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October 21, 2013

VIA HAND DELIVERY
RETURN RECEIPT REQUESTED

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned, as counsel for Covis Pharma Sàrl ("Covis" or "the Company"), submit this petition in five parts (one original plus four copies) under § 505(j)[1] of the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act"), as well as 21 C.F.R. § 10.20, § 10.30, and Part 320, to request that the Commissioner of Food and Drugs require all sponsors of generic versions of Covis' Lanoxin® tablets 0.0625 mg and 0.1875 mg (new drug application ("NDA") 20-405) to conduct and pass all testing that the U.S. Food and Drug Administration ("FDA" or "the Agency") has asked Covis to perform. Specifically, we request that FDA (1) require all sponsors of generic 0.0625 mg and 0.1875 mg strength digoxin tablets relying upon Lanoxin as the reference listed drug ("RLD") to conduct and pass the same validation testing that Covis has conducted at FDA's request – namely, dissolution and blend uniformity testing; and (2) deny any requests from generic drug sponsors to waive these tests for the 0.0625 mg and 0.1875 mg strengths.

A. *Action Requested*

Covis requests that FDA require all abbreviated new drug application ("ANDA") sponsors of 0.0625 mg and 0.1875 mg digoxin tablet dosage strengths that rely upon Covis' Lanoxin tablets as the RLD to conduct and pass the same validation testing that Covis conducted at the request of FDA (dissolution and blend uniformity testing). Covis also asks that FDA deny any requests from generic sponsors to waive these tests for the product.

[1] *Codified at* 21 U.S.C. § 355(j).

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As permitted by the digoxin tablet bioequivalence ("BE") guidance,[2] Covis requested a waiver of testing requirements for the 0.0625 mg and 0.1875 mg Lanoxin tablet dosage strengths through the filing of either an annual report or a changes being effected in thirty days supplement ("CBE-30") to the Lanoxin NDA. FDA may waive certain testing requirements for a lower strength drug that is in the same dosage form and has proportionally similar ingredients as a higher strength drug,[3] as reflected in the digoxin guidance. However, FDA denied the Company's waiver request by requiring submission of a prior approval supplement ("PAS"). FDA also required the submission of dissolution data – even though the 0.0625 mg and 0.1875 mg digoxin tablets are proportionately identical to the marketed 0.125 mg and 0.250 mg strengths (and are indeed part of the same NDA). The FDA inspector who conducted the prior approval inspection after the PAS was filed also instructed Covis to be in full compliance with all blend uniformity testing requirements.

FDA's requirement for a PAS constituted a *de facto* denial of Covis' waiver request. The Agency historically has been, and remains, concerned about digoxin dissolution and blend uniformity as they impact drug product bioavailability ("BA") and potency. Dissolution and blend uniformity testing are integral to drug approval and marketing in general, and essential to narrow therapeutic index ("NTI") drugs such as digoxin in particular. These are critical features of NTI drugs that have a direct impact on patient safety. In the case of Lanoxin tablets, the 0.0625 mg and 0.1875 mg doses have an excipient to active pharmaceutical ingredient ("API") ratio of 800:1 and 490:1, respectively – far in excess of FDA's 5:1 ratio for drugs that may present BE problems[4] and greatly exceeding the United States Pharmacopeia's ("USP's") criteria for content uniformity analysis.[5]

Because digoxin is the quintessential NTI drug[6] (and because Lanoxin has a high excipient to API ratio), it is considered a so-called "bioproblem" drug.[7] FDA historically listed

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[2] FDA, "Guidance on Digoxin" (finalized May 2008), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[3] 21 C.F.R. § 320.22(d); FDA, "Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (March 2003), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf, at 11-12 (hereinafter "BA/BE Guidance").

[4] 21 C.F.R. § 320.33(e)(5).

[5] *See* General Chapter <905> Uniformity of Dosage Units, USP 36/NF 31 (through First Supplement) (official August 1, 2013) (stating that coated or uncoated tablets containing a dose of less than 25 mg or a ratio of drug substance less than 25% must be tested using the content uniformity test); *see also* Digoxin Tablets monograph, USP 36/NF 31 (through First Supplement) (official August 1, 2013) (requiring digoxin tablets to comply with <905>).

[6] *See, e.g.,* Lawrence X. Yu, FDA, "Quality and Bioequivalence Standards for Narrow Therapeutic Index Drugs" (GPhA 2011 Fall Technical Workshop), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM292676.pdf; BA/BE Guidance, at 20.

in its regulations acetyldigitoxin tablets as a bioproblem cardiac glycoside drug for which *in vivo* BA could not be waived.[8] Although this regulation no longer includes a specific list of "bioproblem" drugs,[9] it serves as evidence of FDA's long-standing concerns about BA issues for oral digoxin products. All digoxin ANDA sponsors will inevitably be faced with the same dissolution and blend uniformity issues that Covis as the NDA holder has addressed. These are critical manufacturing issues that are central to the chemistry, manufacturing, and control ("CMC") section of new applications, as well as current good manufacturing practices ("cGMPs") for approved drug products. Therefore, FDA's concerns about dissolution and blend uniformity of digoxin tablet products apply equally to all digoxin sponsors.

FDA has a legal responsibility to treat similarly-situated parties in a similar manner. Because the Agency required Covis to submit dissolution testing (and stated that the Company must be in full compliance with blend uniformity requirements), FDA must also require ANDA sponsors to conduct this same testing and cannot permit waiver of these requirements.

As the RLD NDA holder, Covis is responsible for digoxin pharmacovigilance and for maintaining product labeling. NDA holders generally face a more difficult task with respect to these post-marketing activities than do ANDA holders due to the fragmentation of the market following generic drug approval. The fact that digoxin is an NTI drug and Lanoxin has a high excipient to API ratio only adds to this burden because of the high impact on patient safety. Therefore, Covis has a vested interest in ensuring that all generic digoxin products meet the same contemporary manufacturing standards that FDA has required of the Company. ANDA sponsors should not be permitted to waive them as a matter of due process and equity.

Covis respectfully requests that FDA take the following actions with respect to the 0.0625 mg and 0.1875 mg strengths of Lanoxin tablets:

(1) Require all sponsors of generic 0.0625 mg and 0.1875 mg strength digoxin tablets relying upon Lanoxin as the RLD to conduct and pass the same validation testing that Covis has conducted at the Agency's request – namely, dissolution and blend uniformity testing; and

(2) Deny any requests from generic drug sponsors to waive these tests for the 0.0625 mg and 0.1875 mg strengths.[10]

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[7] 21 C.F.R. § 320.33(c), (e)(5); BA/BE Guidance, at 11.

