



Edward J. Allera  
Barbara A. Binzak Blumenfeld  
Buchanan Ingersoll & Rooney PC  
1700 K Street NW, Suite 300  
Washington, DC 20006

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Re: Docket Nos. FDA-2013-P-1376, FDA-2013-P-1377, and FDA-2015-P-4566

Dear Mr. Allera and Ms. Binzak Blumenfield:

This letter is a consolidated response to your two citizen petitions received by the Food and Drug Administration (FDA or the Agency) on October 21, 2013. It also responds to your third petition, which we received on December 1, 2015.<sup>1</sup>

The first petition (docket number FDA-2013-P-1376) ("Exclusivity Petition") requests FDA to confirm that: (1) two tablet strengths (0.0625 milligrams (mg) and 0.1875 mg) of Lanoxin (digoxin) were not approved<sup>2</sup> in new drug application (NDA) 20405 on September 30, 1997; (2) the Agency recognized 3-year exclusivity for the application, which did not "begin running" in 1997 for the non-marketed tablet strengths; and (3) the Lanoxin NDA holder was eligible for 3-year exclusivity for the 0.0625 mg and 0.1875 mg tablet strengths beginning on October 17, 2013.<sup>3</sup>

The second petition (docket number FDA-2013-P-1377) ("Testing Petition") requests that FDA (1) require all digoxin 0.0625 mg and 0.1875 mg generic drug<sup>4</sup> applicants that rely on Lanoxin as the reference listed drug (RLD)<sup>5</sup> to conduct and pass the same dissolution and blend uniformity

<sup>1</sup> Docket numbers FDA-2013-P-1376 and FDA-2013-P-1377 were originally submitted on behalf of Covis Pharma Sàrl (Covis). Docket number FDA-2015-P-4566 was submitted on behalf of Concordia Pharmaceuticals (Concordia). As noted in the most recent petition, on April 21, 2015, Concordia acquired new drug application (NDA) 20405 for Lanoxin (digoxin) Tablets (Lanoxin) from Covis. All three petitions were submitted by Mr. Edward J. Allera and Barbara A. Binzak Blumenfeld (Buchanan Ingersoll & Rooney PC), on behalf of Covis or Concordia.

<sup>2</sup> FDA does not "partially" or "fully" approve drugs. See 21 CFR 314.105 (describing the approval of New Drug Applications and Abbreviated New Drug Applications). The two tablet strengths referred to in the petition (0.0625 mg and 0.1875 mg) were approved on September 30, 1997 along with four other strengths, only two of which were ultimately marketed. Accordingly, we use the term "approve" throughout this petition response.

<sup>3</sup> On October 17, 2013, FDA approved the Lanoxin NDA holder's Prior Approval Supplement (PAS) which provided for additional dissolution data and updated container labels and prescribing information.

<sup>4</sup> For purpose of this response, the term *generic drug* refers to a new drug product for which approval is sought in an Abbreviated New Drug Application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 *et seq.*)

<sup>5</sup> An RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

validation testing that the Lanoxin NDA holder conducted; and (2) deny any requests from digoxin generic drug applicants to “waive” dissolution and blend uniformity validation testing for the 0.0625 mg and 0.1875 mg strengths.

The third petition (docket number FDA-2015-P-4566) (“Bioequivalence Petition”) requests that FDA amend the May 2008 guidance containing product specific recommendations for digoxin tablets (2008 digoxin guidance)<sup>6</sup> to reflect digoxin’s narrow therapeutic index (NTI) drug status by recommending that generic applicants meet the same bioequivalence criteria recommended for other NTI drugs. The petition also requests that FDA recommend that digoxin generic applicants use scaled four-way, fully replicated crossover design, in vivo fasting and fed studies to establish bioequivalence. The Bioequivalence Petition further requests that FDA recommend a narrower confidence interval (CI) for area under the plasma concentration versus time curve and maximum drug concentration to fall within narrower bioequivalence limits (90-111.11%) as well as a narrower drug substance assay range. Finally, the Bioequivalence Petition asks FDA to make a determination that currently approved generic digoxin oral drug products not meeting these standards are not therapeutically equivalent to Lanoxin and that they should therefore be rated BX in FDA’s Orange Book.<sup>7</sup>

FDA has carefully considered the information in each of the three Petitions. For the reasons explained below, we dismiss the Exclusivity Petition as moot and grant in part and deny in part the Testing and Bioequivalence Petitions.

## I. Background

### A. Digoxin

Digoxin is one of several cardiac glycosides (often referred to collectively as “digitalis”) used to treat a number of cardiovascular conditions. The cardiac or digitalis glycosides are a closely related group of drugs having in common specific effects on the myocardium. Digoxin has been marketed in the United States since 1934 for use in heart failure, atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia. According to currently approved product labeling,<sup>8</sup> digoxin tablets are indicated for the treatment of mild to moderate heart failure in adults, increasing myocardial contractility in pediatric patients with heart failure, and control of resting ventricular rate in adult patients with chronic atrial fibrillation.

In 1990, Burroughs Wellcome & Company (Burroughs)<sup>9</sup> informed FDA that it intended to submit an NDA for digoxin tablets. In a meeting held between FDA and Burroughs on

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<sup>6</sup> For a discussion of the 2008 digoxin guidance, see section G below.

<sup>7</sup> Therapeutic Equivalence (TE) codes are used to determine the substitutability of two drug products. A “BX” code means that a drug product is not considered therapeutically equivalent to an RLD because there are insufficient data to determine therapeutic equivalence. See Orange Book at xix.

<sup>8</sup> Lanoxin (digoxin) tablets labeling, December 1, 2016 available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020405s013lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020405s013lbl.pdf).

<sup>9</sup> In October 1995 Burroughs was acquired by Glaxo Inc., and the merged companies became known as Glaxo Wellcome. In December 2000 Glaxo Wellcome and SmithKline Beecham merged to form GlaxoSmithKline (GSK).

