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"Navigating the Q1/Q2 Letter Quagmire – Industry & FDA Experiences, and How Both Could Improve the Q1/Q2 Controlled Correspondence Process"

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Q1/Q2 – What does it mean?

- **Q1**: Qualitatively the same. Use matching names of compendial standards if such grade materials are used [Same compendial designation (USP/NF), Chemical Abstracts Service (CAS) number and/or Unique Ingredient Number (UNII)]. The later two can be found in the FDA's Inactive Ingredient Database https://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm
- **Q2**: Quantitative sameness generally is interpreted by OGD to mean a concentration that is within 95-105% of the RLD concentration.

  [+/-5% = (Test-Reference)/Reference x 100]

Q1/Q2 – What does it mean? Why is it important?

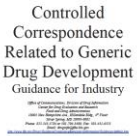
- For certain types of products, FDA's regulations generally require that proposed products be qualitatively (Q1) and quantitatively (Q2) the same as the RLD with respect to inactive ingredients for drug products intended for:

  Parenteral Products (exception ingredients include preservatives, buffers, and antioxidants), Ophthalmic and Otic Products

- There are specific inactive ingredient requirements but changes are permitted.
- Generally, if Q1/Q2, then no in vivo BE. If not Q1/Q2 ,in vivo BE may be required!
- For other products, there is no regulatory (i.e., regulation) requirement to be Q1 and Q2. However, the Agency does require that Q1/Q2 be established if an applicant is considering an in vitro option (e.g., some locally acting drugs, nasal sprays) in lieu of showing in vivo BE.

How do we know if our formulation is Q1/Q2?

- Reverse engineer/de-formulate the Reference Listed Drug (RLD).
- Request a Q1/Q2 Formulation Assessment following the November 2017 Draft Guidance for Industry: “Controlled Correspondence Related to Generic Drug Development”.
  - The FDA provides some certainty with GDUFA II Goal Dates for controlled correspondence. Generally:
    - The agency will review and respond to Standard and Complex Controlled Correspondence within 60 days or 120 days, respectively, of the date of submission.
    - FDA will review and respond to requests to clarify ambiguities in the controlled correspondence response within 14 calendar days of the Agency’s receipt of the request.


Controlled Correspondence Related to Generic Drug Development
Guidance for Industry

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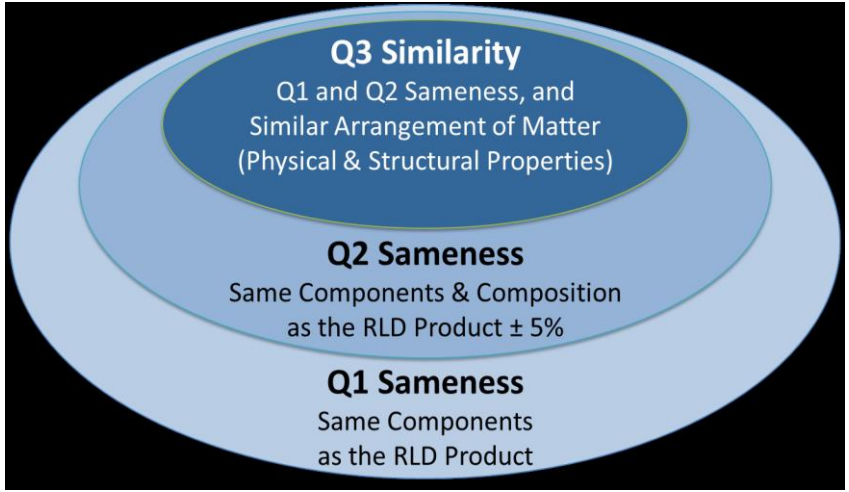
Key Facts

Deformulation (Q1/Q2) analysis of a product, also known as “chemical reverse engineering” is the process of analytically breaking down a material or product’s formulation to separate and determine the specific identity and exact quantity of both its major and minor constituent components. Excipients with high water content exhibits challenge to precise quantification.



Scope

Qualitative (Q1) / Quantitative (Q2): Regulatory Requirement

Deformulation: To establish Q1/Q2 (if required) and supports product development to achieve target product profile that is comparable to the innovator product, as applicable. Generates key information which can help **save significant time and money** when developing a generic version of an innovator’s product.

Roadmap to Understanding Q1 and Q2

RLD Labeling & Literature search for product overview

De-formulation with in house techniques (Wave 1)

Make RLD-like formulations for Analytical testing- (Wave 1)

Multiple RLD Lots procurement (Timely and early access to sufficient samples of the RLD is critical at this phase*)

Method / technique development & verification for complex excipient and/or low level excipients.

De-formulation with External techniques/CROs (Wave 2)

Make RLD like formulation for further testing (Wave 2)

Make RLD like formulation for further testing (Wave 2)

Testing and confirmation

Submit CC(s) seeking approval

Acceptable / Not Acceptable

* Oct 2014, How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD

Q1/Q2 CC can work well for Products required to be Q1/Q2: Example 1

Parenteral Product intended for Administration by Injection

- **Inquiry submitted:** Pursuant to 21 CFR 314.94 (a)(9)(iii), does the FDA agree that the proposed composition of the generic drug is qualitatively (Q1) and quantitatively (Q2) the same as the RLD with respect to submission of the generic as an ANDA to the RLD?

- Table listing Ingredient, Function, Amount (mg/ml),for three proposed formulations

- **Agency Response**: After reviewing your controlled correspondence, the Office of Generic Drugs (OGD) has made a preliminary determination that OGD would not likely refuse to receive an abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act and its implementing regulations based on all three proposed formulations pursuant to the requirements pertaining to inactive ingredients described in 21 CFR 314.101(d)(3) and 21 CFR 314.94(a)(9).

- Reference is made to the definition of quantitative sameness to the reference listed drug (RLD) as stated in the guidance for industry ANDA Submissions - Refuse-to-Receive Standards (December 2016, Revision 2).

