General Considerations for the Quantitative Sameness Evaluation of a Proposed Generic Formulation

Session 2: Qualitative and Quantitative Considerations for Formulation Assessments

Anubhav Kaviratna, Ph.D.
Staff Fellow
Division of Therapeutic Performance 1, Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA
December 6, 2022

Disclaimer:

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Any fictional formulation tables shown in this presentation are for fictitious drug products, designed for EDUCATIONAL PURPOSES ONLY. These fictitious formulation tables are not representative of a complete and accurate FDA approved drug products.

Learning Objectives

- Importance of the quantitative (Q2) assessment
- What is Q2 sameness
- Information needed for a Q2 assessment and other considerations
- How is a Q2 assessment conducted
- Q2 calculation and determination
- Hypothetical RLD and Test formulation
- Considerations for MDE assessment

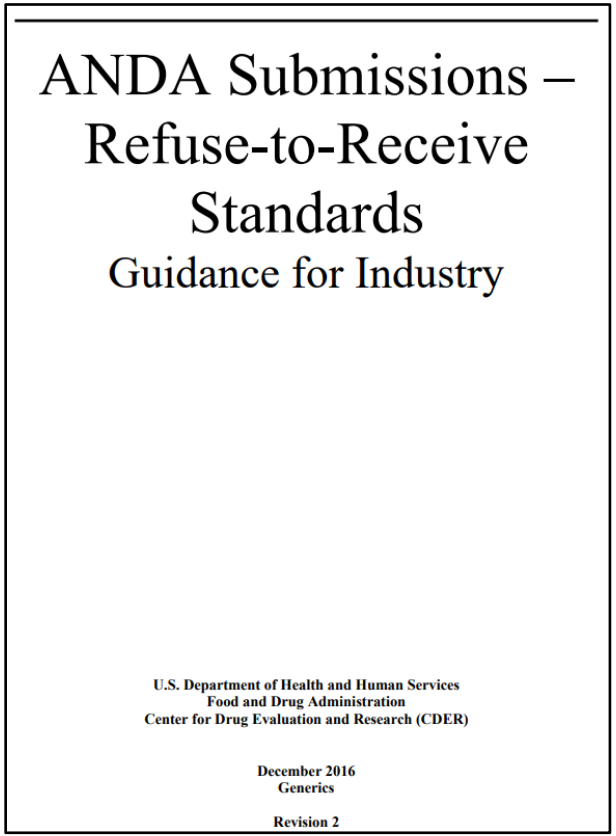
Importance of the Q2 Assessment

- Inactive ingredients, while not intended to exert a therapeutic effect themselves, can play a vital role in facilitating the delivery of the active ingredient to its site of action
  - Wide diversity of function, including but not limited to:
    - Delivery aids (e.g., bulk fillers, vehicle/carrier components, lubricants, glidants)
    - Physicochemical modifiers (e.g., viscosity modifiers, tonicity agents, humectants)
    - Product stability (e.g., buffers/pH adjusters, preservatives, surfactants)
    - Functional (e.g., penetration/absorption enhancers, propellants, modified/controlled release components)
- A drug product's formulation is the foundation of a generic drug development approach and critical to supporting approval
  - Given the wide range of functions that inactive ingredients can perform, sameness in the formulation can help to better ensure the proposed generic will deliver the active ingredient to the site of action in an equivalent manner, thereby reducing potential bioequivalence failure modes

Importance of the Q2 Assessment

- Formulation sameness for many products begins with first ensuring that the inactive ingredients between the test and reference formulation are qualitatively (Q1) the same
- If the test formulation is found to be Q1 the same, the second part of the formulation assessment focuses on ensuring the amounts (quantitative) of the inactive ingredients are the same between the test and reference formulations
- This quantitative (Q2) sameness can contribute to two factors that relate to the role, the amount of each inactive ingredient plays in the formulation
  - Ensuring Q2 sameness provides additional confidence that the function of the inactive ingredient is being performed in an equivalent manner between the test and reference formulation (improving the likelihood for a BE product performance)
    - Examples: similar absorption from equivalent amounts of a penetration enhancer; equivalent conversion of the active ingredient between formulations from equivalent amounts of a pH adjuster that also functions as an in-situ converter
  - An additional benefit for ensuring Q2 sameness is the reduction in likelihood for side effects, either from changes in exposure to the active ingredient, or from unwanted reactions due to higher exposure to the inactive ingredient
    - Examples: higher levels of a penetration enhancer could lead to higher drug absorption between formulations; higher amounts of a surfactant could produce tissue irritation

What Does Q2 Sameness Mean?