December 5, 1990, the Agency discussed the requirements that Burroughs' application would need to meet for approval. On September 30, 1993 Burroughs submitted NDA 20405 for Lanoxin seeking approval for the 0.0625, 0.125, 0.1875, 0.250, 0.375, and 0.500 mg<sup>10</sup> tablet strengths for the treatment of mild to moderate heart failure in patients receiving angiotensin converting enzyme (ACE) inhibitors and diuretics. As part of its Lanoxin NDA, Burroughs requested 3 years of marketing exclusivity<sup>11</sup> for all six strengths for treatment of heart failure in patients receiving ACE inhibitors and diuretics or receiving diuretics alone. Burroughs stated that Lanoxin was eligible for 3-year exclusivity based on two company-sponsored, double-blind, placebo-controlled clinical trials:

**GHBA-436 Study: A Double-Blind, Placebo-Controlled, Parallel, Multicenter Study to Assess the Effects of Digoxin Withdrawal on Exercise Tolerance and Other Measures of Clinical Efficacy in Patients with Chronic Congestive Heart Failure (NYHA Class II-III) in Normal Sinus Rhythm**

**GHBA-437 Study: A Double-Blind, Placebo-Controlled, Parallel, Multicenter Study to Assess the Effects of Digoxin Withdrawal on Exercise Tolerance and Other Measures of Clinical Efficacy in Patients with Chronic Congestive Heart Failure (NYHA Class II-III) in Normal Sinus Rhythm Receiving Concomitant Therapy With Diuretics and an Angiotensin Converting Enzyme Inhibitor**

In 1995, Glaxo Wellcome submitted an amendment to the Lanoxin NDA adding a second manufacturing facility in Zebulon, NC (the other manufacturing facility was in Greenville, NC) for production of the 0.125 mg and 0.250 mg strength tablets. The Greenville facility remained designated in the Lanoxin NDA for manufacturing all six strengths. (Exclusivity Petition at 6-7).

In May 1997 Glaxo Wellcome supplied additional information regarding its request for 3-year exclusivity. In its submission, Glaxo Wellcome claimed that the Lanoxin NDA qualified for 3-year exclusivity for all six strengths because the clinical investigations conducted for the application were essential to approval of its NDA. (Exclusivity Petition at 6).

On September 30, 1997, FDA approved the Lanoxin NDA. The approval letter stated: "Please refer to your September 30, 1993, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lanoxin (digoxin) [0.0625, 0.125, 0.1875, 0.250, 0.375, and 0.500 mg] Tablets."<sup>12</sup> The approval letter then stated:

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the

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<sup>10</sup> The dose strength equivalents in micrograms are 62.5, 125, 187.5, 250, 375, and 500, respectively. The petitions reference dosage strengths in milligrams (mg), while dosage strengths in the original application and approval letter are referenced in micrograms. For consistency, we reference dosage strength in milligrams throughout this petition response.

<sup>11</sup> An application for a drug product that contains an active moiety that has been previously approved may be eligible for 3-year exclusivity if it contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application. See 21 CFR 314.108(b)(4)-(5).

<sup>12</sup> The initial Lanoxin NDA approval included the 0.0625 mg round peach tablets, and the 0.1875 mg round blue scored tablets.

drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The approval letter approved all six strengths but also noted that Glaxo Wellcome had decided not to market the 0.0625, 0.1875, 0.375, and 0.500 mg tablet strengths and that only the 0.125 mg and 0.250 mg tablet strengths were approved to be manufactured at the facility located at Zebulon, NC. All six strengths were listed in the Orange Book as having 3-year exclusivity that expired on September 30, 2000.

In December 2011, Covis acquired the Lanoxin NDA. According to petitioner, in April 2012 Covis sent an email to FDA asking about the regulatory requirements for marketing the 0.0625 mg and 0.1875 mg tablets and seeking a waiver of any testing requirements. (Exclusivity Petition at 9). FDA responded that if Covis wanted to add the non-marketed strengths to the Lanoxin prescribing information it should submit a PAS to FDA for review.<sup>13</sup> (Exclusivity Petition at 9).

On August 30, 2012, Covis submitted a PAS, with the required draft package insert and draft container labels to include the 0.0625 mg and 0.1875 mg strengths.<sup>14</sup> (Exclusivity Petition at 9). In the cover letter for the PAS, Covis stated: "Lanoxin was approved by the agency on 30 September 1997. The approval for this NDA included the following strengths [0.0625, 0.125, 0.1875, 0.250, 0.375, and 0.500 mg]. At the time of approval only the 0.125 mg and 0.250 mg tablets were marketed, as such no labeling was submitted for approval of the other approved strengths."

In January 2013, FDA conducted a prior approval inspection during which inspectors raised concerns regarding the blend uniformity of the 0.0625 mg and 0.1875 mg tablet strengths. FDA issued a complete response letter on February 28, 2013, requesting that Covis provide dissolution profiles with f2 statistical testing<sup>15</sup> comparing both strengths using the approved dissolution testing method. FDA also directed Covis to submit new draft labeling. Covis submitted both the dissolution testing data and draft labeling in April 2013, and in October 2013 FDA approved the PAS. (Exclusivity Petition at 9-10).

Subsequently, FDA moved the 0.0625 and 0.1875 mg strength Lanoxin tablets from the "Discontinued" to the "Prescription" section of the Orange Book.

## B. 3-Year Exclusivity for Certain NDAs

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<sup>13</sup> See emails sent by Alexis Childers, Division of Cardiovascular and Renal Products, to Todd Phillips, Beckloff Associates (U.S. Agent for Covis) on April 24, 2012 and July 2, 2012.

<sup>14</sup> The labeling supplement indicated that the 0.0625 mg strength would be marketed as a 0.0625 mg round peach tablet and the 0.1875 mg tablet strength would be marketed as a 0.1875 mg round blue unscored tablet.