Product Required to be Q1/Q2: Ex 1

- Parenteral Solution

Composition	Function	Formula 1	Formula 2	Formula 3
		mg/mL	mg/mL	mg/mL
Excipient1	Solubilizer	1.00	1.05	1.10
Excipient 2	pH adjustment	q.s. pH 6.0 – 7.5	q.s. pH 6.0 – 7.5	q.s. pH 6.0 – 7.5
Excipient 3	pH adjustment	q.s. pH 6.0 – 7.5	q.s. pH 6.0 – 7.5	q.s. pH 6.0 – 7.5
Excipient 4	Solvent	q.s. to 2 mL	q.s. to 2 mL	q.s. to 2 mL

Issues that can arise *(Quagmire)*

- Formulation Assessment CC scope is narrow and can result in pain points and delays.
  - Consistent with the Agency's past and current practices, FDA does not intend to review proposed formulations that are neither required by regulation nor recommended in guidance to be Q1/Q2 to the RLD.
    - However, prospective applicants may suggest in vitro options for locally acting solid oral dosage forms, for example, that are neither required by regulation nor recommended in guidance to be Q1/Q2 to the RLD.
  - FDA does not intend to provide clarification on why a formulation is not Q1/Q2.
  - In addition, OGD will no longer provide directional guidance on which individual components of a proposed formulation are either too high or too low", and therefore not Q2.
  - A prospective applicant's de-formulation data for multiple lots of the RLD suggesting an excipient manufacturing loss **or for example, moisture loss**, may not agree with the RLD formulation on file with the agency.
  - Issues involving the role of pH modifiers, in-situ salt forming agent, buffers, and errors or non-compliance of RLD labeling with CFR requirements.
- *Some examples illustrating industry pain points follow:*

Products not required to be Q1/Q2 (administrative delay with no bearing on the request): Example 2

Tablets

Inquiry 1 submitted: With respect to the in vitro option offered in the agency's draft PSG, which of the 3 proposed formulations is/are suitable for submission in an ANDA

Table listing ingredient, function, grade/USP/NF, amount per tablet.

Agency response: The agency declined to assign the CC for substantive review because the author included a copy of a previous CC that was not accepted for substantial review and response. OGD recommends that firms only submit any previous, related CCs that was accepted for substantial review and response.

Inquiry 2: Resubmitted with the same 3 formulations as in Inquiry 1.

Agency response: After reviewing your controlled correspondence the preliminary view of the Office of Generic Drugs (OGD) is that, with respect to Formulation x, OGD would likely recommend the following approach to establishing bioequivalence: **Option 1. (In vitro option)** described in the individual product specific draft guidance.

Reference is made to the definition of quantitative sameness to the reference listed drug (RLD) as stated in the guidance for industry ANDA Submissions - Refuse-to-Receive Standards (December 2016, Revision 2).

pH Modifiers

Functional category of inactive ingredient involved in the Q1/Q2 assessment	Brief description of Q1/Q2 issue
pH Modifier- Example a	• Composition that was confirmed Q1/Q2 with pH modifier mentioned as “q.s” was denied upon ANDA submission. ANDA received RTR. • RLD insert does not mention pH adjusters in any form, not even use of word “pH adjuster”. • FDA admitted error in review of CC during a dispute resolution meeting. • Agency directed applicant to resubmit the CC.
pH Modifier- Example b	• CC submitted for Q1/Q2 with mention of pH adjusters declined repeatedly for 4 plus years. All other ingredients fully disclosed in package insert and complied with in CC. • RLD insert does not mention pH adjusters in any form, not even use of word “pH adjuster”. • After 4 years, Agency came back clarifying that the originally submitted composition with use of pH adjusters as q.s. is acceptable.
pH Modifier- Example c	• Composition submitted in CC and confirmed as Q1/Q2 with pH modifier mentioned as “q.s” • After 6 years of ANDA review, Agency has sought exact quantitative compositional disclosures for pH adjusters, defying the original confirmation of q.s for pH adjusters.

Q1/Q2 CC – FDA does not provide clarification on why a formulation is not Q1/Q2. Example: 3

Parenteral Product intended for Administration by Injection

- **Inquiry 1 submitted:** Pursuant to 21 CFR 314.94 (a)(9)(iii), does the FDA agree that the proposed composition of the generic drug is qualitatively (Q1) and quantitatively (Q2) the same as the RLD with respect to submission of the generic as an ANDA to the RLD?
- Table listing ingredients, quantitative amounts and function.

Composition	Formula 1	Formula 2	Formula 3
	mg/mL (Function)	mg/mL (Function)	mg/mL (Function)
API	3 (Active Ingredient)	3 (Active Ingredient)	3 (Active Ingredient)
Excipient 1	1.2 (Solubilizer)	1.2 (pH adjust)	q.s. 1.1 (pH adjust)
Excipient 2	q.s. pH 6.8 (pH adjust)	q.s. pH 6.8 (pH adjust)	q.s. pH 6.8 (pH adjust)
Excipient 3	q.s. (Solubilizer)	q.s. (Solvent)	q.s. (Solvent)

- **Agency Response:** With respect to all of your proposed generic formulations, OGD would not likely grant a waiver of in vivo bioequivalence because bioequivalence would not be self-evident as per 21 CFR 320.22(b)(1). Specifically, all of your proposed formulations are not qualitatively (Q1) the same as the RLD with respect to one or more inactive ingredients, while Formulation 3 is not quantitatively (Q2) the same as the RLD with respect to one or more inactive ingredients.

Q1/Q2 CC – FDA does not provide clarification on why a formulation is not Q1/Q2. (Ex. 3 continued)

Parenteral Product intended for Administration by Injection

- **Inquiry 2 submitted:** Pursuant to 21 CFR 314.94 (a)(9)(iii), does the FDA agree that the proposed composition of the generic drug is qualitatively (Q1) and quantitatively (Q2) the same as the RLD with respect to submission of the generic as an ANDA to the RLD?
- Table listing ingredients, quantitative amounts and function.

