Best Practices for Submitting Formulation Assessment Requests and Avoiding Information Requests: Tips for Submitting a Proposed Formulation Table

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Learning Objectives

- Submit high-quality formulation assessment requests
- Avoid information requests
- Recognize dos and don’ts in submitting a formulation table for assessment

Information Request

- Controlled Correspondence
  - A pathway for requesting information on a specific element of generic drug product development

- Information Request
  - Sent by the Agency when more information is needed to conduct a formulation assessment

Tips for Submitting a Proposed Generic Formulation Table: Function

- Include the function of the ingredient(s)
  - **Parenteral** drug products must contain the same inactive ingredients and in the same concentration as the reference listed drug (RLD) pursuant to 21 CFR 314.94(a)(9)(iii)
    - Exception excipients: Preservatives, Buffers, Antioxidants
  - **Ophthalmic or Otic** drug products must contain the same inactive ingredients and in the same concentration as the RLD pursuant to 21 CFR 314.94(a)(9)(iv).
    - Exception excipients: Preservatives, Buffers, Tonicity agent, Thickening agent
  - **For ophthalmic drug products**, deviation in Q1/Q2 with respect to exception excipients should be accompanied with an appropriate in vivo bioequivalence (BE) study(ies)

Tips for Submitting a Proposed Generic Formulation Table: Units

- Provide the proposed formulation table in all relevant units including mg/mL, %w/w, %v/v, and %w/v, as applicable

Tips for Submitting a Proposed Generic Formulation Table: Excipients Not Present in the Final Products

- Clearly notate when excipients will not remain in the final product

Example:

Component	Function	Quantity (mg/mL)
Water for injection*	Vehicle	q.s.

*Removed during lyophilization

Tips for Submitting a Proposed Generic Formulation Table: Description

- Ensure the proposed formulation table is clear and excipients include adequate details (hydration state, grade, purity, and viscosity, as applicable)

- Common formulation table issues
  - Omission of description
  - Ambiguous description
  - Discrepancy between the formulation table and the footnote

Tips for Submitting a Proposed Generic Formulation Table: Omission

Omission (hydration state)

Component	Function	Quantity (mg/mL)
Edetate Disodium	Chelating agent	1.25

Clear (with hydrate state):

Component	Function	Quantity (mg/mL)
Edetate Disodium Dihydrate, USP-NF*	Chelating agent	1.25

*Edetate disodium dihydrate 1.25mg listed in the composition table is equivalent to 1.13 mg of edetate disodium anhydrous.

Tips for Submitting a Proposed Generic Formulation Table: Discrepancy

Discrepancy:

Component	Hydration State	Conc (%w/v)
Sodium Acetate*	**Trihydrate**	0.22

*0.22% w/v sodium acetate anhydrous is equivalent to 0.365% w/v of sodium acetate trihydrate.

Clear alignment:

Component	Hydration State	Conc (%w/v)
Sodium Acetate*	**Trihydrate**	0.22

*0.22% w/v sodium acetate trihydrate is equivalent to 0.13% w/v of sodium acetate anhydrous.

Tips for Submitting a Proposed Generic Formulation Table: Ambiguity

Ambiguous:

Ingredient	Grade	Function	% w/v	mg/mL	mg/vial
Hydrochloric Acid #	NF	pH adjuster	0.61	6.1	91.5

Hydrochloric Acid NF will be added as 1N Hydrochloric Acid.

Clear:

Ingredient	Grade	Function	% w/v	mg/mL	mg/vial
Hydrochloric Acid #	NF	pH adjuster	0.61	6.1	91.5

The concentration of Hydrochloric acid as listed on the composition table represents 1N Hydrochloric Acid Solution

Ingredient	Grade	Function	% w/v	mg/mL	mg/vial
1N Hydrochloric Acid	NF	pH adjuster	0.61	6.1	91.5

Examples (continued)

Ambiguous:

Component	Function	Quantity (mg/mL)
Benzalkonium Chloride, NF*	Preservative	0.15

*Benzalkonium chloride is added as benzalkonium chloride, 50% solution.

Clear:

Component	Function	Quantity (mg/mL)
Benzalkonium Chloride, NF* 50% Solution	Preservative	0.3

*Benzalkonium chloride 0.3 mg/mL (50% aqueous solution) equivalent to 0.15 mg/mL of Benzalkonium chloride.

Component	Function	Quantity (mg/mL)
Benzalkonium Chloride, NF*	Preservative	0.1

*Benzalkonium chloride will be added as 50% solution, final product will contain 0.1 mg/mL of Benzalkonium chloride.

Examples (continued)

Ambiguous:

Component	Function	Quantity
Hydrochloric acid*	pH adjuster	NA

*Used for adjusting pH

Component	Function	Quantity
Hydrochloric acid*	pH adjuster	-

*Used for adjusting pH

Clear:

Component	Function	Quantity
Hydrochloric acid*	pH adjuster	Q.S.

*Used for adjusting pH

Examples (continued)

Ambiguous:

Component	Function	Quantity (mg/mL)
Edetate disodium (Dehydrate)	Chelating agent	1.25

Clear:

Component	Function	Quantity (mg/mL)
Edetate Disodium Dihydrate, USP-NF*	Chelating agent	1.25

*Edetate disodium dihydrate 1.25mg is equivalent to 1.13 mg of Edetate disodium anhydrous.

Total fill volume

- Indicate total fill volume (total drug content) for **parenteral** drug products
  - parenteral drug products must contain the same concentration and total drug content (fill volume) per container as the RLD
    - Submit separate formulation assessment requests for drug products with multiple strengths such as parenteral drug products with different fill volumes as each fill-volume is a separate drug product

Formulation Table for Co-Packaged drug products

- Include the composition of diluent for co-packaged products for Q1/Q2 assessments
- Examples of co-packaged products
  - A kit that consists of lyophilized power and diluent
  - A kit that consists of three separate components in the following container closure systems: reaction vial (lyophilized), Syringe I (solution), and Syringe II (solution)

Summary

- Tips for submitting a proposed formulation table
- Include the following:
  - Ingredient function
  - Units of measure
  - Description of ingredients (hydration state, grade, purity, viscosity)
  - Total fill volume
  - All components in each package for the co-packaged drug product

References

Guidance for Industry ANDA Submissions – Refuse-to-Receive Standards (Revision 2, Dec. 2016)

Guidance for Industry Controlled Correspondence Related to Generic Drug Development (December 2020)

Code of Federal Regulations


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