<sup>15</sup> "f2" is a similarity factor and FDA interprets the petitioner's request as a request to require a model independent approach using a similarity factor as described in the guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) provide for a 3-year period of exclusivity for certain original NDAs and supplements to NDAs during which time the Agency may not approve certain NDAs approved under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FD&C Act) or ANDAs. Specifically, the statutory provision applicable to supplements as it relates to ANDAs states that:

“If a supplement to an application . . . contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of approval of the supplement.”<sup>16</sup>

The Agency’s promulgating regulations largely mirror the statute.<sup>17</sup> Under the Agency’s regulations, “clinical investigation” means “any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.”<sup>18</sup> A “new clinical investigation” is an “investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.”<sup>19</sup> A new clinical investigation is considered “essential to approval” if, with regard to that investigation, “there are no other data available that could support approval of the application.”<sup>20</sup>

### C. Statutory and Regulatory Basis for ANDA Approval

The Hatch-Waxman Amendments created section 505(j) of the FD&C Act (21 U.S.C. 355(j)), which established the ANDA approval pathway for generic drugs. To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA’s previous finding that the RLD is safe and effective. The ANDA applicant must identify the listed drug on which it seeks to rely, and generally a drug product described in an ANDA must have the same active ingredient(s), conditions of use, dosage form, strength, route of administration, and (with certain permissible differences) labeling as the listed drug it references.<sup>21</sup>

The applicant also must demonstrate that its proposed generic drug is bioequivalent to the RLD. Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

<sup>16</sup> Section 505(j)(5)(F)(iv) of the FD&C Act; see also section 505(c)(3)(E)(iv). These statutory provisions provide for 3-year exclusivity for supplements. Sections 505(j)(5)(F)(iii) and (c)(3)(E)(iii) of the FD&C Act apply to original NDAs.

<sup>17</sup> 21 CFR 314.108(a)(4)-(5).

<sup>18</sup> 21 CFR 314.108(a).

<sup>19</sup> Id.

<sup>20</sup> Id.; see also 21 CFR 314.50(j)(4)(ii).

<sup>21</sup> Sections 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a).

. . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .<sup>22</sup>

In § 314.3(b) of the FDA's regulations,<sup>23</sup> FDA defines *bioequivalence* (in part) as:

the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and to an extent that is not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the human body as the RLD. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action.

The statute, regulations, and case law give FDA considerable flexibility in determining how the bioequivalence requirement is met. The testing methods may include in vivo data (data from a study on human subjects) or in vitro data (data from laboratory studies).<sup>24</sup>

FDA's regulations also describe the types of evidence that may be used to establish bioequivalence:

FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products . . . . The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.<sup>25</sup>

Section 314.94(a)(7) of FDA's regulations sets forth the requirement that an ANDA contain information that shows that the drug product is bioequivalent to the RLD upon which the

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<sup>22</sup> See also 21 CFR 320.1(e) and 320.23(b).

<sup>23</sup> See Final Rule, "Abbreviated New Drug Applications and 505(b)(2) Applications," October 6, 2016 (81 FR 69580).

<sup>24</sup> See section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with the discretion to determine whether in vivo or in vitro bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated approval processes").

<sup>25</sup> 21 CFR 320.24(a).

applicant relies, and section 320.24(b) describes bioequivalence methods in general descending order of accuracy, sensitivity, and reproducibility. They include: (1) in vivo pharmacokinetic (PK) studies in whole blood, plasma, serum, or other appropriate biological fluid, or in vitro tests that have been correlated with and are predictive of human in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety and, when appropriate, its active metabolites, is measured; (3) in vivo pharmacodynamic (PD) effect studies; (4) clinical endpoint studies; and (5) in vitro studies acceptable to FDA that ensure human in vivo availability.<sup>26</sup> In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulations state that FDA has the authority to use “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence.”<sup>27</sup>

FDA has broad discretion to determine how the bioequivalence requirement should be met for a given product or class of products, as long as its determination is not contrary to the governing statute and regulations and is based on a “reasonable and scientifically supported criterion.”<sup>28</sup>

Drug products are considered therapeutically equivalent only if they are pharmaceutical equivalents<sup>29</sup> and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.<sup>30</sup> FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents; (3) they are bioequivalent in that they do not present a known or potential bioequivalence problem and they meet an acceptable in vitro standard, or if they do present a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practices (CGMP) regulations.<sup>31</sup> An “AB” TE code means a drug product is considered to be therapeutically equivalent to the RLD as the drug product meets necessary bioequivalence requirements. A “BX” code means that a drug product is not considered therapeutically equivalent to an RLD because there are insufficient data to determine therapeutic equivalence. “The code BX is assigned to specific drug products for which the data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence.”<sup>32</sup>

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<sup>26</sup> 21 CFR 320.24(b).

<sup>27</sup> Id.; see also *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 20 (D.D.C. 2009) (quoting 21 CFR 320.24(b) in upholding FDA’s sameness determination of generic drug product).

<sup>28</sup> *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992). See also *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 19 (D.D.C. 2009) (the “high degree of deference” given to FDA’s scientific determinations “has been applied to the FDA’s determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic”).

<sup>29</sup> See 21CFR 314.3(b). Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration. See Orange Book at vii. Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same, or compendial, or other applicable standards (i.e., strength, quality, purity, or identity). Id.

<sup>30</sup> Id.

<sup>31</sup> Id.

<sup>32</sup> Id. at xix.

#### **D. Bioequivalence Testing**

For systemically acting drug products, the rate and extent of systemic absorption is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers.<sup>33</sup>

For most systemically acting drugs, standard bioequivalence PK studies are conducted using a two-treatment, two-sequence, two-period crossover study design in healthy subjects. In this design, each subject receives each treatment (i.e., test and reference drug) in random order.<sup>34</sup> Single oral doses of the test and reference drug products are administered, and blood or plasma levels are then measured over time. The rate and extent of drug absorption are statistically evaluated. The relevant PK parameters calculated from these data include the area under the plasma concentration versus time curve (AUC), calculated to the last measurable concentration time (AUC<sub>0-t</sub>), and AUC extrapolated to infinity (AUC<sub>∞</sub>). These parameters represent the extent of absorption. The other relevant PK parameter is the maximum or “peak” drug concentration (C<sub>max</sub>). C<sub>max</sub> and the time at which C<sub>max</sub> occurs (T<sub>max</sub>) reflect the rate of absorption. However, typically only C<sub>max</sub> is statistically evaluated to determine bioequivalence between the test and reference drug products.

Generally, to establish bioequivalence, the calculated 90 percent CI for the ratio of the geometric mean for AUC and C<sub>max</sub> values of the generic test product and the RLD should fall entirely within an 80 percent to 125 percent acceptance interval (0.8 - 1.25).<sup>35</sup> The use of an 80 to 125 percent acceptance interval to compare two products with the same active ingredient, dosage form, route of administration, and strength is a scientific judgment about the best statistical practices for bioequivalence determinations and reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients.