- FDA[1] has generally interpreted "quantitative sameness" to mean a concentration that is within 95 – 105% of the reference listed drug (RLD) concentration
- This suggests that the inactive ingredient in a test formulation does not have to meet an exact value when compared to its RLD formulation to be considered Q2 the same, but rather its concentration must fall within the range of values found within ± 5% of the RLD concentration

What Does FDA Need to Know for a Q2 Assessment?

Hypothetical Example

Ingredient	Function	Weight per Canister (g)	Concentration (%w/w)
API	Active	0.00800	0.071
Citric Acid, USP (anhydrous)	Stabilizing Agent	0.00045	0.004
Purified Water, USP	Cosolvent	0.05610	0.500
Dehydrated Alcohol, USP	Cosolvent	1.68300	14.995
1,1,1,2-tetrafluoroethane (HFA-134a)	Propellant	9.47600	84.430
Total		11.22355	100.00

https://www.pikpng.com/downpngs/hiRwxbo_asthma-attackers-swim-class-asthma-inhalers-clipart

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY. This fictitious product is not representative of a complete and accurate FDA approved drug product.

What Does FDA Need to Know for a Q2 Assessment?

Ingredient	Function	Weight per Canister (g)	Concentration (%w/w)
API	Active	0.00800	0.071
Citric Acid, USP (anhydrous)	Stabilizing Agent	0.00045	0.004
Purified Water, USP	Cosolvent	0.05610	0.500
Dehydrated Alcohol, USP	Cosolvent	1.68300	14.995
1,1,1,2-tetrafluoroethane (HFA-134a)	Propellant	9.47600	84.430
Total		11.22355	100.000

- Inactive Ingredient Concentration
  - Should list the amount of all ingredients, except those used on an, as needed (i.e., quantity sufficient (q.s.)) basis
  - For units, should be reported in % w/w, % w/v, and/or mg/mL, as applicable. However, other unit may be used depending on the dosage form
  - Minimum of two decimal places. With that said, FDA recommends that a consistent number of decimal places be used for all ingredients if an ingredient is reported out to more than two decimal places
  - Provide the nominal amounts (Q2 assessment is NOT performed with overages considered)
  - If a range is more appropriate than a nominal amount or concentration, clearly indicate the reason for providing a range in the composition statement

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

What Does FDA Need to Know for a Q2 Assessment?

Ingredient	Function	Weight per Canister (g)	Concentration (%w/w)
API	Active	0.00800	0.071
Citric Acid, USP (anhydrous)	Stabilizing Agent	0.00045	0.004
Purified Water, USP	Cosolvent	0.05610	0.500
Dehydrated Alcohol, USP	Cosolvent	1.68300	14.995
1,1,1,2-tetrafluoroethane (HFA-134a)	Propellant	9.47600	84.430
Total		11.22355	100.00

- Hydration State
  - Should indicate whether the amount added was from a particular hydrate state, or on an anhydrous basis
  - Depending on the RLD formulation, conversion may be required to compare amounts between formulations, so providing the conversion calculation in a table footnote may help avoid an information request

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

What Does FDA Need to Know for a Q2 Assessment?