Composition	Formula 1	Formula 2	Formula 3
	mg/mL (Function)	mg/mL (Function)	mg/mL (Function)
API	3 (Active Ingredient)	3 (Active Ingredient)	3 (Active Ingredient)
Excipient 1	1.2 (Solubilizer)	1.2 (Solubilizer)	q.s. 1.2 (pH adjust)
Excipient 2	q.s. pH 6.8 (pH adjust)	q.s. pH 6.8 (pH adjust)	q.s. pH 6.8 (pH adjust)
Excipient 3	q.s. (Solvent)	q.s. (Solvent)	q.s. (Solvent)
Nitrogen	--	q.s. (Vial Headspace)	q.s. (Vial Headspace)

Agency Response: With respect to all of your proposed generic formulations, OGD would not likely grant a waiver of in vivo bioequivalence because bioequivalence would not be self-evident as per 21 CFR 320.22(b)(1). Your proposed formulations are not qualitatively (Q1) the same as the RLD with respect to one or more pH adjusters.

Q1/Q2 CC – FDA does not provide clarification on why a formulation is not Q1/Q2. (Ex. 3 continued)

Parenteral Product intended for Administration by Injection

Inquiry 3 submitted: Pursuant to 21 CFR 314.94 (a)(9)(iii), does the FDA agree that the proposed composition of the generic drug is qualitatively (Q1) and quantitatively (Q2) the same as the RLD with respect to submission of the generic as an ANDA to the RLD?

- Table listing ingredients, quantitative amounts and function.

Composition	Formula 1	Formula 2	Formula 3
	mg/mL (Function)	mg/mL (Function)	mg/mL (Function)
API	3 (Active Ingredient)	3 (Active Ingredient)	3 (Active Ingredient)
Excipient 1	1.2 (Solubilizer)	1.2 (Solubilizer)	q.s. 1.2 (Solubilizer)
	q.s. pH 6.8 (pH adjust)	q.s. pH 6.5 – 7.0 (pH adjust)	--
Excipient 2	q.s. pH 6.8 (pH adjust)	q.s. pH 6.5 – 7.0 (pH adjust)	q.s. pH 6.8 (pH adjust)
Excipient 3	q.s. (Solvent)	q.s. (Solvent)	q.s. (Solvent)

Dual functionality!

Agency Response: After reviewing your controlled correspondence OGD has made a preliminary determination that OGD would not likely refuse to receive and abbreviated new drug application (ANDA) submitted pursuant to section 505(J) OF THE FD&C Act and its implementing regulations based on Formulation 1 and Formulation 2.

Locally Acting Solid Oral Dosage Form (Capsules)-Apparent excipient manufacturing losses in RLD: Example 4

- Full ANDA submitted : Day 1
- CRL Major : 15 months later (at goal date)
- Deficiency on waiver request of in vitro bioequivalence study
- Agency Response: Active is locally acting drug. Active capsules are not eligible for a BCS class III waiver request. Based on available information FDA recommends one of the following approaches to establish BE:
  - 1. Test product is qualitatively (Q1) but not quantitatively (Q2) the same as the RLD. You may reformulate test product to be Q1 and Q2 and conduct comparative multimedia dissolution studies.
  - 2. If you want to continue with current formulation you are advised to conduct an in vivo BE study with clinical end point in patients.

Challenge: The conventional evaluation of Q2 sameness, in terms of the mass of each ingredient (on the as-is basis) per capsule that is weighed/input into the manufacturing process ("mg/capsule" approach) has several technical difficulties.

We identified few factors that can impact and/or alter Q2 compositional sameness determination.

- *Impact of process loss on Q2 (Actual quantity added Vs. Quantity tested/recovered)*
- *Water content of components (Theoretical Vs. actual left after processed into drug product)*
- *Mass of each ingredient, possibly not considered during the FDA review*

Locally Acting Solid Oral Dosage Form (Capsules)-Apparent excipient manufacturing losses in RLD: (Ex. 4 cont.)

Response Major : 12 months from CRL 1

- Extensive work conducted on deformulation, patent analysis, analyzing several batches of RLD with validated analytical methods, considering slight differences in excipients moisture content, as well as slight differences in the yields of the excipients due to process losses in the finished dosage form
- *Emphasizing the relevance for Q2 based on amounts on each ingredient found in the finished beads only* (capsule fill) and not just the starting amounts of each of the excipients listed in the master formulae.
- Based on this approach differences between test and reference product ±1% for each excipient
- Also provided supportive permeability studies from small scale batches and did statistical evaluations showing no impact on local availability of active
- No change on original submitted formulation / composition master formulae

FDA feedback: 7 months from our Response

- No further questions related to Q1/ Q2 ***(Success!)***

Locally Acting Solid Oral Dosage Form (Capsules)-Apparent excipient manufacturing losses in RLD: (Ex. 4 cont.)

Comparative Compositional Analyses of 12 lots of RLD and 10 lots Test Product (amount of each component, on the volatile free (v.f.) basis as a percentage of the capsule fill as-is)

		Function	RLD Mean (n=12)	Test Product Mean (n=10)	Test Product vs RLD % diff
Components	API, v.f. basis	Active	0.250	0.255	2.00%
	Excipient A, USP (as exact dihydrate, v.f. basis)	Stabilizer	2.200	2.560	1.63%
	Excipient B, USP (v.f. basis)	Stabilizer	0.700	0.690	-1.43%
	Excipient C, USP (v.f. basis)	Film forming agent	0.600	0.605	-0.83%
	Microcrystalline Cellulose, NF (v.f. basis)	Bead core	93.850	93.340	-0.54%
	Water (without Dihydrate from Excipient A*$2H_2O$)		2.400	2.550	6.25%

Locally Acting Solid Oral Dosage Form (Capsules)-Apparent excipient manufacturing losses in RLD: (Ex. 4 cont.)