[8] 42 Fed. Reg. 1638, 1649 (January 7, 1977) (issuing in new regulations (21 C.F.R. § 320.22(c)) a list of drug products for which a waiver of *in vivo* BA of a solid oral dosage form will not be granted; the list included "acetyldigitoxin tablets" as a cardiac glycoside).

[9] 54 Fed. Reg. 28872, 28911-28912 (July 10, 1989); 57 Fed. Reg. 17950, 17974-17976 (April 28, 1992).

[10] As explained herein and in our companion Citizen Petition, NDA 20-405 included six dosage strengths. Two strengths have been marketed since NDA approval (0.125 mg and 0.250 mg), while Covis has only recently decided to bring two other strengths (0.0625 mg and 0.1875 mg) to market for the first time. The remaining two strengths in NDA 20-405 (0.375 mg and 0.500 mg) have never been marketed. Although this petition refers primarily to the 0.0625 mg and 0.1875 mg strengths, Covis is not foreclosing the applicability of the arguments presented in this

The bases for these requests are established below.

B. *Statement of Grounds*

I. FACTUAL BACKGROUND

Digoxin is a pre-1938 drug that was marketed without an NDA and was "Grandfathered" under the 1938 FFDCA. Despite this long marketing history, FDA has historically had concerns about digoxin's potency and BA, which can pose serious health risks for cardiac patients as a result of the drug's narrow therapeutic margin.[11] Therefore, in 1970, FDA established a batch certification program for digoxin tablets. FDA subsequently determined that the drug could not be considered generally recognized as safe and effective ("GRAS/E"), and all digoxin products for oral use required approved drug applications.[12]

FDA approved the Lanoxin tablets NDA 20-405 on September 30, 1997. However, although the approved NDA includes six dosage strengths (0.0625 mg, 0.125 mg, 0.1875 mg, 0.250 mg, 0.375 mg, and 0.500 mg), only the 0.125 mg and 0.250 mg strengths have ever been manufactured and marketed. The 0.125 mg and 0.250 mg strengths have been manufactured since the 1970s at the historical Wellcome manufacturing site in Greenville, NC[13] and, since the 1997 NDA approval, have been approved to be manufactured at the alternate historical Glaxo manufacturing site in Zebulon, NC.[14]

Based upon these facts and the NDA 20-405 administrative record, we contend in our companion Citizen Petition[15] that FDA did not fully approve four of the six dosage strengths listed in the approval letter (0.0625 mg, 0.1875 mg, 0.375 mg, and 0.500 mg). Notably, FDA never reviewed or approved the labeling for these four never-marketed strengths. Furthermore, before Covis could begin manufacturing and marketing the 0.0625 mg and 0.1875 mg strengths, FDA required a PAS, draft labeling, CMC dissolution data, and a prior approval inspection. Furthermore, the FDA inspector directed Covis to be in full compliance with all blend uniformity

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petition to the 0.375 mg and 0.500 mg strengths at some point in the future. However, at this time, Covis only makes these arguments with respect to the 0.0625 mg and 0.1875 mg tablets.

[11] 39 Fed. Reg. 2471, 2472 (January 22, 1974).

[12] 39 Fed. Reg. 2471, 2471 (January 22, 1974).

[13] The Greenville facility is now owned and operated by DSM Pharmaceuticals, Inc., the Lanoxin tablets contract manufacturer.

[14] According to the 1997 approval letter, "[w]e note that you have decided not to market the 62.5, 187.5, 375, and 500 mcg [microgram] tablet strengths at this time. Only the 125 mcg and 250 mcg tablet strengths are approved to be manufactured at your Zebulon, North Carolina facility." Letter from Raymond Lipicky, FDA, to Elizabeth Nies, Glaxo Wellcome Research and Development (September 30, 1997), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020405ap_Lanoxin_apltr.pdf.

[15] Citizen Petition filed by Edward John Allera and Barbara Binzak Blumenfeld (October 21, 2013).

requirements. Covis' arguments regarding the approval status of the four never-marketed strengths and the impact of this status on the running of three-year exclusivity are presented in the companion petition.

In December 2011, Covis acquired full commercial rights to Lanoxin in the United States and Puerto Rico from GlaxoSmithKline. According to the agreement, Lanoxin tablets continue to be manufactured and supplied in accord with the approved NDA. Covis is listed as the NDA holder for Lanoxin in both the Orange Book[16] and in the Agency's database, "Drugs@FDA."[17]

The 0.0625 mg and 0.1875 mg tablets are now manufactured at the historical Wellcome facility in Greenville, NC, now owned and operated by DSM Pharmaceuticals, Inc. Besides dosage strength, the only differences between the two marketed and two new products are color and labeling. In light of these minor differences, and believing that only an annual report or, at most, a CBE-30 would be necessary, Covis initiated conversations with FDA in April 2012 about bringing the two new strengths to market with a waiver of testing requirements.[18] FDA informed the Company, however, that a PAS was necessary because FDA had never reviewed the labeling for the new strengths and those strengths had never been manufactured. This response was a *de facto* denial of Covis' waiver request. In August 2012, Covis submitted a PAS with the required draft package insert and draft container labels. FDA acknowledged and accepted the PAS.

In January 2013, FDA conducted a prior approval inspection of the Greenville, NC facility. One of the inspector's central concerns as expressed during the inspection was the thorough blending of ingredients in the 0.0625 mg and 0.1875 mg tablets. The inspector directed Covis to be in full compliance with blend uniformity testing requirements, and Covis has in fact performed all necessary blend uniformity testing.

Following the prior approval inspection, the Agency issued Covis a Complete Response letter requesting, among other things, dissolution data for the two alternate strengths. Covis agreed to all items in the letter, and submitted the requested dissolution data and additional draft labeling. Covis received final approval of the PAS, and therefore approval to market the 0.0625 mg and 0.1875 mg dosage strength tablets, on October 17, 2013.