Hypothetical Example

Ingredient	Function	Concentration (%w/v)	Concentration (mg/mL)
API	Active	0.30	3.00
Citric Acid, USP (monohydrate)	Buffer	0.20	2.00
Sodium Citrate Dihydrate, USP	Buffer	0.05	0.50
Benzalkonium Chloride, NF (50% Solution)*	Preservative	0.10	1.00
Sodium Hydroxide, USP	pH Adjuster	QS to pH 6.0	QS to pH 6.0
Purified Water, USP	Vehicle	QS to 100%	QS to 1 mL
Total		100%	1 mL**

* Provided as % w/v
** Density of the final product is 0.99 g/mL

https://www.pocketnurse.com/default/06-69-9264-10-ml-nasal-spray-bottle

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY. This fictitious product is not representative of a complete and accurate FDA approved drug product.

What Does FDA Need to Know for a Q2 Assessment?

Ingredient	Function	Concentration (%w/v)	Concentration (mg/mL)
API	Active	0.30	3.00
Citric Acid, USP (anhydrous)	Buffer	0.20	2.00
Sodium Citrate Dihydrate, USP	Buffer	0.05	0.50
Benzalkonium Chloride, NF (50% Solution)*	Preservative	0.10	1.00
Sodium Hydroxide, USP	pH Adjuster	QS to pH 6.0	QS to pH 6.0
Purified Water, USP	Vehicle	QS to 100%	QS to 1 mL
Total		100%	1 mL**

* Provided as % w/v
** Density of the final product is 0.99 g/mL

- Other Relevant Information
  - Recommend applicants include any calculations/equivalent amount for ingredients that may be added on a volume basis (e.g., mL/mL or % v/v)
  - Recommend to add a note if the inactive ingredient amount represents a dilution (e.g., whether the amount added is from a 25%, 50%, 1N, or 2N solution). Alternatively, both amounts could be provided for the inactive ingredient, or the conversion calculation provided as a table footnote
  - Recommend to note the units for inactive ingredients provided as a dilution (e.g., % w/v, % w/w, and/or % v/v)
  - Provide formulation density to aid conversion calculations if needed

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

Conducting the Q2 Assessment

- Prior to conducting the Q2 assessment, each inactive ingredient amount is evaluated to ensure that sufficient information is provided to determine whether a ±5% difference is present. If more information is needed, information request (IR) can be sent to the applicant for clarification
  - Examples of where clarification is needed to perform a Q2 assessment have included, among others, uncertainty with an inactive ingredient's concentration (e.g., 100%, 50%), and hydration state (e.g., dehydrated/anhydrous, monohydrate, dihydrate), or any conflicting information in the formulation table
- Following any conversion calculations to ensure that all test formulation amounts are in equivalent forms with the RLD formulation's inactive ingredients, the Q2 evaluation is performed by calculating the difference (%) in an inactive ingredient
- The Q2 assessment is performed on the inactive ingredients only
- The Q2 assessment is NOT performed on the API amounts

Q2 Calculation and Determination: Example

Ingredient	RLD Concentration (%w/v)	RLD Concentration (mg/mL)	Test Concentration (%w/v)	Test Concentration (mg/mL)	Difference (%)
API	0.30	3.00	0.300	3.00	ND*
Citric Acid, USP (monohydrate)	0.20	2.00	0.187	1.87	-7
Sodium Citrate Dihydrate, USP	0.05	0.50	0.051	0.51	2
Benzalkonium Chloride, NF (50% Solution)	0.10	1.00	0.100	1.00	0
Sodium Hydroxide, USP	QS to pH 6.0	QS to pH 6.0	QS to pH 6.0	QS to pH 6.0	N/A
Purified Water, USP	QS to 100%	QS to 1 mL	QS to 100%	QS to 1 mL	N/A

[(T – R) / R] x 100 = % difference

Q2 assessment does not include API

[(0.187 – 0.200) / 0.200] x 100 = -7%

[(0.051 – 0.05) / 0.05] x 100 = 2%

[(0.1 – 0.1) / 0.1] x 100 = 0%

N/A = Not applicable

N/A = Not applicable

***ND – Not determined**

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

What About pH Adjusters?