#### **E. Dissolution and Validation Testing**

##### **1. Dissolution Testing**

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<sup>33</sup> Section 505(j)(8)(B) of the FD&C Act; guidance for industry *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (BA/BE Guidance) at 6; and draft guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Dec. 2013) at 3.

<sup>34</sup> See draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Dec. 2013) at 3.

<sup>35</sup> Orange Book Preface, Section 1.3, *Statistical Criteria for Bioequivalence*; see also BA/BE Guidance and guidance for industry *Statistical Approaches to Establishing Bioequivalence*. To pass a CI limit of 80 to 125 percent, the value would be at least 80.00 percent and not more than 125.00 percent. See draft guidance for industry, *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application* (Dec. 2013).

FDA's regulations state that the information submitted to support applications must include process quality controls for the drug product and the specifications necessary to ensure the identity, strength, quality, purity, and bioavailability of the drug product, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container closure systems, stability dating, particle size, and crystalline form.<sup>36</sup>

In vivo dissolution of the dosage form is critical for drug absorption into the systemic circulation. Specifically, dissolution involves disintegration of the solid dosage form followed by solubilization of the drug under physiological conditions. Solubilized drug is then absorbed into the systemic circulation by permeation across the membranes of the gastrointestinal tract. Because only solubilized drug can passively cross biologic membranes, in vitro dissolution may be relevant to the prediction of in vivo performance. Based on this general consideration, in vitro dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, are used to (1) assess the lot-to-lot quality of a drug product; (2) guide development of new formulations; and (3) ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process.<sup>37</sup>

## 2. Blend Uniformity Testing

Under CGMP regulations, control procedures must be established for manufacturing each commercial batch of all drug products to monitor the output and validate the performance of processes that could be responsible for causing variability, including the adequacy of mixing to ensure uniformity and homogeneity, where appropriate.<sup>38</sup> Blend uniformity testing is one way to assure adequacy of mixing and homogeneity to meet the CGMP requirements.

### F. Narrow Therapeutic Index (NTI) Drugs<sup>39</sup>

The specific term *narrow therapeutic index* is not defined in FDA regulations. However, section 320.33 of the regulations defines *narrow therapeutic ratio* as follows:

1. There is less than a two-fold difference in median lethal dose ( $LD_{50}$ ) and median effective dose ( $ED_{50}$ ) values or there is less than a two-fold difference in minimum toxic concentrations and minimum effective concentrations in the blood, and
2. Safe and effective use of the drug products requires careful titration and patient monitoring.

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<sup>36</sup> 21 CFR 314.50(d)(1)(ii)(a) and 314.94(a)(9)(i).

<sup>37</sup> See United States Pharmacopeia, Chapter 711, *Dissolution* (2011); see also Armenante and Muzzio, *Inherent Method Variability in Dissolution Testing: The Effect of Hydrodynamics in the USP II Apparatus*, (technical report submitted to FDA that can be found at [http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4187B1\\_01\\_04-Effect-Hydrodynamics.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4187B1_01_04-Effect-Hydrodynamics.pdf)).

<sup>38</sup> 21 CFR 211.110(a)(3).

<sup>39</sup> Other terms have been used synonymously with *narrow therapeutic index*. These terms include *narrow therapeutic range*, *narrow therapeutic ratio*, *narrow therapeutic window*, and *critical-dose drugs*.

Although the regulations highlight the importance of careful dose titration and patient monitoring, the clinical practicality of this definition is questionable, because the median lethal dose and median effective dose frequently are not available during drug development or even after approval.<sup>40</sup>

FDA has described *narrow therapeutic range* drug products as those containing drug substances that are “subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation.”<sup>41</sup>

Definitions of NTI drugs were discussed at FDA advisory committee meetings held in 2010 and 2011.<sup>42</sup> As a result of those discussions, FDA now uses the term *narrow therapeutic index* and considers NTI drugs to be those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or that may result in persistent or significant disability or incapacity.<sup>43</sup>

FDA assesses whether drugs have a narrow therapeutic index on a case-by-case basis, focusing on whether a particular drug has the following characteristics: (1) there is little separation between therapeutic and toxic doses (or the associated blood/plasma concentrations), (2) sub-therapeutic concentrations may lead to serious therapeutic failure, (3) patients are subject to therapeutic monitoring based on PK or PD measures, (4) the drugs have low-to-medium (i.e., no more than 30 percent) within-subject variability (meaning that when the same subject is administered the same dose of the same drug product, no more than a 30 percent difference in the rate and extent of absorption of the drug is observed), and (5) in clinical practice, doses are often adjusted in very small increments (less than 20 percent).<sup>44</sup> The assessment of whether a drug has

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<sup>40</sup> See L.X. Yu et al., “Novel bioequivalence approach for narrow therapeutic index drugs,” *Clin Pharmacol Ther*, 2015, 97(3):287.

<sup>41</sup> See BA/BE Guidance; draft guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (May 2015).

<sup>42</sup> U.S. Food and Drug Administration, April 13, 2010, Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee: Topic 1, revising the Bioequivalence approaches for critical-dose drugs, <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm209318.htm> (2010) (2010 Advisory Committee).

U.S. Food and Drug Administration, July 26, 2011, Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee: bioequivalence issues and quality standards relative to narrow therapeutic index (NTI) drug products, <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm266768.htm> (2011) (2011 Advisory Committee).

<sup>43</sup> See 2011 Advisory Committee meeting, <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm266768.htm> (2011). See also L.X. Yu et al., “Novel bioequivalence approach for narrow therapeutic index drugs,” *Clin Pharmacol Ther*, 2015, 97(3):286-291.

<sup>44</sup> See L.X. Yu et al.; see also draft guidance containing product specific recommendations for *Warfarin Sodium* (Dec. 2012) (warfarin sodium guidance), draft guidance containing product specific recommendations for *Digoxin* (Aug 2017) (2017 digoxin guidance).

a narrow therapeutic index generally is reflected in the applicable product-specific recommendation for that drug product.<sup>45</sup>

Doses of NTI drugs often must be adjusted in very small increments because the potential adverse reactions associated with sub- or supra-therapeutic drug concentrations can be serious, even life-threatening.<sup>46</sup> In most cases, therapeutic concentrations cannot be reduced to give larger separation from concentrations related to toxicity, or increased to ensure efficacy.<sup>47</sup> For example, supra-therapeutic levels of warfarin (measured through PD monitoring of prothrombin time and international normalized ratio) can lead to major or fatal bleeding events, and drugs that are indicated for treatment of epilepsy or for immunosuppression can cause severe therapeutic failure at sub-therapeutic concentrations.<sup>48</sup> Accordingly, NTI drugs must be carefully dosed and monitored.