Applying conventional mg/capsule approach and examples with MCC containing all free / unbound water found in RLD to show that differences in moisture content result in "artificial" Q2 failure

- **MCC is most abundant component in formulation**
- **USP/NF allows water content of up to 7.0%**
- **Comparing as is data found in RLD deformulation is 2.7% water and all assigned to MCC**
- **Now let us consider, 4% or 6% water content in MCC**
- **Manufacturing includes drying step which can result in process losses**

	Amount of water in MCC (%)	Resulting Difference between Test product and RLD
Based on water found in deformulation: RLD	2.7	2.4
Theoretical amount in MCC: A	4.00	3.8
Theoretical amount in MCC: B	6.00	**5.8**

Therefore assessing Q2 sameness based on the volatiles-free basis was evaluated and may provide to be useful in Q2 assessments rather than using the conventional "mg/capsule" approach.

Locally Acting Solid Oral Dosage Form (Capsules)-Apparent excipient manufacturing losses in RLD: (Ex. 4. cont.)

Initial composition Submitted in CC1 versus the results of analytical testing on volatile free basis

		Function	Composition submitted in CC1	Test Product determined in Analytical Testing - Mean (n=10)
Components	API, v.f. basis	Active	0.26	0.255
	Excipient A, USP (as exact dihydrate, v.f. basis)	Stabilizer	1.48	1.520
	Excipient B, USP (v.f. basis)	Stabilizer	0.69	0.690
	Excipient C, USP (v.f. basis)	Film forming agent	0.64	0.605
	Microcrystalline Cellulose, NF (v.f. basis)	Bead core	93.05	94.280
	Water (without Dihydrate from Excipient A*2H2O)		-	2.451

Locally Acting Solid Oral Dosage Form-Tablets (low amount of Excipient due to Analytical Technique(s) Sensitivity): Example 5

- Product developed, BE study with clinical endpoint started
- After starting BE, FDA issued new Specific Product Guidance with possibility to be:
  - Option 1: Q1/Q2, in vivo BE with PK endpoint, comparative dissolution in several FDA recommended media
  - Option 2: if not Q1/Q2 BE study with clinical endpoint, in vivo BE study with PK endpoints, comparative dissolution in defined FDA recommended media
- Goal was to fullfil Option 1

Inquiry 1 submitted

- Table listing ingredients, function, grade/USP/NF, amount per tablet (including single excipients from film coat)
- **Agency response**: OGD would likely recommend the following approach to establishing bioequivalence: Option 2 described in drug product-specific bioequivalence guidance.

Locally Acting Solid Oral Dosage Form-Tablets (low amount of Excipient due to Analytical Technique(s) Sensitivity): (Ex. 5 cont.)

- RLD extensively de-formulated (4 RLD batches fully quantitatively analyzed, 15 RLD batches physically deformulated)
- De-formulation challenges
  - low content of excipients (e.g 0.3 %) for which the ±5% relative range corresponds to very small absolute range (< ± 0.015%)
  - variability of analytical method(s) ± 10 % ICP-OES, LC-RID, ICP MS)
  - one low content excipient is present in both core and coat

Inquiry 2

- **Agency response:** OGD would likely recommend the following approach to establishing bioequivalence: Option 2 described in drug product-specific bioequivalence guidance.

Inquiry 3 (related to the coating excipients Q1/Q2)

- **Agency response**: preliminary view of OGD is that the individual components of the coating material do not have to be Q1/Q2 to the RLD; however the level at which all the inactive ingredients (including coating materials) are used in your proposed generic drug product must be justified using the criteria cited in the Guidance for Industry; ANDA Submissions – Refuse-to-Receive Standards (December 2016, Version 2). Reference is made to the draft product specific bioequivalence guidance document.

Locally Acting Solid Oral Dosage Form-Tablets (low amount of Excipient due to Analytical Technique(s) Sensitivity): (Ex. 5 cont.)

Inquiry 4

Table listing ingredient, function, grade/USP/NF, amount per tablet

Agency response: OGD would likely recommend the following approach to establishing bioequivalence: Option 2 described in drug product-specific bioequivalence guidance.

Next Steps→

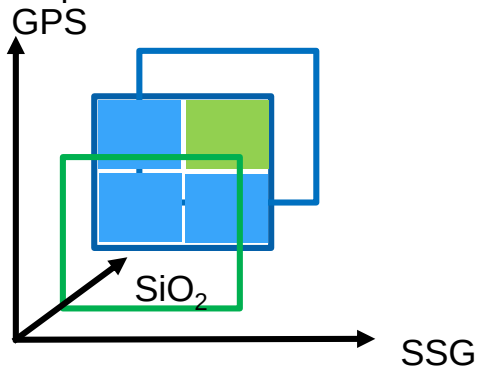
Excipients with high probability to be correct were fixed

For determination of selected critical excipients (critical = most probable to be out of the +/- 5% range due to variability in analytical method) design area approach was used to cover the concentrations which were not covered with the previous CCs and considered the IIG limits for the relevant excipients

- **Statistical approach used**

– multidimensional design space was used to include other variables and to cover the full range of deformulation results / define number of different possibilites

– Out of total predicted number of different possibiity, IIG level allowed us to exclude formulations which would be outside of allowed IIG limits



Locally Acting Solid Oral Dosage Form-Tablets (low amount of Excipient due to Analytical Technique(s) Sensitivity): (Ex. 5 cont.)

Inquiry 5

- Having two strengths of the product, with linear formulation 6 possibilities were submitted in one inquiry
- Table listing ingredient, function, grade/USP/NF, amount per tablet
- **Agency response:**

After reviewing your controlled correspondence, the preliminary view of the Office of Generic Drugs (OGD) is that, with respect to your proposed formulation entitled “Proposal 2,” OGD would likely recommend the following approach to establishing bioequivalence: Option 1 described in the product specific guidance.