II. THE RELATIONSHIP BETWEEN NTI DRUGS, CGMPS, AND CMC

cGMPs are essential for the manufacturing of safe and effective drug product. A core subset of cGMPs – namely, CMC – must be submitted to the Agency as part of any NDA or ANDA. Within these CMC core requirements, dissolution and blend uniformity data are critical to approval and manufacture of NTI drugs such as digoxin. Without these data and information, a digoxin product cannot be safely approved, manufactured, or marketed, and FDA's request that

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[16] *Available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[17] *Available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[18] Electronic mail message from Todd Phillips, Beckloff Associates, Inc. (U.S. agent for Covis Pharma Sàrl) to Alexis Childers, FDA (April 23, 2012).

Covis submit dissolution data and ensure compliance with blend uniformity testing is illustrative of this fact. The Agency must therefore require that ANDA sponsors also perform this critical testing before the Agency approves those drugs, as these manufacturing issues remain the same regardless of the applicant or application type. FDA did not waive these testing requirements for Covis, and the Agency must therefore not do so for ANDA sponsors.

A. NTI Drugs

NTI drugs are those that have a small difference between an effective and a lethal dose, making approval and dosing of these drugs inherently challenging. FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (hereinafter "Advisory Committee") addressed numerous aspects of NTI drugs in 2010 and 2011, including how to define an NTI drug and how BE should be established. The Advisory Committee recommended defining NTI drugs as those in which a small difference in blood concentration or dose may lead to serious therapeutic failures and/or adverse drug reactions. These drugs are characterized by (1) steep dose/response curves for safety and efficacy in the usual dosing interval, or small concentration differences between effective and toxic doses; (2) a need for therapeutic monitoring based on pharmacokinetic or pharmacodynamic measures; and (3) small intra-subject variability.[19] FDA recognizes that digoxin clearly meets these NTI criteria,[20] and this fact is not disputed.

The Advisory Committee also considered BE requirements for NTI drugs in light of these important characteristics, and recommended the following measures: (1) narrowing the traditional BE range for the 90% confidence interval of the geometric mean ratio between test and reference products for both area under the curve and maximum concentration from 80-125% to 90-111.11%; (2) using a fully-replicated crossover BE study design; (3) adopting a reference-scaled average BE approach; and (4) narrowing API potency from 90-110% to 95.0-105.0%.[21]

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[19] *See generally* briefing information for the July 26, 2011 Advisory Committee meeting, *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM263465.pdf; Lawrence Yu, FDA, "Approaches to Demonstrate Bioequivalence of Critical Dose Drugs" (slides presented at April 13, 2010 Advisory Committee meeting), *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM209319.pdf. These criteria are similar to the ones in FDA's regulations for drugs with a "narrow therapeutic ratio" (less than two-fold difference between the median lethal dose and the median effective dose, or less than two-fold difference in minimum effective and minimum toxic concentrations in the blood; and careful dosage titration and patient monitoring is required for safe and effective drug use). 21 C.F.R. § 320.33(c).

[20] Briefing information for the July 26, 2011 Advisory Committee meeting, *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM263465.pdf, at 10-12; FDA, "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (March 2003), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf, at 20.

[21] *See generally* Advisory Committee Summary Minutes (July 26, 2011), *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforP

Although any generic drug must be bioequivalent to the RLD, FDA and the Advisory Committee have recognized the particular importance of these issues to NTI drugs such as digoxin.

B. cGMPs and CMC

Compliance with cGMPs is essential not only for approved drug products, but also for approval of new applications and FDA therapeutic equivalence evaluation decisions. cGMPs cover many aspects of drug production,[22] including personnel; facilities; equipment; records and reports; components, containers, and closures; production and processing controls; and packaging and labeling controls. From a historical point of view, FDA has noted that "[i]n the early 1990s, if an ANDA was approvable, except for an unsatisfactory current good manufacturing practice (CGMP) inspection for the primary API supplier, the application would not be approved until the CGMP issues were resolved."[23] FDA still takes this position today, and new drug and generic drug approvals depend upon a review of the manufacturer's compliance with cGMPs.[24] Failure to meet cGMPs can result in withholding approval of pending NDAs.[25]

cGMPs are also an integral part of FDA's therapeutic equivalence rating system for generic drugs. To be listed as therapeutically equivalent to an RLD in the Orange Book, a drug product must meet several criteria, including being manufactured in accordance with cGMP regulations and having identical content uniformity, disintegration times, and/or dissolution rates when applicable.[26]

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harmaceuticalScienceandClinicalPharmacology/UCM272111.pdf; *see also* FDA, Advisory Committee Transcript (July 26, 2011), *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM272112.pdf, at 245 (Dr. Yu, FDA: "[L]ast year, you already proposed a bioequivalence limit of 90 to 111.111 percent. We thought it was a good approach. So, therefore, we didn't ask you for additional deliberation and the vote here.").

[22] 21 C.F.R. Part 211.

[23] FDA, "Guidance for Industry – Alternate Source of the Active Pharmaceutical Ingredient in Pending ANDAs" (December 2000), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072853.pdf, at 1.

[24] FDA, "Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations" (last updated September 7, 2012), *available at* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm.

[25] *See, e.g.,* FDA warning letter to Daniel Movens, Caraco Pharmaceutical Laboratories, Ltd. (October 31, 2008), *available at* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048080.htm (until cGMP violations are corrected, "FDA may withhold...approval of pending new drug applications" that list as a manufacturer a deviating facility).

[26] Orange Book (33rd ed.) (2013), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf, at vii; 21 C.F.R. § 320.1(c).

Within cGMPs there is a core subset of CMC requirements that must be met for any drug application prior to approval. Both NDAs[27] and ANDAs[28] must contain specific CMC information about the drug *substance*, including process controls used for manufacture and packaging, as well as specifications used to ensure the identity, strength, quality, and purity of the drug substance. Applications must also contain CMC drug *product* data and information describing (1) the components used to manufacture the product and the components' specifications; (2) the manufacturing and packaging procedures and in-process controls; (3) the container closure system; and (4) the specifications necessary to ensure the identity, strength, quality, purity, and potency of the product. All of these CMC elements for new applications form part of the required cGMPs for approved drug products.

Data about cGMPs in general, and CMC in particular, are necessary for the approval of an application. If this information is lacking, then the Agency may not approve the application and the drug product(s) may not be marketed, even if other elements of cGMPs are satisfied.

C. Dissolution and Blend Uniformity

Dissolution and blend uniformity are critical to NTI drugs such as digoxin, as well as drugs with high excipient to API ratios such as Lanoxin tablets. Dissolution and blend uniformity form part of the required CMC data in an application,[29] which in turn form part of the required cGMP data necessary for FDA to approve an application.