NTI drugs are monitored based on PK or PD measures that are predictive of clinical response. The value of PK or PD monitoring for an NTI drug is associated with the degree of within-subject variability inherent in the PK or PD measures of the drug.<sup>49</sup> To be clinically useful, the PK or PD measure chosen for therapeutic monitoring of an NTI drug should possess low-to-medium within-subject variability so that the measure can be used to predict the clinical response of the patient.<sup>50</sup>

For several NTI drugs, FDA has recommended in draft guidances that one acceptable method for establishing the bioequivalence is a four-way, fully-replicated crossover study design that permits both variability comparison and mean comparison. Details on how to implement the reference-scaled bioequivalence approach are described in these draft guidances containing product specific recommendations for NTI drugs.<sup>51</sup>

#### **G.     Guidances Containing Product Specific Recommendations for Digoxin Tablets**

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<sup>45</sup> See draft guidance, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) (“FDA recommends that applicants consult this general guidance in conjunction with any relevant product-specific guidance when considering the appropriate BE study for a proposed product.) See e.g. warfarin sodium guidance, 2017 digoxin guidance. Guidances containing product specific recommendations for generic drug development can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

<sup>46</sup> See L.X. Yu et al. at 286.

<sup>47</sup> See id. at 287.

<sup>48</sup> Id.

<sup>49</sup> Id.

<sup>50</sup> See id. at 287-288.

<sup>51</sup> See, e.g., draft guidances containing product-specific recommendations for tacrolimus, warfarin sodium, carbamazepine, phenytoin sodium, levothyroxine sodium, and sirolimus. See also guidance for industry, *Statistical Approaches to Establishing Bioequivalence*; see also L.X. Yu et al. at 288 citing Westlake, W.J. *Bioavailability and Bioequivalence of Pharmaceutical Formulations. Pharmaceutical Statistics for Drug Development* (Marcell Dekker, New York, 1988) at 329-352, and guidance for industry, *Statistical Approaches to Establishing Bioequivalence*.

In the 2008 digoxin guidance, the Agency recommended that ANDA applicants conduct two single-dose, two-way crossover in vivo studies with a 0.250 mg dose in normal, healthy males and females under fasting and fed conditions. It further recommended that applicants conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the method outlined by USP-NF.<sup>52</sup>

The 2008 digoxin guidance also recommended that ANDA applicants demonstrate bioequivalence to digoxin based on the 90 percent CIs for the standard PK measures of AUC and C<sub>max</sub>. If an ANDA applicant cannot establish reliable blood drug levels using a single dose of one 0.250 mg tablet, the 2008 digoxin guidance recommended that ANDA applicants use a single dose of two 0.250 mg tablets.

The 2011 Advisory Committee recommended the use of a reference scaled bioequivalence approach and narrower assayed potency standards for NTI drugs.<sup>53</sup> After a comprehensive review by the Agency, FDA today issued the 2017 digoxin guidance. This guidance recommends that digoxin ANDA applicants conduct two single-dose, four-way, fully replicated crossover in-vivo studies, with a 0.250 mg dose in normal healthy males and females under fed and fasting conditions. It also recommends that ANDA applicants conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the methodology established by USP. The 2017 digoxin guidance further advises that ANDA applicants demonstrate bioequivalence to digoxin based on 90 percent CIs for the standard pharmacokinetic measures of AUC and C<sub>max</sub>.

As with other FDA guidances containing product specific recommendations, the 2008 and 2017 digoxin guidances are not binding.<sup>54</sup> Regulated parties “can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.”<sup>55</sup>

## II. Discussion

### A. Exclusivity Petition

You claim that the current holder of the Lanoxin NDA (Concordia) is eligible for 3-year exclusivity for the 0.0625 mg and 0.1875 mg strengths, beginning on the date the PAS adding these strengths to Lanoxin labeling was approved (October 17, 2013), rather than on the approval date of the Lanoxin NDA (September 30, 1997). The Exclusivity Petition states that although all six strengths were eligible for 3 years of exclusivity at the time the Lanoxin NDA was approved in 1997, the exclusivity period never “began running” for the non-marketed strengths because they were not approved.<sup>56</sup>

<sup>52</sup> Product-specific dissolution methods are listed at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>.

<sup>53</sup> See 2011 Advisory Committee meeting.

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm266768.htm> (2011).

<sup>54</sup> See 21 CFR 10.115(d) (“Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or the FDA”).

<sup>55</sup> See 21 CFR 10.115(d)(2).

<sup>56</sup> Exclusivity Petition at 2.

We have carefully reviewed the issues raised in the Exclusivity Petition, as well as the administrative record related to the Lanoxin NDA and PAS. As noted above, the 0.0625 mg and 0.1875 mg strengths were approved on September 30, 1997, when FDA approved the Lanoxin NDA, and like the other strengths approved in the NDA, these strengths were protected by 3-year exclusivity until September 30, 2000. However, even if Lanoxin was eligible for 3-year exclusivity for the 0.0625 mg and 0.1875 mg tablet strengths beginning on October 17, 2013, the requests in the Exclusivity Petition are moot because that exclusivity would have expired on October 17, 2016.<sup>57</sup>

Accordingly, the Exclusivity Petition is dismissed as moot.