- 13 months was time required from issuing PSG until positive FDA answer

In-Situ Salt Forming agent and Buffers

Functional category of inactive ingredient involved in the Q1/Q2 assessment	Brief description of Q1/Q2 issue
In-situ salt forming agent- Example a	• RLD insert under the composition section does not mention quantity of the ingredient that in-situ forms a salt with active ingredient. • Elsewhere in the insert, the mention of converted salt form of active ingredient is disclosed. • Does CFR allow such liberty for the non-disclosure for Innovator?
Buffers- Example b	• Buffers are not disclosed quantitatively in the composition section of RLD PI. • Buffers are qualitatively described in the RLD PI. • Does CFR allow such liberty for the non-disclosure for Innovator?

Errors or Non-Compliance of RLD Labeling with CFR Requirements

Functional category of inactive ingredient involved in the Q1/Q2 assessment	Brief description of Q1/Q2 issue
Error in RLD PI- Example a	• Description section of RLD PI and the data elements section mention completely different pH adjuster (HCl vs Acetic acid) • Applicant who does not check both sections would end up having issues with Q1/Q2.
Non compliance of RLD PI with CFR- Example b	• RLD PI before Sep 2014 had only qualitative disclosure of inactives, when the regulations mandate quantitative disclosure of inactives. • Post Sep 2014, the RLD PI was revised for quantitative composition disclosure.

Deformulation

Potential Deformulation Challenges that can impact Q1/Q2

Due to complex, multi-component formulation, establishing a reliable analytical method for estimation of some of the formulation components and grades can be challenging:

- Low drug or excipient content or non-uniform distribution (e.g. if the API is less than 5% of the total tablet weight)
- Very small particle size of the drug – *method is not sensitive enough to identify API dynamics and quantity (if added in functional coating etc.)*
- Complexities in the excipients crystallinity (e.g. if the formulation consists of a number of crystalline/non-crystalline excipients) – *interference of a dominating excipient like lactose or quantification/identification challenges for two crystalline excipients*
- Solid state transformation of the API (e.g. if the API is present in its metastable form, it may undergo process/solvent/temperature- mediated transformations)
- Close similarity between the physicochemical profile of the API and excipient(s), in terms of bi-refringence pattern/melting point/solubility – *Needs multiple validated tools (methods & instruments) to effectively minimize interference and facilitate identification/quantification*
- Combination drug products

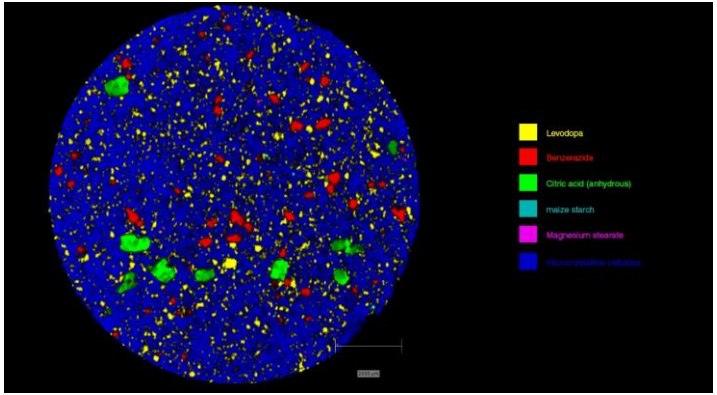
Mitigation to challenges

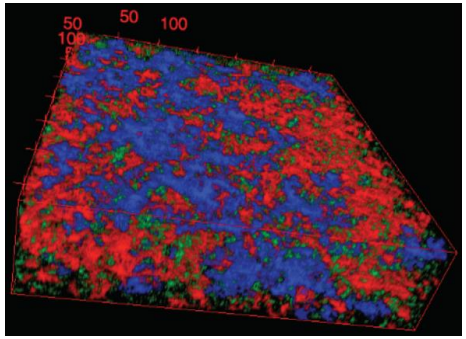
- Need a diverse spectrum of separation techniques for accurate (need to demonstrate adequate recovery) and precise analysis, often requiring complex instrumentation
- CMC analytical support including multi-disciplinary, multi-technique analytical method development and validation using techniques such as: organic techniques, elemental, thermal, imaging, XRD, surface analysis and physical
- Impact assessment as a function of de-formulation studies by evaluating de-formulation result against % label claim in IID *(note may not be the most updated)* and literature.

Additional Examples of Deformulation Study

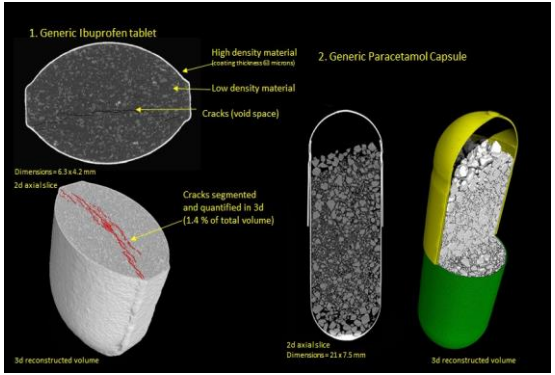
.....one Analytical technique may not be adequate to determine Q1/Q2

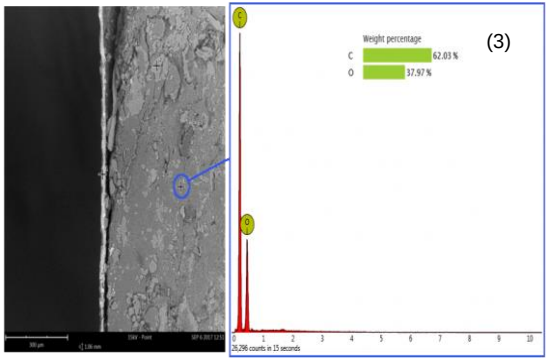
Advances in 3D Raman Imaging – Tablet Microstructure[1]





Segregating and identifying excipient system[2]





[1]American Pharmaceutical Review 19(6) · January 2016 [2] unavailable [3] www.nanoscience.com/applications/medical/pharmaceutical-deformulation/

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Questions

1. Q1/Q2 sameness issues continues to be one of the top 5 reasons for Refusal to Receive on new ANDAs, has increased the number of controlled correspondences that are reviewed by FDA and has slowed the development process for ANDA sponsors resulting in delayed access to low cost medication for patients.
   a) Why did the agency stop providing directional guidance on which of the individual components of a proposed formulation are either too high or too low?
   b) Why does the agency intend on not providing clarification on why a formulation is not Q1/Q2?