FDA recognized the complexity of ensuring BA and potency from proper blend uniformity and dissolution methods in 1974 when the Agency first addressed the problems of oral digoxin product uniformity:

> Because of the narrow margin between therapeutic and toxic levels of digoxin and the potential for serious risk to cardiac patients using digoxin products which may vary in bioavailability, the Commissioner has determined that immediate actions must be taken to assure better uniformity of all digoxin products for oral use.[30]

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[27] FFDCA § 505(b)(1)(D), *codified at* 21 U.S.C. § 355(b)(1)(D); 21 C.F.R. § 314.50(d)(1).

[28] FFDCA § 505(j)(2)(A)(vi), *codified at* 21 U.S.C. § 355(j)(2)(A)(vi) [cross-referencing statutory requirements for NDAs]; 21 C.F.R. § 314.94(a)(9)(i) [cross-referencing the CMC requirements for NDAs at 21 C.F.R. § 314.50(d)(1)].

[29] The CMC section of an application must include tests, analytical procedures, and acceptance criteria for dissolution rate for a drug product. 21 C.F.R. § 314.50(d)(1)(ii)(a) [NDA requirements]; 21 C.F.R. § 314.94(a)(9)(i) [ANDA regulations cross-referencing CMC requirements for NDAs at 21 C.F.R. § 314.50(d)(1)]. Similarly, the CMC section must include in-process controls, which includes in-process testing requirements to ensure the adequacy of mixing for uniformity and homogeneity. 21 C.F.R. § 314.50(d)(1)(ii)(a) [NDA requirements]; 21 C.F.R. § 314.94(a)(9)(i) [ANDA regulations cross-referencing CMC requirements for NDAs at 21 C.F.R. § 314.50(d)(1)]; 21 C.F.R. § 211.110(a)(3) [setting forth requirement for adequacy of mixing].

[30] 39 Fed. Reg. 2471, 2472 (January 22, 1974).

One such action included establishing procedures to monitor the formulation of digoxin products to ensure that any reformulated product met all *in vitro* test requirements and had uniform batch-to-batch BA.[31]

In the ensuing decades, digoxin production and testing methods evolved. As a result, the Agency reassessed its labeling and other testing requirements. For example, FDA listed the cardiac glycoside "acetyldigitoxin tablets" as a drug for which FDA shall not waive *in vivo* BA testing of a solid oral dosage form.[32] The Agency later removed this list for a number of reasons, including subsequent statutory changes rendering the regulation unnecessary and the fact that the list of bioproblem drugs had not been updated in several years.[33] Nonetheless, this historical FDA regulation serves as evidence that the Agency has long had concerns about the BA of some drug products, including digoxin.

As a further example of FDA's reassessment of digoxin requirements, the Agency recognized the need to adjust the labeled dosages for oral digoxin as BA improved. If the labeling was not revised, then existing dosages – when applied to a more contemporary product with better BA – could result in overdosage.[34] The Agency also recognized that there was often a clinically-significant variation in BA between digoxin batches produced by different manufacturers, as well as between batches made by a single manufacturer. Because of this data – and because there appeared to be a "general correlation" between BA and dissolution – the USP digoxin monograph was later amended to include a dissolution requirement.[35] The historical oral digoxin marketing conditions regulation (21 C.F.R. § 310.500) was also revoked in part because, as a result of amending the USP digoxin monograph, "[t]he dissolution requirements specified in § 310.500 for digoxin tablets are now obsolete."[36] This evolving digoxin dissolution standard highlights the criticality of this information to any digoxin application, whether an NDA or an ANDA.

FDA recognized that, based upon the administrative record of NDA 20-405, the application was lacking critical contemporary dissolution data for the 0.0625 mg and 0.1875 mg dosage strengths. Furthermore, the FDA inspector verbally instructed Covis to be in compliance with blend uniformity testing requirements. These are critical CMC data necessary for NDA approval. Without such contemporary data, the Agency did not have the information necessary

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[31] 39 Fed. Reg. 2471, 2472 (January 22, 1974).

[32] 42 Fed. Reg. 1638, 1649 (January 7, 1977).

[33] 54 Fed. Reg. 28872, 28911 (July 10, 1989).

[34] 41 Fed. Reg. 17755, 17756 (April 28, 1976).

[35] 65 Fed. Reg. 70573, 70573 (November 24, 2000); 65 Fed. Reg. 70538, 70539 (November 24, 2000). FDA's dissolution methods database for "digoxin tablets" says to "Refer to USP." FDA, "Dissolution Methods," *available at* http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm. The USP digoxin tablets monograph contains the current digoxin dissolution method. USP 36/NF 31, First Supplement (official August 1, 2013).

[36] 65 Fed. Reg. 70538, 70539 (November 24, 2000).

to fully approve the 0.0625 mg and 0.1875 mg dosage strengths. These facts illustrate that these two strengths were not fully approved in 1997. Therefore, the data that Covis supplied in 2012 and 2013 was an essential *pre*-approval requirement that cannot be waived.

II. ARGUMENTS IN SUPPORT OF PETITION

As an NTI drug and one with a high excipient to API ratio (*i.e.*, a bioproblem drug), manufacturing issues are central to the safety and efficacy of any digoxin tablet product. Patients always depend upon accurate API content in a drug product; however, the issue is even more acute when dosing an NTI drug that can have a life-or-death effect on a patient. As we have discussed, cGMPs, CMC, dissolution, and blend uniformity are integrally related aspects of FDA's ability to approve a drug application and assign a therapeutic equivalence rating, as well as a manufacturer's ability to make the drug product. The Agency did not permit Covis to waive any testing requirements, instead requiring the Company to submit a PAS and dissolution testing, and directing the Company to be in compliance with blend uniformity testing requirements before introducing the two new dosage strengths to the market. Therefore, FDA must treat ANDA digoxin sponsors similarly and not grant testing waivers for generic digoxin tablets. Only this approach will ensure that safe and effective generic digoxin tablets are approved and available to all patients, regardless of whether they take the Covis drug or a generic drug.