#### B. Testing Petition

The Testing Petition requests that FDA require all applicants seeking approval of generic 0.0625 mg and 0.1875 mg strength digoxin tablets to conduct and pass the same dissolution and blend uniformity validation testing that the NDA holder for Lanoxin conducted, and to deny any requests from generic applicants to waive such requirements. According to the Testing Petition, because digoxin is an NTI drug, there are “critical manufacturing issues” related to CMC and CGMP requirements that must be addressed in all digoxin applications. Accordingly, you argue that both the NDA holder and digoxin ANDA applicants must be subject to the same validation testing requirements.<sup>58</sup>

FDA requires applications to contain CMC information relating to quality controls for drug products and the specifications necessary to ensure the identity, strength, quality, purity, potency and bioavailability of drug products. The information relating to in-process tests and controls is required as appropriate for a particular submission.<sup>59</sup> While FDA requires applications to contain information concerning in-process tests and controls to evaluate formulation and product quality, FDA does not impose specific testing requirements. Depending on formulation and manufacturing processes of an applicant’s specific drug product, FDA recognizes that different tests may be appropriate. For powdered blends (including digoxin tablets), FDA recommends

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<sup>57</sup> We note that no applications for the 0.0625 mg and 0.1875 mg tablet strengths were approved during this time period.

<sup>58</sup> We note that the Testing Petition is focused specifically on dissolution and blend uniformity testing and not bioequivalence. However, the Testing Petition also claims that FDA constructively denied the NDA holder’s purported request for a waiver of bioequivalence testing for the 0.0625 mg and 0.1875 mg strength Lanoxin tablets by requiring the company to submit a PAS with additional testing data. (Testing Petition at 2). We disagree. A PAS generally is required for any major changes to the labeling that affect CMC information and other requirements under 21 CFR 201.57 (e.g., dosage form and strength, how supplied). See 21 CFR 314.70(b)(2); guidance for industry *Changes to an Approved NDA or ANDA*. Because the approved labeling for Lanoxin in 1997 omitted the 0.0625 mg and 0.1875 mg strengths, marketing these two strengths required a labeling change that could be effected only by a PAS. Additionally, the tablets the Lanoxin NDA holder intended to market were modified from the tablets that were approved in the original NDA. Whereas the initial NDA approval included 0.1875 mg round blue scored tablets, the PAS and labeling supplement were approved for 0.1875 mg round blue unscored tablets. Changing the scoring pattern on a finished tablet is a change to the drug product that prompted FDA’s request for comprehensive dissolution data to verify that the change did not affect clinical performance. Such a request for additional dissolution is part of the normal review process of ensuring the quality of a finished product and does not constitute a denial of a waiver request.

<sup>59</sup> 21 CFR 314.50(d)(1)(ii)(a), and 314.94(a)(9)(i).

using a science and risk-based sampling approach to ensure (1) adequacy of blend mixing and (2) that sampling of the blend is done at a suitable juncture in the manufacturing process.<sup>60</sup>

For ANDA applicants, the 2017 digoxin guidance specifies that to demonstrate bioequivalence comparative dissolution testing should be conducted on 12 dosage units each of all strengths of the test and reference products in accordance with the methodology outlined by USP.<sup>61</sup> Even if ANDA applicants do not follow the testing recommendations in the 2017 digoxin guidance, they still must satisfy the CMC-related requirements of 21 CFR 314.50(d)(1) and 314.94(a)(9) by providing sufficient information concerning in-process tests and controls in an application. ANDA applicants also must satisfy the CGMP requirements of 21 CFR 211.110 by establishing and following written procedures that describe the in-process controls, tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.

After considering all relevant medical, scientific and regulatory information concerning NTI drugs such as digoxin, as well as the arguments raised in the Testing Petition, FDA believes that requiring digoxin ANDA applicants to utilize the same dissolution and blend uniformity testing methods and acceptance criteria as the Lanoxin NDA holder is not warranted. Different formulations of drug products as well as differences in manufacturing sites and processes often require different testing methods to demonstrate adequacy of mixing, and the adherence to one test methodology may not be sufficient even within a particular formulation. Consequently, FDA encourages firms to adopt innovative approaches to ensure adequacy of mixing.<sup>62</sup> FDA recognizes the importance of ensuring product quality of all drug products; in particular NTI drugs. The Agency reviews each application closely for the sufficiency of the CMC and CGMP information that it contains.

To the extent the Testing Petition requests that all future digoxin ANDA applicants be required to provide CMC information as outlined in sections 314.50 and 314.94 of FDA regulations and that manufacturers adhere to the CGMP requirements in 21 CFR 210-211, including 21 CFR 211.110, the Petition is granted. To the extent the Testing Petition requests that future ANDA applicants referencing Lanoxin be required to conduct the same dissolution and blend uniformity validation testing that was conducted for the Lanoxin NDA, the Testing Petition is denied.

### C. Bioequivalence Petition

You request that FDA amend the 2008 digoxin guidance to “reflect digoxin’s NTI status.” (Bioequivalence Petition at 3). Specifically, you request that FDA recommend that ANDA applicants for digoxin meet the bioequivalence criteria recommended by the Agency in other guidances containing product-specific recommendations for NTI drugs (i.e., a four-way, fully replicated crossover design in both the fasting and fed states using a referenced-scaled average bioequivalence (RSABE) methodology). In addition, you request that ANDA applicants for

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<sup>60</sup> See guidance for industry, *Questions and Answers on Current Good Manufacturing Practices-Production and Process Controls*, Question #16.

<sup>61</sup> See 2017 digoxin guidance. Product-specific dissolution methods are listed at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>.

<sup>62</sup> See guidance for industry *PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance*.

digoxin be required (1) to demonstrate that PK measures are within a 90 to 111.11 percent CI for both AUC and  $C_{max}$  (instead of the standard 80 to 125 percent interval), and (2) to narrow the drug substance assay range to between 95 and 105 percent (instead of the standard 90 to 105 percent).