Ingredient	Function	Concentration (%w/v)	Concentration (mg/mL)
API	Active	0.30	3.00
Citric Acid, USP (anhydrous)	Buffer	0.20	2.00
Sodium Citrate Dihydrate, USP	Buffer	0.05	0.50
Benzalkonium Chloride, NF (50% Solution)*	Preservative	0.10	1.00
Sodium Hydroxide, USP	pH Adjuster	QS to pH 6.0	QS to pH 6.0
Purified Water, USP	Vehicle	QS to 100%	QS to 1 mL
Total		100%	1 mL**

* Provided as %w/v
** Density of the final product is 0.99 g/mL

- pH Adjusters
  - Not considered exception excipients for parenteral, ophthalmic or otic products 21 CFR 314.94(a)(9) (iii-iv)
  - Can be provided as either Q.S. to a pH value/range, or a specific amount
  - A specified minimum amount, potential range, and supporting justification may be requested for a pH adjuster with an additional function in the formulation that requires a specific amount (e.g., solubilizer, in-situ converter)
  - Prospective applicants can consider referring to the pH adjuster guidance[2] if they feel the Agency's response to the formulation assessment for a parenteral, otic, or ophthalmic product continues to be negative, and they believe this to be related to pH adjuster(s)

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

Possible Scenarios with pH Adjusters

Ingredient	Function	RLD Concentration (%w/v)	Test Concentration (%w/v)	Q2 outcome
Sodium Hydroxide, USP	pH Adjuster	QS	Fixed	Q2
Sodium Hydroxide, USP	pH Adjuster	QS to pH 6.0	QS to pH 6.0	Q2
Sodium Hydroxide, USP	pH Adjuster	Fixed	Fixed	Q2*
Sodium Hydroxide, USP	pH Adjuster	Fixed	QS	NOT Q2

- pH Adjusters (possible scenarios)
  - Q2 assessment for pH adjusters in the Test formulation would depend on if the RLD concentration is Q.S. (as needed) or Fixed (specified/known)
  - * indicates Q2 assessment and determination will be made according to the fixed concentrations of pH adjusters in RLD and T formulation

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

What About Buffers?

Ingredient	Function	Concentration (%w/v)	Concentration (mg/mL)
API	Active	0.30	3.00
Citric Acid, USP (anhydrous)	Buffer	0.20	2.00
Sodium Citrate Dihydrate, USP	Buffer	0.05	0.50
Benzalkonium Chloride, NF (50% Solution)*	Preservative	0.10	1.00
Sodium Hydroxide, USP	pH Adjuster	QS to pH 6.0	QS to pH 6.0
Purified Water, USP	Vehicle	QS to 100%	QS to 1 mL
Total		100%	1 mL**

* Provided as % w/v
**Density of the final product is 0.99 g/mL

- Buffers with Q2 Differences
  - For buffers where the equilibrium ratio (concentration) of buffer components may not be within ±5% of the original amount of each component added, additional information on total buffer concentration (buffer capacity) being ±5% of the RLD with a similar pH may be supportive for justification

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

Q2 Calculation and Determination: Buffer Example

Ingredient	RLD Concentration (%w/v)	RLD Concentration (mg/mL)	Test Concentration (%w/v)	Test Concentration (mg/mL)	Difference (%)
API	0.30	3.00	0.300	3.00	ND
Citric Acid, USP (monohydrate)	0.20	2.00	0.187	1.87	-7
Sodium Citrate Dihydrate, USP	0.05	0.50	0.051	0.51	2
Benzalkonium Chloride, NF (50% Solution)	0.10	1.00	0.100	1.00	0
Sodium Hydroxide, USP	QS to pH 6.0	QS to pH 6.0	QS to pH 6.0	QS to pH 6.0	N/A
Purified Water, USP	QS to 100%	QS to 1 mL	QS to 100%	QS to 1 mL	N/A

- While the amount of citric acid monohydrate in the test formulation is outside ±5%, the **total citrate** (comprised of both the molar amounts of citric acid monohydrate and sodium citrate dihydrate at equilibrium) can be used in the Q2 evaluation