A. All 0.0625 mg and 0.1875 mg Digoxin Tablet Generic Drug Sponsors Must Conduct Appropriate Dissolution and Blend Uniformity Testing

As we have shown, FDA has historical concerns about digoxin dissolution and blend uniformity as they impact BA and product potency. These concerns led to FDA's voluntary certification program in the early 1970's,[37] as well as FDA's conclusion that oral digoxin products are not GRAS/E and require approved applications.[38] Indeed, in 1974, FDA determined that there was "sufficient evidence to invoke authority" under FFDCA § 505(j) to "fully investigate this question to demonstrate the bioavailability of these products and to correlate bioavailability in vivo with the dissolution rate of digoxin tablets in vivo."[39]

When the API level in a drug product is extremely low, BA/BE, potency, dissolution, and blend uniformity are especially critical drug features. By regulation, the Agency has held out both NTI drugs[40] and drugs with a greater than 5:1 excipient to API ratio[41] as those drugs for which FDA should recognize the potential BE problems. Digoxin is the quintessential example

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[37] 39 Fed. Reg. 2471 (January 22, 1974).

[38] 39 Fed. Reg. 2471, 2472 (January 22, 1974).

[39] 39 Fed. Reg. 2471, 2472 (January 22, 1974).

[40] 21 C.F.R. § 320.33(c).

[41] 21 C.F.R. § 320.33(e)(5).

of an NTI drug,[42] and the excipient to API ratio in the 0.0625 mg and 0.1875 mg Lanoxin tablets is two orders of magnitude greater than the 5:1 ratio the Agency has set as a benchmark for BE concerns. Likewise, the USP General Chapter on dosage unit uniformity states that tablets with a drug dose of less than 25 mg or a ratio of drug substance less than 25% should follow the content uniformity test to ensure uniformity of dosage units.[43] The 0.0625 mg and 0.1875 mg Lanoxin tablets clearly meet these criteria as well. These facts highlight the critical nature of these characteristics and manufacturing elements of oral digoxin products.

From a safety perspective, no difference exists between a digoxin product approved under an NDA or an ANDA. All digoxin products, regardless of the sponsor or type of application, must have the dissolution and blend uniformity data necessary for FDA approval and subsequent marketing. Therefore, it is just as important for a generic sponsor to be able to demonstrate the safety of its generic digoxin drug through appropriate validation testing as it is for Covis. As a result, generic sponsors cannot be permitted to waive these requirements.

B. FDA Must Not Waive Testing Requirements for Generic Digoxin Tablets

By denying Covis' request to waive testing requirements for two new strengths of digoxin tablets, FDA *de facto* determined that a waiver was not appropriate. Although FDA permits waivers in certain circumstances, the unique characteristics of and concomitant safety concerns about a particular drug product may cause FDA to deny a waiver request. The Agency can determine the kind and amount of data necessary for a drug to meet the FFDCA standards.[44]

In this case, FDA determined that dissolution testing and blend uniformity data were important prior to approval and marketing of the two new strengths. As a result, FDA cannot conclude that the information is not just as important for a generic 0.0625 mg or 0.1875 mg tablet. The Agency cannot therefore waive the testing requirements for other sponsors when it determined that a waiver was inappropriate for Covis. Significant, negative public health consequences could arise for those patients taking generic digoxin tablets if generic sponsors are permitted to bypass critical testing and FDA review of those tests.

As discussed, dissolution and blend uniformity testing are integrally related to both cGMP and CMC. This data is central to application approval, FDA's therapeutic equivalence evaluations and rating decisions, and continued safe product manufacturing. If the dissolution

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[42] *See, e.g.*, Lawrence X. Yu, FDA, "Quality and Bioequivalence Standards for Narrow Therapeutic Index Drugs" (GPhA 2011 Fall Technical Workshop), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM292676.pdf; BA/BE Guidance, at 20.

[43] General Chapter <905> Uniformity of Dosage Units, USP 36/NF 31 (through First Supplement) (official August 1, 2013); Digoxin Tablets monograph, USP 36/NF 31 (through First Supplement) (official August 1, 2013) (requiring digoxin tablets to comply with <905>).

[44] 21 C.F.R. § 314.105(c) ("[t]hus, FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.").

and blend uniformity characteristics cannot be assured for a digoxin tablet product under an NDA without appropriate testing, then they cannot be assured for a generic product under an ANDA without undergoing the same testing. Furthermore, in the case of blend uniformity, FDA has stated in draft guidance that applicants should not submit a supplement requesting the deletion of blend uniformity analysis when testing from commercial batches if that blend uniformity test is used to ensure cGMP compliance.[45] Although this draft guidance has since been withdrawn due to its scope and specific methodologies,[46] the principles tying blend uniformity to CMC and cGMP remain relevant and applicable today. Therefore, there is no rational scientific basis for the Agency to treat digoxin tablets approved in an NDA and an ANDA differently. Doing so has the potential to cause damaging results.

On April 25, 2008, Actavis Totowa LLC initiated a Class I (*i.e.,* patient-level) recall[47] of its Digitek® brand digoxin tablets (0.125 mg and 0.250 mg) on a nationwide basis. The stated reason for the voluntary recall was the possible double-thickness of digoxin tablets, which could result in digitalis toxicity in some patients due to receiving double the labeled dose.[48] In May 2008, FDA published a digoxin tablet BE guidance that currently permits waivers for the 0.125 mg strength tablets.[49] It is speculation to suggest that the timing of the guidance release and the recall were related, or to question whether it was wise for FDA to permit waivers in the midst of a digoxin recall. At a minimum, the Agency was well-aware of the potential manufacturing issues related to an NTI drug such as digoxin. Of note, Mylan (the ANDA holder) had been granted a waiver on the 0.125 mg dosage strength in the original 1999 NDA approval.[50] The Mylan ANDA is now on the Orange Book's discontinued list.[51]

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[45] FDA, "Draft Guidance for Industry – ANDAs: Blend Uniformity Analysis" (August 1999), *available at* FDA docket 99D-2635, at 3.

[46] 67 Fed. Reg. 35120 (May 17, 2002).

[47] 21 C.F.R. § 7.3(m)(1).

[48] The products were distributed by Mylan under the "Bertek" label and by UDL Laboratories under the "UDL" label. FDA, Recall – Firm Press Release, "Actavis Totowa (formerly Amide Pharmaceutical, Inc.) Recalls All Lots of Bertek and UDL Laboratories Digitek® (digoxin tablets, USP) as Precaution" (April 25, 2008), *available at* http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2008/ucm112435.htm; FDA, MedWatch Safety Information, "Digitek (digoxin tablets, USP)" (posted April 28, 2008), *available at* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm084304.htm; FDA, Enforcement Report 08-32 (August 13, 2008) (stating that Actavis Totowa LLC was recalling its two digoxin tablet strengths due to superpotency). UDL Laboratories initiated its own Class I recall of its products. FDA, Enforcement Report 08-34 (August 27, 2008).