2. Would a new ANDA be RTR'd if it was Q1/Q2 identical to the RLD but did not describe the function of a "non-exception" inactive ingredient identical to that as described in the referenced NDA, even if the function described in the ANDA could be scientifically justified?

Questions

3. How important is to identify/specify grades of excipient for the Q1/Q2 controlled correspondence? Especially where there are DIFFERENCES IN CHARACTERISTICS AND/OR PERFORMANCE BETWEEN GRADES

a) The excipient is a diluent or non-functional excipient
Microcystalline Cellulose, NF or need to define Microcystalline Cellulose grades
[For e.g. water content of Avicel Grades; PH112/113 ≤ 1.5; PH103 ≤ 3.0; PH102/101/300 ≤ 5.0; OR Asahi Corp. Ceolus KG-802 ≤ 6.0]

b) Highly soluble in the dosage form system (oral liquid or sterile solution or Lyophilized product for solution)

c) Does not pose any significant impact on viscosity (that is measurable) in the formulation
*Hypromellose, USP: In certain formulations especially oral solids, the viscosity grade **may not** have a measurable impact on drug release or flowability (in case of oral suspension containing more than one polymer).The formulation system can be confounded with process variables/ other components of the formulation.*
[For e.g. – Methocel grades (E3 vs. E5) / Pharmacoat 603 vs. 606; Methocel grades (E4M Premium vs. K4M Premium /Metolose 65SH/90SH) – Some of them may be assigned under same USP designation (2208, 2906, 2910)]

Questions

4. Is it mandatory to present excipient quantity (Q2) as intended to be used for ANDA/Exhibit batches in Q1/Q2 controlled correspondence? OR a total quantity/dosage unit is acceptable?

a) Talc in blending and functional coating of an extended release oral solid dosage form

b) Talc in blending and non-functional coating of a oral solid dosage form.

c) Intra-granular & extra-granular use of disintegrant (or any other excipient) in a tablet dosage form. Report total?

d) Use of a buffering agent in parenteral formulation during manufacturing and also during pH adjustment.

5. What advice does the agency have for ANDA applicants when it appears that there are RLD excipient manufacturing losses ?

a. Is there value in presenting such data to the agency as part of a CC?

b. Under what circumstances would the agency consider an applicant's RLD de-formulation data showing apparent RLD excipient manufacturing losses and/or differences in excipient moisture content?

Thank you

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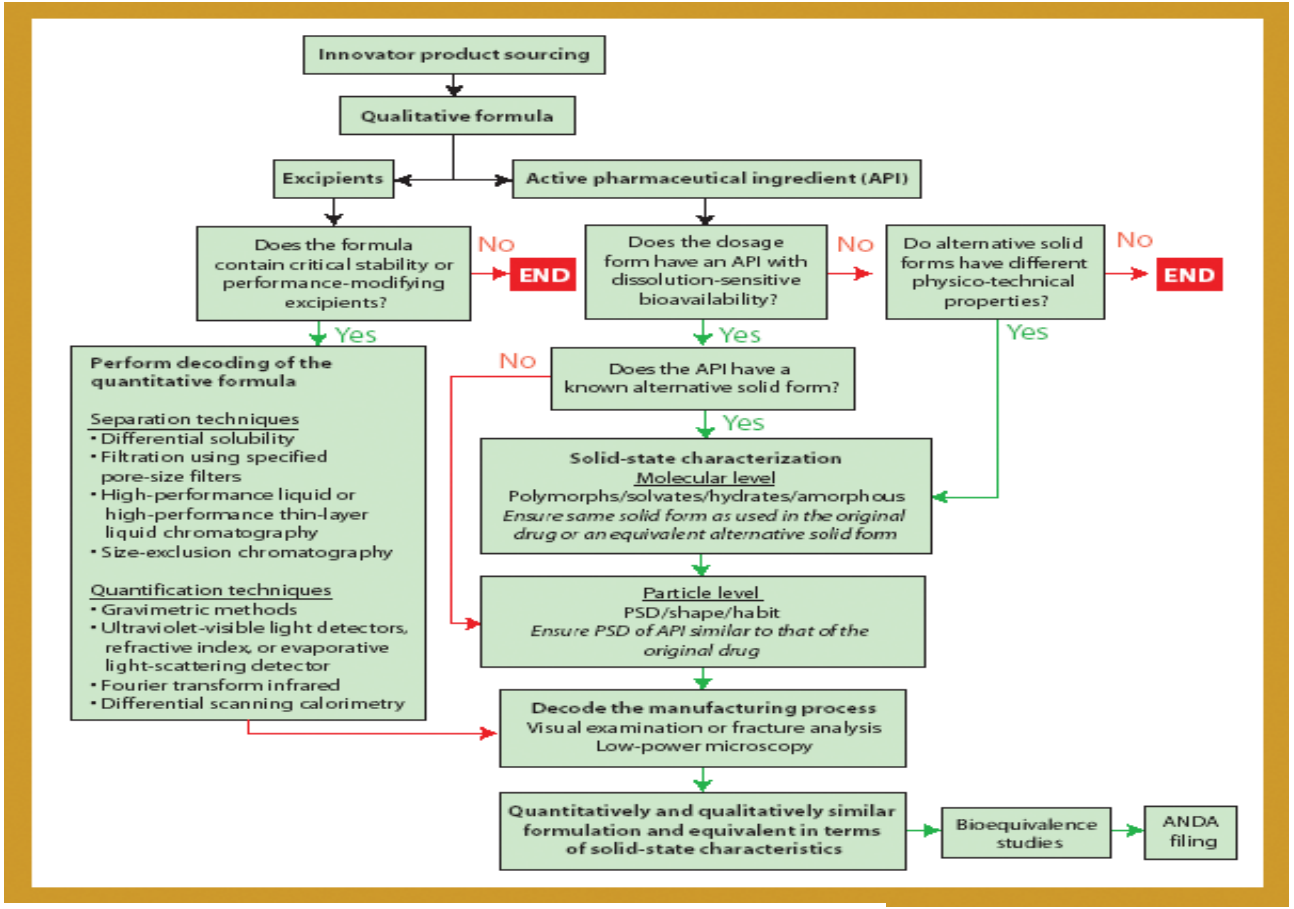
Backup

Decoding and Analytical Techniques



Ref source: The Role of Reverse Engineering in the Development of Generic Formulations
Aug. 2005, By Pharmaceutical Technology Editors ,Pharmaceutical Technology, Volume 29, Issue 8

Common techniques and Instruments Used in Pharmaceutical Deformulation

- ***Solid-state characterization*** (including particle size of API / excipients using digital microscope etc.)
- ***Liquid-state characterization*** (Like pH, viscosity, density, specific gravity, osmolality, zeta potential..)
- ***Polymorphic Form determination***
  - XRD / XRPD, ie determining polymorph of API in semisolid
- ***SEM*** to evaluate process (Like spray drying, milling, extrusion/milling...)
- ***Imaging*** to evaluate distribution of excipients, active and thickness of coatings, layers in tablets (interfaces), etc (Eg. How API distributed in microbeads in extended release capsule)
  - NIR Chemical Imaging, Raman Microscopy, Terahertz spectrometry, LIBS, SEM-EDS, TOF-SIMS
- ***Hygroscopicity*** Investigation
- ***Molecular Weight determination*** (especially to identify the grade of polymer used or degradation of MW on stability or during formulation processing)
  - Size Exclusion Chromatography (SEC) and/or AF4
  - Dilute Solution Viscosity Testing (IV)
  - Melt Flow Index Testing (MFI)

Common techniques and Instruments Used in Pharmaceutical Deformulation (cont.)

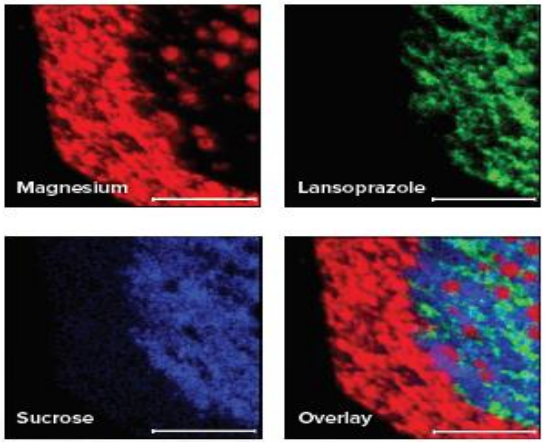
- ***Molecular Structure determination if a polymer is a homo-polymer or a copolymer***
  - Fourier Transform Infrared Spectroscopy (FTIR)
  - Nuclear Magnetic Resonance Spectroscopy (NMR)
  - Branching of Polymer: AF4
- ***Morphology***
  - Scanning Electron Microscopy (SEM)
  - Transmission Electron Microscopy (TEM)
  - Atomic Force Microscopy (AFM)
- ***Thermal Properties***
  - Differential Scanning Calorimetry (DSC)
  - Rheology Testing
  - Thermogravimetric Analysis (TGA)
  - Dynamic Mechanical Testing (DMA)
- ***Metal Analysis:*** ICP-OES, ICP-MS, LIBS, etc
- **Anion or Cation determination**: Ion-exchange, etc
- ***Others –*** Tensile strength, compression testing, durometer testing, flexural testing, MS and special detectors (MALS, RI, CAD, Light Scattering, etc), HPLC-IR...

Example of Deformulation Study

Solid oral dosage analysis

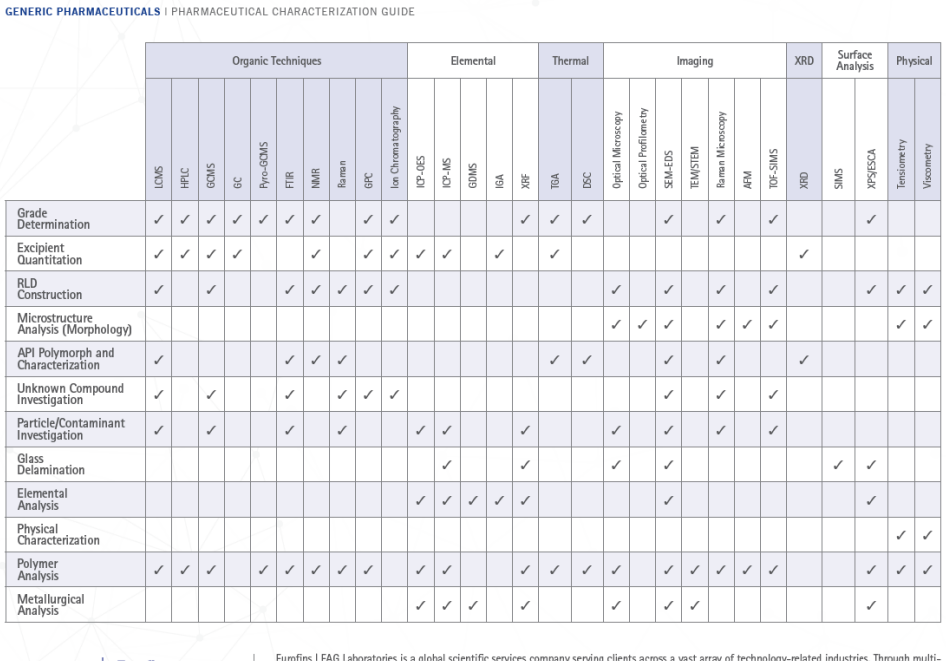
From tablets to extended release capsules, we investigate many different dosage systems to see how they are put together. We perform excipient characterizations and quantitations using a similar approach as other delivery systems. We also perform many cross-sectional studies to ascertain the location of the excipients within the capsule/tablet/bead to gain insight as to how the delivery system was constructed. We answer questions such as:

- **Is there a sugar sphere core?**
- **Are there multiple applications of API or excipient form layers?**
- **Is there a disintegrant dispersed throughout the drug product with the API?**



TOF-SIMS cross-sectional images of an antacid drug product show the presence of Mg, both in the talc exterior and $MgCO_3$ particles in the core; the API lansoprazole, and sucrose present with the lansoprazole. TOF-SIMS is extremely useful for APIs with an elemental makeup similar to the excipients present. While SEM-EDS data provides an elemental map, TOF-SIMS presents a molecular map from observing ions evolved from a surface.

Ref source: EAG: Eurofins Material Science, downloaded from Web Sept. 2, 2019, https://r.search.yahoo.com/_ylt=A0geKaPdVW1dzQ4Adi5XNyoA;_ylu=X3oDMTEybmQ0M3FsBGNvbG8DYmYxBHBvcwMyBHZ0aWQDQjg3MDVfMQRzZWMDc3I-/RV=2/RE=1567475293/RO=10/RU=https%3a%2f%2fwww.eag.com%2feu%2fresources-type%2fgeneric-pharmaceuticals-rld-reverse-engineering%2fm-032618-generic-pharma%2f/RK=2/RS=yV.xviv0b.h5n7PMdTrqDzgYMPw-



GENERIC PHARMACEUTICALS | PHARMACEUTICAL CHARACTERIZATION GUIDE

	Organic Techniques										Elemental					Thermal		Imaging							XRD	Surface Analysis		Physical	
	LCMS	HPLC	GCMS	GC	Pyro-GCMS	FTIR	NMR	Raman	GPC	Ion Chromatography	ICP-OES	ICP-MS	GDMS	IGA	XRF	TGA	DSC	Optical Microscopy	Optical Profilometry	SEM-EDS	TEM/STEM	Raman Microscopy	AFM	TOF-SIMS	XRD	SIMS	XPS/ESCA	Tensiometry	Viscometry
Grade Determination	✓	✓	✓	✓	✓	✓	✓		✓	✓					✓	✓	✓			✓		✓		✓			✓		
Excipient Quantitation	✓	✓	✓	✓			✓		✓	✓	✓	✓		✓		✓									✓				
RLD Construction	✓		✓			✓	✓	✓	✓	✓								✓		✓		✓		✓			✓	✓	✓
Microstructure Analysis (Morphology)																		✓	✓	✓		✓	✓	✓				✓	✓
API Polymorph and Characterization	✓					✓	✓	✓								✓	✓			✓		✓			✓				
Unknown Compound Investigation	✓		✓			✓		✓	✓	✓										✓		✓		✓					
Particle/Contaminant Investigation	✓		✓			✓		✓			✓	✓			✓			✓		✓		✓		✓					
Glass Delamination												✓			✓			✓		✓						✓	✓		
Elemental Analysis											✓	✓	✓	✓	✓					✓							✓		
Physical Characterization																												✓	✓
Polymer Analysis	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓			✓	✓	✓	✓		✓	✓	✓	✓	✓			✓	✓	✓
Metallurgical Analysis											✓	✓	✓		✓			✓		✓	✓						✓		

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Ref source: EAG: Eurofins Material Science, downloaded from Web Sept. 2, 2019, https://r.search.yahoo.com/_ylt=A0geKaPdVW1dzQ4Adi5XNyoA;_ylu=X3oDMTEybmQ0M3FsBGNvbG8DYmYxBHBvcwMyBHZ0aWQDQjg3MDVfMQRzZWMDc3I-/RV=2/RE=1567475293/RO=10/RU=https%3a%2f%2fwww.eag.com%2feu%2fresources-type%2fgeneric-pharmaceuticals-rld-reverse-engineering%2fm-032618-generic-pharma%2f/RK=2/RS=yV.xviv0b.h5n7PMdTrqDzgYMPw-

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Abbreviation used

Abbreviation	Explanation	Abbreviation	Explanation
RLD	Reference Listed Drug	BA	Bioavailability
QbD	Quality by Design	PK	Pharmacokinetic
Q1	Qualitatively same	IVRT	In Vitro Release Testing
Q2	Quantitatively same	MDI	Metered-Dose Inhaler
Q3	Physico-chemical sameness / Microstructure sameness	DPI	Dry Powder Inhaler
API	Active Pharmaceutical Ingredient	PSD	Particle Size Distribution
FDA	Food & Drug Administration	CMC	Chemistry, Manufacturing, Control
PSG	Product Specific Guidance	GDUFA	Generic Drug User Fee Amendments
OGD	Office of Generic Drugs	PFS	Pre-Filled Syringe
ANDA	Abbreviated New Drug Application	Q.S.	Quantity sufficient
CC	Controlled Correspondence	NIR	Near-Infrared Spectroscopy
QTPP	Quality Target Product Profile	LIBS	Laser Induced Breakdown Spectroscopy
CQA	Critical Quality Attribute	SEM-EDS	Scanning electron microscopy - Energy Dispersive X-Ray Spectroscopy
IID	Inactive Ingredient Database	XRD/XRPD	X-Ray (Powder) Diffraction
TE	Therapeutic Equivalence	XRF	X-Ray Fluorescence
PE	Pharmaceutical Equivalence		
BE	Bioequivalence		