

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Colesevelam Hydrochloride

November 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Office of Generic Drugs.

This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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 guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

In September 2019, FDA issued a draft product-specific guidance for industry on generic colesevelam hydrochloride. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Colesevelam hydrochloride

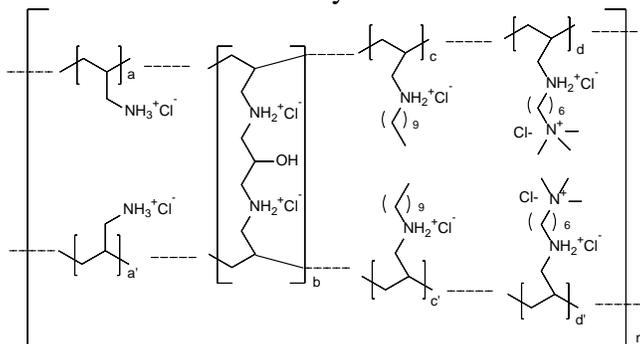
Dosage Form; Route: For suspension; oral

Overview:

This draft guidance provides recommendations for the development of generic drug product, colesevelam hydrochloride for suspension, using colesevelam hydrochloride as the active pharmaceutical ingredient (API). First, the FDA provides recommendations for demonstrating API sameness. Second, the FDA provides recommendations for demonstrating bioequivalence of the product.

Recommendations for Demonstrating API Sameness

Figure 1. Schematic Structure of Colesevelam Hydrochloride¹



where:

$$\mathbf{a + a' = 2}$$

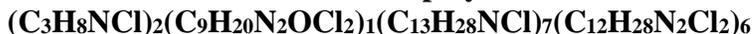
$$\mathbf{b = 1}$$

$$\mathbf{c + c' = 7}$$

$$\mathbf{d + d' = 6}$$

m = amount of extended polymeric network

Molecular formula for a basic polymeric unit:



The structure of colesevelam hydrochloride is shown in Figure 1, with substituents on the polymer backbone and their relative numbers.² The molecular formula of the basic unit of colesevelam hydrochloride is also shown. Sameness of colesevelam hydrochloride can be established based on the reaction scheme and comparative physicochemical characterizations. Generic drug applicants are advised to perform side-by-side comparative testing using the test API and the API extracted from the reference product.³ The method of API extraction should be documented and submitted to the FDA in the abbreviated new drug application (ANDA). At least three batches of the test API and three batches of API extracted from reference product should be characterized to assess API sameness and robustness in the manufacturing process.

¹ See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-141_welchol.cfm. Colesevelam hydrochloride is a cross-linked synthetic polymer with three different substituents (a, a'; c, c'; and d, d') on the backbone and a cross-linking group (b), as illustrated by the "double chain" schematic drawing of a basic polymeric unit. Comparative characterization is recommended to demonstrate API sameness including the relative ratio, and any associated batch-to-batch ranges, of each substituent in a basic polymeric unit. Note that the ratios and molecular formula included in this guidance are approximate and should only be used as a reference.

² See footnote 1.

³ Based on documents available at

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/210895Orig1s000TOC.cfm and

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-141_welchol.cfm, colesevelam hydrochloride is the active ingredient in Welchol tablets, Welchol for suspension, and Welchol chewable bar. Depending on the extraction method, it is recommended that the applicant consider whether the same extraction process should also be applied to the test API before conducting the side-by-side characterization to the API extracted from the reference product.

The sameness of colesevelam hydrochloride active ingredient can be demonstrated by showing equivalence between the test and the reference product per the following three criteria:

1. Fundamental reaction scheme
2. Chemical structure and composition
3. Physicochemical properties

1. Equivalence of fundamental reaction scheme

According to the RLD labeling, colesevelam hydrochloride is a poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide.⁴ The FDA recommends that generic drug applicants follow the synthetic transformation indicated in the product labeling to manufacture generic colesevelam hydrochloride. If alternative synthetic transformation is proposed, the applicant should contact the FDA to obtain concurrence, as the API obtained by such an approach may need additional characterizations besides the ones outlined in this draft guidance to demonstrate API sameness.

2. Equivalence of chemical structure and composition

The generic drug applicant should define the chemical structure and composition of the proposed colesevelam hydrochloride (i.e., define the descriptive (a+a'), b, (c+c'), and (d+d') values) using data obtained from the manufacturing process and characterization. The structure and composition of the test API should be equivalent to the structure and composition of the reference API.

Since the physicochemical characterizations of the colesevelam hydrochloride API alone may not be sufficient to support its chemical composition, generic drug applicants are advised to characterize the cross-linked poly(allylamine hydrochloride) intermediate, as per the approaches described in the draft guidance for sevelamer hydrochloride,⁵ and to perform studies to quantify the disappearance of the alkylating agents used in the process over time. Findings from these studies can be used to define the structure and composition of the test API, and should be reported to the FDA. The following studies are recommended:

- a. Degree of cross-linking: To quantify the degree of cross-linking in the intermediate by quantitative peak-area analysis using Solid State ¹³C Nuclear Magnetic Resonance (¹³C SSNMR) spectroscopy⁶
- b. Other characterizations for the intermediate, including glass transition temperature (T_g): To confirm the quantification of the degree of cross-linking in the intermediate⁷
- c. Alkylation studies: To quantify the degree of alkylation in the active ingredient, information on the disappearance of alkyl halide starting materials (1-bromodecane

⁴ See the labeling information of Welchol.

⁵ Draft product-specific guidance on *Sevelamer Hydrochloride*.