[49] FDA, "Guidance on Digoxin" (finalized May 2008), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[50] *See* FDA approval package for ANDA 40-282, "Review of an Amendment: Bioequivalent Study and Dissolution Testing" (submission date February 22, 1999), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/40282_Digoxin.pdf, at 11. The ANDA was originally approved on December 23, 1999 for Amide Pharmaceutical, Inc.

[51] FDA electronic Orange Book, *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

Following publication of the digoxin tablet BE guidance, Caraco Pharmaceutical Laboratories, Ltd. announced a voluntary Class I recall of all of its 0.125 mg and 0.250 mg digoxin tablets due to size variances that could deliver more or less drug to patients.[52] It is not known if FDA permitted Caraco to waive testing requirements in its ANDA, which was approved on January 31, 2003.[53] Nonetheless, digoxin tablet manufacturing issues have continued to present tangible health risks to patients.

These two digoxin tablet recalls support the critical nature of manufacturing issues to NTI drugs such as digoxin. In addition to the Mylan ANDA, at least one other ANDA for the 0.125 mg and 0.250 mg strengths that was approved before publication of the guidance in May 2008 was permitted to waive testing requirements[54]; in the case of two other ANDAs (one approved prior to[55] and one approved after[56] the digoxin tablet BE guidance), no public FDA documents address whether or not a waiver had been granted. Regardless of whether or not waivers were or *should have* been permitted for the 0.125 mg or 0.250 mg dosage strengths in the past, waivers cannot be granted for 0.0625 mg and 0.1875 mg generic digoxin tablet products that rely upon Covis' drug as the RLD. FDA required Covis to submit CMC dissolution data for the 0.0625 mg and 0.1875 mg strengths, and directed the Company to have the necessary blend uniformity data. Covis was not allowed to waive these requirements. The Agency similarly cannot permit generic sponsors to waive these requirements, as the manufacturing concerns will be no different for generic sponsors than they were for Covis.

C. FDA Must Hold NDA and ANDA Sponsors to the Same Testing Standards for Digoxin Tablets

In many instances, both pioneer and generic drug sponsors must meet the same pre-approval and post-approval requirements. For example, much of the content of NDAs and ANDAs is identical, including the need to supply CMC data and information.[57] All sponsors

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[52] FDA, Recall – Firm Press Release, "Caraco Pharmaceutical Laboratories, Ltd. Announces a Nationwide Voluntary Recall of All Lots of Digoxin Tablets Due to Size Variability" (March 31, 2009), *available at* http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2009/ucm128443.htm.

[53] ANDA 76-363. There is no approval documentation listed on FDA's Drugs@FDA webpage. This ANDA is also listed as discontinued in FDA's electronic Orange Book.

[54] *See, e.g.,* bioequivalence review for ANDA 76-268 (approved July 26, 2002), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/anda/2002/076268_digoxin_toc.cfm
("The formulation for the 0.125 mg tablet is proportionally identical to that of the 0.25 mg tablet, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 0.125 mg tablet of the test product is granted.").

[55] ANDA 77-002, approved October 30, 2007.

[56] ANDA 78-556, approved July 20, 2009.

[57] FFDCA § 505(b)(1)(D), *codified at* 21 U.S.C. § 355(b)(1)(D) [NDA requirements]; 21 C.F.R. § 314.50(d)(1) [NDA requirements]; FFDCA § 505(j)(2)(A)(vi), *codified at* 21 U.S.C. § 355(j)(2)(A)(vi) [ANDA requirements cross-referencing statutory requirements for NDAs]; 21 C.F.R. § 314.94(a)(9)(i) [ANDA requirements cross-referencing the CMC requirements for NDAs at 21 C.F.R. § 314.50(d)(1)].

must also register their establishments and list their products,[58] and maintain product adverse event reporting and other pharmacovigilance measures.[59] Furthermore, all manufacturing facilities are subject to inspection,[60] and all manufacturers must submit annual reports to their applications.[61] Although FDA permits testing waivers in certain cases, appropriate testing to ensure product safety remains even more essential in the case of NTI drugs and drugs with high excipient to API ratios. In the case of digoxin tablets, FDA must treat NDA and ANDA sponsors in a similar manner by requiring the same essential dissolution and blend uniformity testing. FDA *de facto* denied Covis' waiver request, and the Agency cannot therefore grant waivers to generic sponsors.

Under the Administrative Procedure Act ("APA"),[62] a federal court must set aside and hold unlawful any federal agency actions, findings, or conclusions found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.[63] Courts have held that an administrative agency action will be considered arbitrary and capricious and thus unlawful if the administrative agency fails to treat similarly-situated parties in the same manner.[64] An agency can only depart from precedent when it provides a "legitimate reason" for the deviation.[65]

Because FDA's concerns about digoxin tablet dissolution and blend uniformity cannot be restricted to only NDA sponsors, the Agency must treat both Covis and any ANDA sponsor of a

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[58] FFDCA § 510(b), (c), (j), *codified at* 21 U.S.C. § 360(b), (c), (j); 21 C.F.R. § 207.20(a).

[59] FFDCA § 505(k), *codified at* 21 U.S.C. § 355(k); 21 C.F.R. § 314.80; 21 C.F.R. § 314.81.

[60] FFDCA § 704, *codified at* 21 U.S.C. § 374.

[61] FFDCA § 505(e)(5)(A), *codified at* 21 U.S.C. § 355(e)(5)(A); FFDCA § 505(k), *codified at* 21 U.S.C. § 355(k); 21 C.F.R. § 314.81(b)(2)

[62] 60 Stat. 237 (June 11, 1946).

[63] 5 U.S.C. § 706(2)(A).

[64] Bracco Diagnostics, Inc. v. Shalala, 963 F.Supp. 20, 27-28 (D.D.C. 1997) (*citing* Allergan v. Shalala, 6 Food and Drug Rep. 389, 391 (No. 94-1223) (D.D.C. 1994)) ("[i]f an agency treats similarly situated parties differently, its action is arbitrary and capricious and in violation of the APA.").

