2 batch formula are consistent in presenting each active and inactive ingredients and their amount.

Challenge Question #1

The following should be included in the Composition Statement of Drug Product?

A. Name of all active ingredients and inactive ingredients
B. Reference Quality Standard of all ingredients
C. Primary Function of inactive ingredients
D. Quantitative Information
E. All

Challenge Question #2

Which of the following is NOT needed in statement of ingredients in Labeling?

(choose more than 1 if Not true)

A. Names of all active ingredients and inactive ingredients

B. pH adjustors

C. Grade or type of inactive ingredients

D. Polymorphic form of API

E. Processing aid used in drug product manufacturing

Resources

- Guidance for Industry - Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs (Draft, April 2024)

- USP <1059> Excipient Performance

Summary

- Composition Statement (eCTD 3.2.P.1) should include **clearly identified ingredients and their quantitative amounts.**
- Statement of Ingredients in labeling (eCTD 1.14) should list **complete ingredients that are consistent with composition statement**
- Batch formula and manufacturing batch records (eCTD 3.2.P.3 and 3.2.R) should be **consistent with Composition Statement**

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