## 1. Digoxin is a Narrow Therapeutic Index Drug

Your request for narrower bioequivalence criteria is premised on digoxin being classified as an NTI drug. FDA considers digoxin to be an NTI drug because it exhibits the five general characteristics that FDA uses to assess whether a drug is an NTI drug.<sup>63</sup> First, there is little separation between the therapeutic and toxic doses (or the associated blood/plasma concentrations). Digoxin has a narrow therapeutic range of 0.5 to 2.0 milligrams per milliliter (mg/mL) with the therapeutic index (toxic concentration/effective concentration ratio) estimated at 1.4.<sup>64</sup> Second, the effectiveness of digoxin decreases markedly at sub-therapeutic levels.<sup>65</sup> Additionally, sub-therapeutic digoxin concentrations increase the potential for associated cardiac side effects or other severe side effects. Third, digoxin is subject to routine monitoring of clinical response and serum/plasma concentrations as the standard of care. Fourth, while there are currently no data to estimate the true within-subject variability of digoxin, the within-subject variability of digoxin has been estimated based on derived analysis of variance (ANOVA) root mean square error (RMSE) from two-way crossover bioequivalence studies. The mean (range) RMSE estimates are reported as AUC 21.7 percent (13.3, 32.2) and  $C_{max}$  21 percent (14.3, 26.1).<sup>66</sup> These values should be larger than the actual within-subject variability, because the estimates include potential differences between the test and reference products. We therefore conclude that digoxin has low to medium within-subject variability. Fifth, digoxin doses can be adjusted in very small increments due to the availability of multiple dose strengths. According to product labeling, when digoxin is co-administered with other products that are known to increase exposure to digoxin, the digoxin dose can be adjusted in small increments by 15 percent.<sup>67</sup> This indicates that even small changes (i.e., 15 percent) in digoxin concentration are critical for the desired clinical outcome.

## 2. Bioequivalence Criteria for Digoxin

You urge FDA to amend the 2008 digoxin guidance to incorporate the 2011 Advisory Committee's recommendation that generic applicants establish bioequivalence by conducting fully replicated, four-way crossover fasted and fed studies.

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<sup>63</sup> See L.X. Yu et al.

<sup>64</sup> See Lanoxin (digoxin) tablets labeling, December 1, 2016 available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020405s013lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020405s013lbl.pdf); L.X. Yu et al.; see also digoxin at ClinicalPharmacology.com: <http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=190&sec=monmp>.

<sup>65</sup> Ragab AR et al, "Clinical utility of serum digoxin level in cardiac patients for diagnosis of chronic digitalis toxicity," *Journal of Clinical Toxicology*, 2012, 2(9).

<sup>66</sup> See L.X. Yu et al., at 288.

<sup>67</sup> Lanoxin (digoxin) tablets labeling, December 1, 2016 available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020405s013lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020405s013lbl.pdf)

After carefully considering all of the arguments raised in the Bioequivalence Petition and after reviewing the available literature and scientific information on the subject,<sup>68</sup> we agree that because digoxin is an NTI drug, fully replicated, four-way crossover bioequivalence studies in fasted and fed states are recommended. In addition, as discussed above, the Agency considers the RSABE methodology to be appropriate for digoxin bioequivalence studies. We note, however, that to demonstrate bioequivalence, the studies must meet acceptance criteria for both means and within-subject variability. The Agency’s approach for establishing bioequivalence to digoxin is consistent with the position recommended by the 2011 Advisory Committee, and is consistent with the approach outlined in draft guidances for other NTI drugs.<sup>69</sup> The 2017 digoxin guidance reflects the Agency’s current thinking on bioequivalence study design recommendations for digoxin. To the extent the Bioequivalence Petition requests FDA to adopt for digoxin the 2011 Advisory Committee’s recommendation to use four-way crossover bioequivalence studies for NTI drugs, the request is granted.

### **3. Acceptance Intervals**

The Bioequivalence Petition argues that because Lanoxin is an NTI drug, the bioequivalence CI should be narrowed to a fixed range of 90 to 111.11 percent for both AUC and C<sub>max</sub> and a drug substance potency range of 95 to 105 percent (Petition at 2). To this end, the Bioequivalence Petition urges that we fully adopt the 2011 Advisory Committee’s recommendations on bioequivalence CIs for NTI drugs.

#### **a. AUC and C<sub>max</sub>**

Generally, FDA considers drug products to be bioequivalent when the 90 percent CIs for C<sub>max</sub> and AUC of the test/reference PK parameter ratios fall within an 80 to 125 percent acceptance interval.<sup>70</sup> This approach is based on the assumption that a 20 percent difference between the test and reference products is not clinically significant.<sup>71</sup> However, for NTI drugs where small differences in dose or blood concentration may lead to serious therapeutic failure and/or adverse drug reactions, a 20 percent difference in blood concentration or drug exposure may be unacceptable. The 2010 Advisory Committee voted that the average bioequivalence limits of 80 to 125 percent are not sufficient for NTI drugs. That Advisory Committee also commented that “the requirements for confidence intervals should perhaps be narrower (90 to 111 percent)”<sup>72</sup> and that “replicate studies are important.”<sup>73</sup>

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<sup>68</sup> See L.X. Yu et al., at 286-291.

<sup>69</sup> See guidances containing products specific recommendations for tacrolimus, warfarin sodium, carbamazepine, phenytoin sodium, levothyroxine sodium, and sirolimus. All FDA guidance documents can be found at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/>.

<sup>70</sup> See guidance for industry, *Statistical Approaches to Establishing Bioequivalence* at 2.

<sup>71</sup> Jiang W et al., “A bioequivalence approach for generic narrow therapeutic index drugs: evaluation of the reference-scaled approach and variability comparison criterion,” *The AAPS Journal*, 2015, 17(4):891-901.

<sup>72</sup> For a discussion of the use of replicate studies to establish bioequivalence, see guidance for industry, *Statistical Approaches to Establishing Bioequivalence*.

<sup>73</sup> See 2010 Advisory Committee meeting, <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm209318.htm> (2010).

FDA has considered both the 2010 and 2011 Advisory Committees' recommendations and statements and evaluated various approaches to demonstrating bioequivalence to NTI drugs.<sup>74</sup> These approaches included (1) direct narrowing of average bioequivalence limits and (2) a RSABE approach where bioequivalence limits are scaled based on the RLD's within-subject variability (the bioequivalence limits are capped at 80 to 125 percent) along with within-subject variability comparison. After thoroughly considering both options, we have concluded that the RSABE approach represents the most appropriate approach for establishing bioequivalence of NTI drugs. The Agency has performed simulations supporting the use of reference-scaled approach and variability comparison criteria.<sup>75</sup> These simulations show that the fixed average bioequivalence limits of 90 to 111.11 percent can be too strict for generic drugs with medium within-subject variability. Therefore, we believe that a fixed narrower bioequivalence CI of 90 to 111.11 percent generally is not appropriate for digoxin.

FDA's recommended approach for NTI drugs is to use reference-scaled average bioequivalence limits (capped at the conventional bioequivalence limits of 80 to 125 percent) and to perform variability testing. This approach is described more fully in the 2017 digoxin guidance. Accordingly, the Bioequivalence Petition's request to require a fixed bioequivalence acceptance interval of 90 to 111.11 percent is denied.