[65] Bracco Diagnostics, Inc. v. Shalala, 963 F.Supp. 20, 27-28 (D.D.C. 1997) (*citing* Allergan v. Shalala, 6 Food and Drug Rep. 389, 391 (No. 94-1223) (D.D.C. 1994)); Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983) ("[t]he scope of review under the 'arbitrary and capricious' standard is narrow and a court is not to substitute its judgment for that of the agency. Nevertheless, the agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'"); IRS v. Federal Labor Relations Authority, 963 F.2d 429, 434 (D.C.Cir. 1992) ("'[d]ivergence from agency precedent demands an explanation';...where no reasonable explanation is provided, [the courts] have no choice but to vacate the decision under review" (internal citation omitted)); Airmark Corp. v. FAA, 758 F.2d 685, 691-92 (D.C.Cir. 1985) ("[w]e recognize, of course, that 'an agency is free to alter its past rulings and practices . . . it is equally settled that an agency must provide a reasoned explanation for any failure to adhere to its own precedents'" (internal citations omitted)).

digoxin tablet product that relies upon Covis' drug as the RLD in the same manner. To depart from this precedent, FDA is required to provide a sufficient reason. As established above, there is no scientific basis for FDA to allow ANDA sponsors to waive the testing requirements that Covis has been required to meet when the scientific and medical concerns remain the same for all digoxin tablets, regardless of the sponsor or type of application. This is the case particularly in light of FDA's longstanding stated concern about the dissolution, blend uniformity, BA, and potency concerns about digoxin products, as well as the recent recalls of certain generic versions of digoxin tablets due to manufacturing issues. As a result, no waivers can be granted for generic sponsors of 0.0625 mg and 0.1875 mg digoxin tablets.

D. As the NDA Holder, Covis Maintains Responsibility for its Labeling in the Marketplace

As the Lanoxin NDA holder, Covis has ongoing responsibilities to collect, monitor, and report adverse events associated with Lanoxin to FDA. As typically occurs after approval of a first generic drug, approval of generic 0.0625 mg and 0.1875 mg digoxin tablets will lead to market fragmentation and adverse event reporting responsibilities for multiple companies. Despite this fact, Covis will remain liable for updating its labeling based upon these reported adverse events, and generic sponsors will rely on these changes for their own labeling. As a result, Covis has a vested interest in ensuring that FDA enforces appropriate BE requirements for digoxin. Allowing a generic sponsor to manufacture and market its product after waiving critical testing and validation parameters would introduce drug variability into generic digoxin products that would put patients at risk. It would also put Covis at risk in the marketplace for liability resulting from adverse events due to brand-to-generic substitution.

1. Adverse Event Reporting, Pharmacovigilance Requirements, and Labeling Changes

An NDA holder is required to review all adverse drug experience information that it has or obtains from any foreign or domestic source. This information may come from commercial product marketing, postmarketing clinical investigations or epidemiological/surveillance studies, literature reports, and unpublished scientific papers.[66] Although ANDA holders are similarly required to review and report adverse drug experience information,[67] such reporting following generic drug approval reflects a different reality.

First, adverse event reports may not distinguish which product (pioneer or generic) caused the adverse event. Second, NDA holders may receive reports of adverse events that occurred with generic products, although the pioneer company is still obliged to report the event to FDA. Third, the reporting of adverse events by multiple companies results in a fractured drug safety profile because multiple sources are responsible for reporting (and multiple identical reports could be submitted). Finally, the NDA holder has no control over whether a physician writes a prescription for the brand or generic drug product, or whether a pharmacist dispenses a

[66] 21 C.F.R. § 314.80(b).

[67] 21 C.F.R. § 314.98(a).

generic drug in place of the brand product.[68] All of these factors make it difficult for an NDA holder to re-create a clear picture of the adverse event profile of the drug and to detect any resulting safety signals following generic drug approval.

FDA recognizes that a drug's safety profile will evolve after approval and use in the general population when more patient variables are introduced.[69] Pharmacovigilance constitutes the scientific and data-gathering activities that relate to the detection, assessment, and understanding of adverse events, and includes the identification and evaluation of safety signals.[70] The Agency has identified numerous steps that a sponsor can and should take to identify safety signals that evolve from the adverse event reports and the related information that the company regularly reviews.[71] Statistical significance between the cause and reported effect does not have to be established, and safety risks can depend upon many factors.[72] Based upon these new or changing safety signals, manufacturers must amend a drug's labeling to account for new product uses or warnings by filing a CBE supplement.[73] FDA also has the statutory authority to require an NDA sponsor to make labeling changes for safety reasons of which the Agency becomes aware.[74]

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[68] Courts recognize that all fifty states have some generic drug substitution law. *See, e.g.,* Wyeth, Inc. v. Weeks, 2013 WL 135753 (Ala. 2013), at *15 ("[i]t is recognized that generic substitutions are allowed in all 50 states.").

[69] FDA, "The Clinical Impact of Adverse Event Reporting" (October 1996), *available at* http://www.fda.gov/downloads/Safety/MedWatch/UCM168505.pdf, at 1-2; FDA, "Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" (March 2005), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071696.pdf, at 3 (hereinafter "Good Pharmacovigilance Guidance").

[70] Good Pharmacovigilance Guidance, at 4.

[71] *See generally* Good Pharmacovigilance Guidance.

[72] For example, strength of the association; the temporal relationship between the event and the drug use; consistency of findings; evidence of dose/response; biologic plausibility; relationship between disease and seriousness of the event; potential to decrease the risk in the population; feasibility of further studies; and degree of benefit the drug provides relative to other treatments. Matrixx Initiatives, Inc. v. Siracusano, 131 S.Ct. 1309, 1320 (2011) (*citing* FDA Good Pharmacovigilance Guidance). Matrixx was an investor class action suit in which investors alleged Matrixx violated the federal securities laws by not disclosing materially relevant information about one of the company's products, Zicam. In its *amicus* brief, the United States stated that "[a]s petitioners acknowledge, FDA does not apply any single metric for determining when additional inquiry or action is necessary, and it certainly does not insist upon 'statistical significance.'" Brief for the United States as *Amicus Curiae* Supporting Respondents (November 12, 2010).

[73] 21 C.F.R. § 314.70(c)(6)(iii)(A).

[74] FFDCA § 505(o)(4), *codified at* 21 U.S.C. § 355(o)(4); FDA, "Guidance for Industry: Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act" (July 2013), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf (hereinafter "505(o)(4) Guidance"). When a change is made to an NDA that is also the RLD, the Agency will notify ANDA holders of the changes, and the ANDA holders should then submit a CBE to incorporate those changes. 505(o)(4) Guidance, at 11.