⁶ Berendt et al., "Spontaneous Carbonate Formation in an Amorphous, Amine-Rich, Polymeric Drug Substance: Sevelamer HCl Product Quality". *J. Pharm. Sci.* 101 (2012), pp. 2681-2685.

⁷ Hudson et al., "Enhancement and Restriction of Chain Motion in Polymer Networks". *Int. J. of Pharm.* 430 (2012), pp. 34 – 41.

and (6-bromohexyl)-trimethylammonium bromide) over time during the alkylating process should be provided.

3. Equivalence of physicochemical properties

Generic drug applicants should also perform side-by-side comparative physicochemical characterizations of the test API and the reference API. Methods used and results from the characterizations should be reported to the FDA. The sameness claim should be supported by the following:

- a. ^{13}C SSNMR spectra
- b. Data for C, H, N, Cl, and Br content by elemental analysis
- c. Chloride content by titration, to quantify the degree of protonation
- d. Total titratable amines by titration
- e. Bromide content by titration
- f. Particle size with particle size distribution
- g. Swelling Index
- h. Spectroscopic characterizations by Fourier Transformation Infrared spectroscopy (FT-IR) and Raman spectroscopy
- i. Glass transition temperature by Differential Scanning Calorimetry (DSC)
- j. Thermogravimetric Analysis (TGA)

Recommendations for Demonstrating Bioequivalence of Drug Product

1. Type of study: In vitro equilibrium binding
Design: With and without acid pre-treatment, and incubation at pH 6.8
Strength: 3.75 gm/packet
Subjects: Not applicable
Additional comments: The equilibrium binding study is considered the pivotal bioequivalence (BE) study. This study should be conducted by incubating the test product and reference product with at least eight different concentrations of total bile salts, with and without acid pretreatment. Each bile salt-containing incubation medium should contain glycocholic acid (GCA), glycochenodeoxycholic acid (GCDA) and taurodeoxycholic acid (TDCA). Total bile salt concentrations should be spaced along the spectrum until the maximum binding is clearly established. All incubations should be conducted at 37°C. Each binding study should be repeated at least 12 times. In addition, data should be provided demonstrating that the length of time selected for incubation with the total bile salt-containing medium yields maximum binding.
2. Type of study: In vitro kinetic binding
Design: Without acid pre-treatment
Strength: 3.75 gm/packet
Subjects: Not applicable
Additional comments: The kinetic binding study should be used to support the pivotal equilibrium binding study. The kinetic binding study should be conducted by incubating the test and reference products for at least eight different lengths of time, with two

different constant total bile salt concentrations, without acid pre-treatment. The total bile acid concentrations used should be 0.3 mM and 3.0 mM, similar to concentrations used in the in vitro kinetic binding studies of cholestyramine drug product. Times should be selected along the spectrum until the maximum binding is clearly established. All incubations should be conducted at 37°C. Each binding study should be repeated at least 12 times.

For additional details on the study design, refer to the draft product-specific guidance on *Cholestyramine powder; oral*.

3. Type of study: In vitro equilibrium binding with water and beverages
Design: With and without acid pre-treatment, and incubation at pH 6.8
Strength: 3.75 gm/packet
Subjects: Not applicable
Additional comments: The study design for the equilibrium binding study with water and beverages should be the same as that described for the in vitro equilibrium binding study above (including the same total bile salt concentrations used) except that the study samples are pre-treated with water, three kinds of diet soft drinks, and three types of fruit juices at mild acidic or neutral pH (grapefruit juice excluded). After pre-treatment with water or beverages at 37°C, the samples should be centrifuged and supernatant should be discarded. The pre-treated samples should then be subjected to either acid pre-treatment or no acid pre-treatment, and incubation with total bile salts as described for the in vitro equilibrium binding study above.

Each binding study should be repeated at least 12 times.

4. Type of study: In vitro kinetic binding with water and beverages
Design: Without acid pre-treatment
Strength: 3.75 gm/packet
Subjects: Not applicable
Additional comments: The study design for the kinetic binding study with water or beverages should be the same as that described for the in vitro kinetic binding study (including the same two constant total bile salt concentrations) above except that the study samples are pre-treated with water, three kinds of diet soft drinks, and three types of fruit juices at mild acidic or neutral pH (grapefruit juice excluded). After pre-treatment with water or beverages at 37°C, the samples should be centrifuged and supernatant should be discarded. The pre-treated samples should then be subject to incubation with total bile salts as described for the in vitro kinetic binding study above.

Each binding study should be repeated at least 12 times.

Analytes to measure: Unbound bile salts in filtrate (to calculate bile salts bound to resin)

For the in vitro equilibrium binding study and the equilibrium study with water and beverages, the Langmuir binding constants k_1 and k_2 should be determined based on total bile salt binding

(GC+GCDC+TDC). The test to reference ratio should be calculated for k_1 . The 90% confidence interval (CI) should be calculated for k_2 with the acceptance criteria of 80% to 120%.

For the in vitro kinetic binding study and the kinetic study with beverages, the test to reference bound bile salt ratios at the various times should be compared but not subjected to the 90% CI criteria.

Bioequivalence based on (90% CI): The Langmuir binding constant k_2 from the equilibrium binding study

Waiver request of in vivo testing: Not applicable

Waiver requests of in vitro equilibrium and kinetic binding studies: 1.875 gm/packet strength based on (i) acceptable in vitro equilibrium binding and kinetic binding studies on the 3.75 gm/packet strength, (ii) proportionally similar 1.875 gm/packet formulation to the 3.75 gm/packet strength.

Revision History: Recommended August 2010; Revised June 2011, March 2012, June 2013, January 2016, September 2019, November 2021

Unique Agency Identifier: PSG_022362