#### b. Drug Substance Assay Range

As part of an NDA or ANDA, an applicant must provide CMC information concerning the drug substance and drug product.<sup>76</sup> This information must contain details concerning the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and drug product.<sup>77</sup> Specifications are a "list of tests, references to analytical procedures and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described."<sup>78</sup> In other words, specifications establish a set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. Specifications are one part of a total control strategy designed to ensure product quality and consistency for the drug substance and drug product.

The Agency undertakes a rigorous scientific review of CMC information in all drug product applications and applies appropriate risk-based quality standard principles, including consideration of the drug's therapeutic ratio. Specifically, product quality standards for NTI drugs take into account the unique patient risks that NTI drugs present, as well as the Agency's science and risk-based review. However, a drug's therapeutic ratio is only one of several factors FDA considers.

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<sup>74</sup> For a review of the Agency's evaluation of alternative bioequivalence approaches, see Jiang W et al., "A bioequivalence approach for generic narrow therapeutic index drugs: evaluation of the reference-scaled approach and variability comparison criterion," *The AAPS Journal*, 2015, 17(4):891-901.

<sup>75</sup> Id.

<sup>76</sup> 21 CFR 314.50(d)(1) and 314.94(a)(9)(i).

<sup>77</sup> 21 CFR 314.50(d)(1)(i) and (ii).

<sup>78</sup> See guidance for industry on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Dec. 2000).

The drug substance assay range for the approved digoxin ANDAs and Lanoxin is consistent with the current USP Monograph (USP 38) range of 90 to 105 percent and is consistent with the ranges for other NTI drugs.<sup>79</sup> You have not provided any relevant scientific information to support your position that an assay range of 95 to 105 percent is warranted. Instead, you rely on the recommendations of the 2010 and 2011 Advisory Committees. At this time, FDA has declined to accept the Advisory Committees' recommendation regarding a narrower drug assay range. Any future Agency recommendation regarding drug substance assays for NTI drugs will be communicated in accordance with FDA's good guidance practices.<sup>80</sup> Accordingly, your request to narrow the drug substance assay range to 95 to 105 percent is denied.

#### **4. Orange Book TE Code for Currently Approved Digoxin ANDAs**

You request that FDA determine that approved generic digoxin tablets are not therapeutically equivalent to Lanoxin and therefore should be assigned a TE code of BX in the Orange Book (rather than the current TE code AB).<sup>81</sup> You state that FDA should change the TE rating of these generic drugs to BX because: (1) the design of the bioequivalence studies for approved ANDAs does not meet the 2010 and 2011 Advisory Committees' recommendations for NTI drug bioequivalence study design or acceptance criteria, (2) digoxin has a history of bioavailability, dissolution and content uniformity issues that exacerbate bioequivalence testing, and (3) the 2008 and 2009 recalls of digoxin generics establish that the generic products are not meeting CGMP requirements. (Bioequivalence Petition at 18-19).<sup>82</sup>

Drug products are considered therapeutically equivalent only if they are pharmaceutical equivalents<sup>83</sup> and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.<sup>84</sup> FDA classifies as

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<sup>79</sup> See USP 38/NF 33, through First Supplement (August 1, 2015).

<sup>80</sup> See 21 CFR 10.115.

<sup>81</sup> See Orange Book at xv and xix.

<sup>82</sup> You also made several assertions regarding tablet splitting concerns with digoxin and stated that you intend to revise the labeling for Lanoxin to indicate that tablet splitting is not recommended. (Bioequivalence Petition at 27). We will address those issues, if and when any such labeling revision is submitted. You also referenced the drug substitution policies of certain States and argue that these actions "demonstrate awareness that such substitutions [of NTI drugs] can be harmful to patients." (Bioequivalence Petition at 30-31). As the Orange Book preface notes, "[t]hese evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists..." and "[t]herapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, intended to reduce the cost of drugs to consumers." See Orange Book at iv and x. Therefore, while FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product, individual state substitution policies may differ from these recommendations.

<sup>83</sup> Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration. See Orange Book at vii. Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same, or compendial, or other applicable standards (i.e., strength, quality, purity, or identity). Id.

<sup>84</sup> Id.

therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents; (3) they are bioequivalent in that they do not present a known or potential bioequivalence problem and they meet an acceptable in vitro standard, or if they do present a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with CGMP regulations.<sup>85</sup> As noted above, an “AB” TE code means a drug product is considered to be therapeutically equivalent to the RLD as the drug product meets necessary bioequivalence requirements. A “BX” code means that a drug product is not considered therapeutically equivalent to an RLD because there are insufficient data to determine therapeutic equivalence. “The code BX is assigned to specific drug products for which the data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence.”<sup>86</sup>

You have not provided data demonstrating that any of the currently approved ANDAs that reference Lanoxin as the RLD are not therapeutically equivalent to Lanoxin. You assert that design of the bioequivalence studies that supported some of the currently approved ANDAs do not meet the 2011 Advisory Committee recommendations. As described above, we recommend applicants use the RSABE approach for establishing bioequivalence of NTI drugs but do not accept the Advisory Committees’ recommendations for the direct narrowing of the bioequivalence limits for digoxin. We note that FDA made a determination at the time of approval that the five currently approved ANDAs were bioequivalent and therapeutically equivalent to Lanoxin, and your Petition does not present any new scientific data to demonstrate that these products are not therapeutically equivalent to Lanoxin.

You also refer to certain recalls in 2008 and 2009 as evidence that manufacturers are not meeting appropriate CGMP specifications for digoxin. We agree that meeting CGMP specifications is necessary for all drugs, including NTI drugs. If FDA finds new evidence of a CGMP problem, we will evaluate what, if any, action is needed.

Accordingly, your request to assign a BX TE code to each of the five approved digoxin ANDAs is denied.

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<sup>85</sup> Id.

<sup>86</sup> Id. at xix.

### III. Conclusion

For the reasons explained above, the Exclusivity Petition is dismissed as moot, and the Testing and Bioequivalence Petitions are granted in part and denied in part.

Sincerely,



A handwritten signature in blue ink, appearing to read "Janet Woodcock".

for

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research