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

Q2 Calculation and Determination: Buffer Example

- Quantitative comparison of moles of citrate between the RLD and Test
  - Total mol citrate in RLD = (citric acid monohydrate *in grams*)/(molecular weight of citric acid monohydrate) + (sodium citrate dihydrate *in grams*)/(molecular weight of sodium citrate monohydrate)
  - Total mol citrate in Test = (citric acid monohydrate *in grams*)/(molecular weight of citric acid monohydrate) + (sodium citrate dihydrate *in grams*)/(molecular weight of sodium citrate monohydrate)

Total citrate	RLD	Test	Difference (%)
	mol	mol	
Citrate ($C_6H_5O_7^{3-}$)	1.12176×10^{-5}	1.06329×10^{-5}	-5

$$\frac{(1.06329 \times 10^{-5} - 1.12176 \times 10^{-5})}{(1.12176 \times 10^{-5})} \times 100$$

-5.212

Rounded to the nearest whole number

-5 **% Difference**

Q2 Calculation and Determination: Buffer Example

Ingredient	RLD Concentration (%w/v)	RLD Concentration (mg/mL)	Test Concentration (%w/v)	Test Concentration (mg/mL)	Difference (%)
API	0.30	3.00	0.300	3.00	ND
Citric Acid, USP (monohydrate)	0.20	2.00	0.187	1.87	-5
Sodium Citrate Dihydrate, USP	0.05	0.50	0.051	0.51	
Benzalkonium Chloride, NF (50% Solution)	0.10	1.00	0.100	1.00	0
Sodium Hydroxide, USP	QS to pH 6.0	QS to pH 6.0	QS to pH 6.0	QS to pH 6.0	N/A
Purified Water, USP	QS to 100%	QS to 1 mL	QS to 100%	QS to 1 mL	N/A

- This could be a way to provide additional information to justify a % difference in the case of buffers

This is a fictional formulation table for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY.
This fictitious product is not representative of a complete and accurate FDA approved drug product.

Considerations for Maximum Daily Exposure

- Ensuring Q2 sameness helps to reduce the likelihood for side effects from differences in drug exposure or from reactions to the inactive ingredients
- An additional consideration is that even if a test formulation is within the Q2 sameness limits, an inactive ingredient that falls within 0 – 5% of its RLD amount could raise safety concerns, if this amount of inactive ingredient represents a higher level than what has been approved for similar products (i.e., similar administration route and dosing regimen)
- In this situation, an evaluation of the maximum daily exposure (MDE) for this inactive ingredient may be needed. Note that MDE evaluation is NOT part of a Q2 sameness evaluation
- The Inactive Ingredient Database[3] (IID) provides information on inactive ingredients present in FDA-approved drug products

Key Takeaways

- Inactive ingredients can play many important roles in facilitating the delivery of the active ingredient to its site of action
- For many types of products, establishing BE between a test and reference product includes establishing that the test formulation is quantitatively (Q2) the same as its RLD
- The Q2 assessment is performed, only if Q1 assessment is successful
- To conduct the Q2 sameness assessment, the submitted formulation table should include sufficient information to avoid receiving an IR for clarification, including the table format, units, and the hydration state, where applicable
- The Q2 assessment for buffers may include evaluation of the total molar content of each component when at equilibrium
- While not included in the Q2 assessment, when the inactive ingredient amounts fall within 0 – 5% of the RLD amount, an assessment of the inactive ingredient MDE may be needed to determine if additional supportive information should be included in an ANDA submission for justification

References

1. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/anda-submissions-refuse-receive-standards-rev2
2. Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use | FDA
3. Inactive Ingredient Search for Approved Drug Products (fda.gov)

Acknowledgements

- Office of Research and Standards
  - Division of Therapeutic Performance I and II
- Office of Bioequivalence
- Office of Safety and Clinical Evaluation
- Office of Generic Drug Policy
- Office of Regulatory Operations
  - Division of Filing Review

U.S. FOOD & DRUG ADMINISTRATION

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION