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Demonstrating Bioequivalence for Soluble Powder Oral Dosage Form Products and Type A Medicated Articles Containing Active Pharmaceutical Ingredients Considered to Be Soluble in Aqueous Media

Guidance for Industry

This guidance document makes revisions to the draft guidance withdrawn in March 2017. Among the revisions, we revised the method for defining drug solubility, provided information on how to conduct the solubility assessment, provided instructions on how to calculate the maximum dose for testing drug solubility, and provided recommendations for handling situations where there are multiple species on the label.

Submit comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2019-D-3764.

For further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at either https://www.fda.gov/animal-veterinary or https://www.regulations.gov.

U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Demonstrating Bioequivalence for Soluble Powder Oral Dosage Form Products and Type A Medicated Articles Containing Active Pharmaceutical Ingredients Considered to Be Soluble in Aqueous Media

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This document describes how the Center for Veterinary Medicine (CVM) intends to evaluate requests for waiving the requirement for performing *in vivo* bioequivalence studies (biowaivers) for animal drugs administered orally as soluble powders or as Type A medicated articles manufactured from active pharmaceutical ingredients (APIs) considered to be soluble in aqueous media (water-soluble APIs). This document expands upon CVM's Guidance for Industry (GFI) #35, "Bioequivalence Guidance,"[1] to include biowaivers for soluble powder oral dosage form products as well as Type A medicated articles manufactured from APIs considered to be soluble in aqueous media, and it offers particular focus on criteria for the waiver of the requirements for submitting *in vivo* bioequivalence study data. This guidance does not address Type A medicated articles manufactured from APIs considered to be insoluble in aqueous media.

This guidance is applicable to generic investigational new animal drug (JINAD) files and to abbreviated new animal drug applications (ANADAs). Although the recommendations in this guidance refer to ANADAs, the general principles described may also be applicable to new animal drug applications (NADAs), supplemental NADAs, and investigational new animal drug (INAD) files.

The recommendations in this guidance are premised on the assumption that a sponsor will be bridging between identical dosage forms (e.g., their Type A medicated article for use in complete feed to the approved reference Type A medicated article for use in complete feed). Therefore, you should not use the recommendations in this guidance to compare the solubility of two drug products where the API will be administered in differing manners (e.g., drinking water versus complete feed; complete feed for administration throughout the day versus top dress). CVM encourages sponsors to contact the Center to discuss that type of comparison.

The granting of a waiver from the requirement to perform an *in vivo* bioequivalence study does not imply that a drug product is approvable. For drug product approval, all applicable legal

[1] https://www.fda.gov/media/70115/download

requirements must be met (see, e.g., sections 512(c)(2) and 512(n) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA's guidance documents should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

An ANADA must include information to show that the proposed generic new animal drug and reference listed new animal drug (RLNAD) are bioequivalent.[2] This requirement is patterned very closely on the approval requirements for human generic drugs.[3]

The Center for Drug Evaluation and Research's (CDER) regulations implementing the bioequivalence requirement for human generic drugs can be found in 21 CFR part 320. In most cases, there must be an *in vivo* demonstration of no significant differences in the rate and extent of drug availability associated with the proposed generic and reference drug products when administered at the same molar dose under similar conditions.[4] In certain circumstances, however, the demonstration of bioequivalence does not need to be established on the basis of *in vivo* studies.[5] For several categories of human drug products, including oral solutions, bioequivalence is considered self-evident under specified conditions.[6] In other circumstances, a large body of research on human intestinal physiology has been used to support a determination of product bioequivalence of solid oral dosage forms based on the use of *in vitro* approaches. In this regard, the human Biopharmaceutics Classification System (BCS) criteria have been applied to support the use of an *in vitro* approach to document product bioequivalence for highly soluble, rapidly dissolving, and orally administered drug products.[7] However, because of the physiological differences between the gastrointestinal (GI) tract of humans and that of veterinary species, and because of the additional complexities associated with drugs that are administered as medicated feeds, the human BCS criteria cannot be applied to support the use of an *in vitro* approach for demonstrating product bioequivalence for orally administered veterinary drug products.

CVM has issued guidance on *in vivo* bioequivalence studies, which includes a list of some of the product categories, including oral solutions and other solubilized forms, that may be eligible for a waiver from the requirement to perform *in vivo* bioequivalence studies.[2] This guidance

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[2] Section 512(n)(1)(E) of the FD&C Act.

[3] Section 505(j)(2)(A)(iv) of the FD&C Act.

[4] 21 CFR 320.1(e) and 320.21(b).

[5] 21 CFR 320.21(b) and (f), and 320.22.

[6] 21 CFR 320.22(b)(3).

[7] See CDER Guidance for Industry, "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System," December 2017, Pages 2 and 11-12. (https://www.fda.gov/media/70963/download)

provides additional information and recommendations regarding bioequivalence waivers for soluble powder oral dosage form products intended for use in animal drinking water, and Type A medicated articles manufactured from APIs considered to be soluble in aqueous media and intended for use in animal feed.

III. Human Food Safety Considerations

The granting of a waiver from the requirement to perform an *in vivo* bioequivalence study (biowaiver) does not imply that a drug product is approvable. For drug product approval, all applicable legal requirements must be met, which includes addressing the tissue residue portion of the Human Food Safety (HFS) technical section of the application (sections 512(c)(2)(A)(viii), 512(c)(2)(B), and 512(n)(1)(A) of the FD&C Act). For products that receive a biowaiver using the concepts of this guidance, the sponsor should contact the Division of Human Food Safety (HFV-150) directly to discuss what, if any, additional information may be needed to satisfy the requirements for approval.

IV. Biowaivers for Soluble Powder Oral Dosage Form Products

A. Qualifying for a waiver from the requirements for performing an *in vivo* bioequivalence study (biowaiver)

CVM believes it is appropriate to grant biowaivers for oral dosage forms known as "soluble powders" that meet the solubility requirements discussed in this guidance. Such products are intended for administration to animals via the drinking water that is provided on an ad libitum basis under most husbandry systems.

The conceptual basis for granting biowaivers for "soluble powders" is that if an API is in solution before administration, the drug product's formulation will usually not influence the bioavailability of the active ingredient. If the test and reference formulations contain essentially the same inactive ingredients, then from a mechanistic perspective, the rate-limiting step in systemic API absorption will be either: (a) the rate of gastric transit; or (b) the permeability of the API across the gastrointestinal (GI) mucosal membranes. Typically, both these variables are formulation independent, relying solely on the API and the characteristics of the GI tract of that animal species. Similarly, because the rate-limiting step is the API movement down the GI tract and its lateral diffusion across the viscous intestinal contents, if an API acts locally within the GI tract (i.e., not systemically absorbed), the local exposure to the dissolved API in the proposed and reference drug product formulations will be equivalent if the API is already in solution. The only exceptions of which CVM is aware are when the formulation of the drug product contains substances other than the API that could cause a direct pharmacologic effect (e.g., altered GI transit time, membrane permeability, or drug metabolism) or when there is inactivation of the API.

B. Data to support a waiver from the requirement to perform an *in vivo* bioequivalence study (biowaiver) request

For soluble powder oral dosage form products, CVM recommends that justification of requests for biowaivers be made by a demonstration of solubility. CVM recommends that sponsors make

these biowaiver requests before submitting an ANADA. The following should be provided in the biowaiver request:

1. **Information about the API(s):**

   CVM recommends that the API(s) used to support a biowaiver request for soluble powder oral dosage forms be provided from the same supplier of the API(s) that will be used to formulate the proposed drug product during production. CVM recommends that the applicant identify the source of the API(s) and provide a certificate of analysis (COA) for the API(s). If the API has a United States Pharmacopeia (USP) monograph, the API should at a minimum comply with the monograph specifications. The acceptability of the API(s) will be determined upon review of the Chemistry, Manufacturing, and Controls (CMC) Technical Section.

2. **Information about the formulation:**

   The formulation of the proposed drug product should be submitted. The formulation should be such that there are no differences between the RLNAD and the proposed drug product that would have an effect on the bioavailability of the API. There should be no inactive ingredients in the proposed drug product's formulation likely to cause adverse pharmacologic effects. The API should be qualitatively (Q1) and quantitatively (Q2) the same as the API used in the RLNAD.[8] The solubility of the drug product should be determined under the range of physical conditions that a user of the product would typically encounter when reconstituting the soluble powder with animal drinking water (i.e., well or municipal water) in the field. This study is the same as the reconstitution study outlined in GFI #5, "Drug Stability Guidelines," section IV.F. *Soluble Powders and Drinking Water*.[9] The reconstitution data for soluble powder oral dosage form products should be submitted in the Chemistry, Manufacturing, and Controls (CMC) Technical Section.

V. Biowaivers for Type A Medicated Articles Manufactured from Water-Soluble Active Pharmaceutical Ingredients

A. Qualifying for a waiver from the requirements for conducting an *in vivo* bioequivalence study (biowaiver)

Type A medicated articles that contain APIs that are not classified as water soluble are not the subject of this guidance. The determination of the water solubility of APIs is discussed in section V.E. *Solubility Determination*.

With respect to eligibility for a biowaiver, CVM believes there is no reasonable basis for drawing a distinction between APIs intended for administration to animals via drinking water and APIs intended to be administered via feed, provided these APIs have similar solubility

[8] Current Standards & Emerging Issues of Pharmaceutical Equivalence. AAPS/EUFEPS/FIP Workshop. Mei-Ling Chen, Ph.D. November 13–14, 2010.

[9] See CVM GFI #5, "Drug Stability Guidelines," December 2008. (https://www.fda.gov/media/69957/download)

characteristics. A water-soluble API present in a Type A medicated article and mixed into a feed matrix rapidly dissolves when exposed to the fluids of the GI tract. If such an API readily goes into solution across the range of physiological pH values, it will also readily go into solution when exposed to the fluids in the GI tract. Accordingly, such medicated feeds will effectively behave as oral solutions immediately after consumption by the animal. Therefore, CVM intends to review biowaiver requests for Type A medicated articles containing water soluble APIs based on a demonstration of solubility of the API, as well as an evaluation of the drug product formulation, to ensure that there are no ingredients in the proposed formulation likely to cause pharmacologic or pharmacodynamic differences from the RLNAD.

The criteria detailed in this guidance assume that the *in vivo* dissolution of the test and reference products represents the only factor influencing the relative bioavailability of both products. However, for compounds that are fully soluble and systemically absorbed, there is the potential for certain excipients to alter drug absorption and or pre-systemic metabolism (liver or intestinal), and hence affect the relative bioavailability of the products. Therefore, for Type A medicated articles containing water-soluble APIs that are systemically absorbed, the formulation of the proposed product should be such that there are no differences in the formulations of the proposed drug product and the RLNAD that would have an effect on the bioavailability of the API. Further, there should be no inactive ingredients in the proposed drug product's formulation likely to cause adverse pharmacologic effects.

Type A medicated articles may contain biomass drug substances, which are APIs produced through fermentation that are not subjected to extensive post-fermentation purification. Biomass drug substances may contain the active molecule(s), microorganisms used for production, other metabolites produced by the microorganisms used for production, and media components. Biomass drug substances are only used as the drug substance in Type A medicated article formulations. Because certain biomass drug substances are well-accepted and routinely used components of Type A medicated articles, CVM will consider the potential for the biomass drug substance component of a Type A medicated article to cause adverse pharmacologic effects or effects on API bioavailability in the same manner that it considers these effects with respect to other excipients.

B. Data to support a waiver from the requirement to perform an *in vivo* bioequivalence study (biowaiver) request

For Type A medicated articles containing water-soluble APIs, CVM recommends that requests for biowaivers be made by a demonstration of solubility. CVM recommends that sponsors make these biowaiver requests before submitting an ANADA. The following should be provided in the biowaiver request:

1. Information about the API(s):

CVM recommends that the API(s) used to support a biowaiver request be provided from the same supplier of the API(s) that will be used to formulate the proposed drug product during production. CVM recommends that the applicant identify the source of the API(s), indicate if the API(s) is a biomass drug substance (if applicable), and provide a COA for the API(s). If the API has a USP monograph, the API should at a minimum comply with the monograph specifications. The

acceptability of the API(s) will be determined upon review of the Chemistry, Manufacturing and Controls (CMC) Technical Section.

2. Information about the formulation:

The formulation of the proposed drug product should be submitted. The formulation should be such that there are no differences between the RLNAD and the proposed drug product that would have an effect on the bioavailability of the API. There should be no inactive ingredients in the proposed drug product's formulation likely to cause adverse pharmacologic effects. The API should be qualitatively (Q1) and quantitatively (Q2) the same as the API used in the RLNAD. Sponsors should address the inactive ingredients in their formulation and any potential impact they may have on the bioavailability of the API(s) or the likelihood to cause adverse pharmacologic effects. If supporting data or information regarding any potential impact of the inactive ingredients on the bioavailability of the API(s) or their likelihood to cause adverse pharmacologic effects is available, it should be submitted.

3. Solubility Data:

Solubility data including method validations, and chromatograms as appropriate, should be submitted with each biowaiver request for Type A medicated articles. The solubility of the API should be determined in aqueous media. The inherent ability of the API to dissolve in aqueous media is critical to using the solubility data in support of any request for granting a biowaiver. Solubility data should represent a pH range that is inclusive of all the pH values expected in the gastric/ruminal environment for all the major species on the RLNAD label.

CVM recommends that the Shaker flask method be used for solubility determinations, employing an appropriate dissolution time and temperature, relevant to the labeled species. CVM-recommended times and temperatures for major species are documented in Table 1 of section V.E. *Solubility Determination.*

C. Manufacturing process

If the process used to manufacture the Type A medicated article has the potential to alter the solubility of the API, thereby potentially impacting bioequivalence of the generic product to the RLNAD, then CVM may request additional data regarding solubility of the API in the final formulation.

D. CVM evaluation of solubility data

Sponsors should submit solubility data, analytical method validations, and additional documentation such as chromatograms in support of their biowaiver request. CVM will evaluate the acceptability of the solubility data for the purposes of a biowaiver based on the criteria as documented below. If a sponsor wishes to propose an alternative to meeting the bioequivalence requirements, the sponsor may request a meeting with CVM to discuss their approach prior to

requesting a biowaiver. In general, CVM will evaluate data submitted with a biowaiver request using the following criteria:

1. **Calculation based on the Maximum Daily Dose:**

   In this scenario, the entire daily dose is administered in a single feeding event. Therefore, a demonstration that the maximum administered dose, as indicated on the RLNAD label, is soluble in the minimum fluid volume, in the specified time, for the indicated species (Table 1) will suffice as evidence for granting a biowaiver.

2. **Calculations based on the Dosage Adjusted Approach:**

   In this scenario, the dose is administered as multiple feeding events through the day. The number of feeding events by which the dose is divided is species dependent (Table 1). Therefore, the aqueous solubility is to be evaluated based on the highest expected mg of API per mL of gastric fluid at any point in time. This assessment is determined based on the API concentration in the feed and characteristics of the gastric physiology of the target animal species.

   a. **API concentration:**

      The API concentration should be calculated by using the amount of API in the Type A medicated article likely to be consumed per feeding event, e.g., dividing the daily dose into the number of feeding events that the target animal species typically takes to consume their daily ration (Table 1). This scenario is typically applicable to situations where the animals do not consume their rations on a continual basis through the day. An exception to this approach is seen in poultry, where due to their continuous feeding behavior, the solubility assessments of Type A medicated articles intended for use in poultry is to be based upon the highest approved (undivided) mg/kg/day dose.

   b. **Gastric physiology:**

      The animal physiology is critical as it determines the gastric residence time (how long it takes for the consumed medicated feed to exit the stomach or rumen), the gastric fluid volume of the target animal species (Table 1), the pH range over which solubility measurements must be made, and the temperature at which solubility should be determined.

      The solubility of the API, when tested based on the API concentration, is defined by the highest expected daily dose (mg of API) that will go into solution when tested in a manner consistent with the most conservative conditions associated with the approved product label (e.g., the largest dose to fluid volume ratio, minimum time of dissolution, and the broadest pH range over which solubility is demonstrated). When this level of solubility of the API is demonstrated, CVM will consider the API to be eligible for a biowaiver.

If there are multiple species on the labeling, solubility should be based on the most conservative mg/mL scenario (i.e., use the species that produces the highest dose to gastric fluid volume ratio).

This method of defining API solubility is similar to that described for categorizing compounds when using the BCS and to the BCS-based approach described in CDER guidance[10]. In this case, the appropriate fluid volume for testing API solubility depends on the target animal species/class for which the medicated feed is intended. For example, a conservative estimate of ruminal fluid volume (fluid volume available for drug solubilization) for steers is 47 L. The sponsor should provide the estimated daily drug intake (mg/kg body weight) based on the labeled drug concentration (grams of drug per ton) in the feed administered to the animal (e.g., the Type C medicated feed) and the highest amount of medicated feed (kg/day) expected to be consumed by an individual animal. When using this approach, CVM recommends using the species-specific animal data estimates summarized in Table 1.

E. Solubility determination

For the purposes of granting a biowaiver under this guidance, CVM is interested in the physiologically relevant solubility of the API in aqueous solutions. As such, the addition of compounds, such as surfactants used to increase the solubility of the API in aqueous media, is not considered acceptable. If the use of surfactants is required to achieve acceptable solubility data, then the API is not considered to be fully soluble in water, and therefore is no longer covered under the scope of this guidance. If the use of a buffer results in any effect that may increase the solubility of the API or drug product, that waiver request will also be denied.

The preferred method for determination of solubility is by use of the Shaker flask method[11] containing an aqueous media for the indicated time and temperature relevant to the labeled species (Table 1). Solubility should be confirmed using a validated assay procedure that can distinguish the API from its degradation products. The media used for testing should represent a pH range that is inclusive of all the pH values expected in the gastric environment for all the major species on the RLNAD label and as described in section V.F.2. *Media composition and pH considerations* below. When the conditions within the GI tract are markedly different across labeled species, appropriate media composition for testing API solubility should be discussed with CVM.

[10] See CDER Guidance for Industry, "Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System," December 2017.

[11] USP 1236.

Table 1. Standard Conditions for Use in Determining Experimental Conditions

Species *	Gastric Fluid Volume in Liters	Gastric resident times (hours)	Temperature (ºC)	Feeding events per day
Cattle [1, 3]	47 #	8	36.7 – 39.3	2
Swine [3]	0.5	1	38.7 – 39.8	2
Horse [2, 3]	1.5	0.25	37.2 – 38.2	2
Chicken [3]	0.01 ‡	2	40.6 – 43.0	N/A
Turkey [4]	0.04 ‡	2	40.6 – 41.5	N/A

* CVM acknowledges that the estimates for the indicated species are very conservative. If alternate data points are used, that use must be adequately justified. CVM notes that in certain instances the appropriate variable may be less than that indicated in the table, as is the case when dealing with younger animals.

Fluid volume of the rumen.

‡ Includes the fluid volumes of both the proventriculus and the ventriculus.

[1] Martinez, M. N., Apley, M. D. Drug solubility classification in the bovine. J. vet. Pharmacol. Therap. 35 (Suppl. 1), 93–97, 2012.

[2] The Equine Hospital Manual first edition, ed. Kevin Corley and Jennifer Stephen, Chapter 5, page 282. Wiley Blackwell, 2008.

[3] The Merck Veterinary Manual: http://www.merckvetmanual.com/appendixes/reference-guides/normal-rectal-temperature-ranges .

[4] Some Factors Affecting Body Temperature of Turkeys: *Poultry Science*, Volume 34, Issue 2, 1 March 1955, Pages 369–371, https://doi.org/10.3382/ps.0340369

F. Technical parameters to consider include:

1. Use of the Shaker flask:

- The temperature of the solution within the flask should be within the physiological range of the healthy animal for the major indicated species on the label. Temperatures should be maintained within ± 0.5°C of the indicated temperature throughout the study to ensure solubility is not affected by variation in temperature.

- After the appropriate period of shaking (based on Gastric residence time as described in Table 1), prior to sampling, there should be an excess of API apparent on the bottom of the flask.

- The supernatant (liquid above the solid) should be filtered to remove undissolved particles not apparent to the naked eye.

- Samples for analysis should be taken from the filtered supernatant. The supernatant solution may need to be diluted before analysis to be within the linear range of the analytical method and to avoid possible precipitation.

2. Media composition and pH considerations:

- For monogastric animals: pH 1.2, 4.6 (acetate buffer), and 7.5 phosphate buffer.

- For ruminants: For the purposes of generating data for a biowaiver request, the media should be buffered at a pH of 4.5 (acetate buffer) and 7.5 (lactate buffer).

- For poultry: The sponsor should justify the sets of conditions under which solubility will be tested. Without agreed upon justification, the default conditions would be the same conditions as those described for monogastric animals.

- Solution pH should be verified after addition of the API to the buffer solution. If the pH changes significantly after addition of the API, we would conclude that the buffers selected are inadequate to control fluctuations in pH.

- The pH of the solution should be verified to be consistent throughout the assessment of the API solubility. At a minimum the pH should be verified at the time the sample is taken for analysis.

Note that the buffers used may need to be modified if there are concerns that the buffer itself may alter the inherent solubility of the API or drug product (e.g., common ion effect). However, the inclusion of organic compound-containing buffer systems is not considered to be acceptable.

3. Other considerations:

- CVM recommends a minimum of three replicate determinations of solubility under each pH condition. Depending on study variability, additional replication may be necessary to provide a reliable estimate of solubility.

- A visual determination of solubility alone is insufficient. For the determination of solubility, the concentration of the API in the selected media must be determined using a validated quantitative assay method.[12]

[12] 21 CFR 514.1(b)(5)(vii)(a)

VI. GLOSSARY

For purposes of this guidance document, the following definitions apply:

Active Pharmaceutical Ingredient (API): A substance used in a finished pharmaceutical product, intended to furnish pharmacological activity or to otherwise have direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease or to have direct effect in restoring, correcting, or modifying physiological functions of the body.

Bioavailability: 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. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

Bioequivalence: 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.

Biomass Drug Substance: An active ingredient, which is an unpurified fermentation product derived from the cultivation of microorganisms, that is intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the animal.

Biowaiver: A waiver from the requirement to perform an *in vivo* bioequivalence study (21 USC 360b(n)(1)(E)).

Qualitative (Q1), Quantitative (Q2) and Structural Similarity (Q3):
Q1 means qualitative similarity between generic and reference listed products, while Q2 represents quantitative similarity of composition. Q3 describes structural similarity and refers to the arrangement of matter and state of aggregation of the product.