Both pioneer and generic drug sponsors are required to collect, review, and submit to FDA adverse events, and to engage in pharmacovigilance efforts to identify safety signals warranting labeling changes. However, in practice the vast majority of these responsibilities lie with the NDA holder, particularly after several recent U.S. Supreme Court decisions, as described below.

2. NDA Holders Retain Responsibility for Updating Drug Labeling

As Wyeth v. Levine[75] confirmed, NDA manufacturers retain responsibility for their product labeling at all times. Wyeth marketed an anti-nausea brand drug which, if improperly administered, can result in irreversible gangrene. The drug labeling warned of this gangrene danger, but the plaintiff argued that the labeling failed to tell clinicians to use one safer method instead of an alternative, more risky method.[76] The Court noted that manufacturers have the means to make a change to a drug's labeling through the CBE process if the manufacturer is adding or strengthening a warning, contraindication, precaution, or adverse reaction.[77]

In holding that state failure-to-warn laws were not preempted by federal law, the Court clarified the responsibilities of manufacturers with respect to their product labeling:

> Wyeth suggests that the FDA, rather than the manufacturer, bears primary responsibility for drug labeling. Yet through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.[78]

Wyeth did not address the responsibilities of generic drug companies with respect to maintaining their labeling. The Court did so, however, two years later in Pliva.

Pliva v. Mensing,[79] which consolidated two cases, held that federal law pre-empted state law requiring generic companies to change their drugs' labeling because it was impossible to comply simultaneously with both state and federal laws. Pliva involved lawsuits by two consumers who were prescribed a drug which, when used for long periods of time, can cause a severe neurological disorder. The plaintiffs were prescribed the brand name drug, but their pharmacists filled the prescriptions with generic versions of the drug.[80] The Court noted that the

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[75] 555 U.S. 555 (2009).

[76] Wyeth, 555 U.S. at 559-560.

[77] Wyeth, 555 U.S. at 568.

[78] Wyeth, 555 U.S. at 570-571.

[79] 131 S.Ct. 2567 (2011).

[80] Pliva, 131 S.Ct. at 2572-2573.

brand company must ensure the accuracy and adequacy of its labeling, while the generic company must ensure its warning label is the same as the brand's label.[81] Because generic drug labels must be identical to brand drug labels, FDA interprets its CBE regulation as applying to generics only when the generic company changes a label to match the pioneer or FDA tells the generic company to make a labeling change: "[t]he FDA argues that CBE changes unilaterally made to strengthen a generic drug's warning label would violate the statutes and regulations requiring a generic drug's label to match its brand-name counterpart's."[82] Therefore, the generic companies could not use the CBE process to strengthen the generic drugs' labeling absent the pioneer company's efforts to do so.[83] Thus, the responsibility belongs to Covis.

The Supreme Court's most recent decision in Mutual Pharmaceutical Co., Inc. v. Bartlett[84] follows the Wyeth and Pliva line of reasoning. Mutual involved a patient who received a generic version of a nonsteroidal anti-inflammatory pain reliever. The patient suffered extremely debilitating adverse effects, the severity of which was not communicated on the drug labeling at the time the patient took the drug. The patient sued the generic drug manufacturer in New Hampshire state court on a design-defect claim,[85] and the District Court awarded damages and the Court of Appeals affirmed. The Supreme Court, however, reversed the decision. The majority held that New Hampshire's requirement that a product not be "unreasonably dangerous" was preempted by federal law that expressly prohibits generic drug manufacturers from making unilateral labeling changes. The Court stated that New Hampshire's "unreasonably dangerous" standard can be satisfied by either changing a drug's design or changing the labeling. In this case, Mutual could not change the drug's design, and it could not change the labeling as discussed in Pliva.

Based upon this case law, Covis must continue to review, assess, and report adverse events after any generic digoxin drug product is approved. Covis must also continue to engage in its pharmacovigilance efforts, reporting safety signals to FDA and making appropriate labeling changes as required. This case law also establishes that any generic digoxin sponsor – although required to review, report, and assess adverse events – cannot, under Pliva or Mutual,

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[81] Pliva, 131 S.Ct. at 2574 (*citing* 21 U.S.C. § 355(b)(1) and Wyeth, 555 U.S. at 570-571 for the proposition that pioneer companies must ensure the accuracy and adequacy of its labeling; and 21 U.S.C. § 355(j)(1)(A)(v), 21 U.S.C. § 355(j)(4)(G), 21 C.F.R. § 314.98(a)(8), and 21 C.F.R. § 314.127(a)(7) for the proposition that a generic drug's labeling must be the same as the brand drug's labeling).

[82] Pliva, 131 S.Ct. at 2575.

[83] The Court acknowledged the plaintiffs' argument that the manufacturers cannot prove impossibility preemption because they did not try to work with FDA to strengthen the labeling. The Court analyzed the Supremacy Clause and determined, however, that pre-emption does not require speculation about how parties *could* work together to possibly reconcile conflicting state and federal law duties. Pliva, 131 S.Ct. at 2578-2581.

[84] 133 S.Ct. 2466 (2013).

[85] The plaintiff also sued on a failure-to-warn claim, but the District Court dismissed that claim after her physician admitted that he had not read the drug box labeling or package insert.

make unilateral labeling changes to strengthen any warnings.[86] Covis will therefore continue to bear the responsibility for maintaining adequate and accurate Lanoxin labeling – even if Lanoxin is no longer the market leader after generic drug approval of a new dosage strength. This requirement also puts Covis at a heightened risk for product liability cases involving a generic digoxin drug product.[87]

For these reasons, FDA must ensure, as a matter of science and due process, that all digoxin products (the seminal example of an NTI drug) meet the highest and same standards of CMC and cGMP. Therefore, there is no basis for waiving this testing requirement for any applicant.

3. *Some Courts have Determined that Brand Drug Manufacturers Can be Held Liable for Injuries Due to Patient's Use of a Generic Drug*

After the U.S. Supreme Court's decisions in Wyeth and Pliva, the Supreme Court of Alabama determined that brand drug manufacturers can be held liable for a plaintiff's injuries under state product liability law – even when the patient used the generic and not the brand drug.

In Wyeth, Inc. v. Weeks,[88] the Supreme Court of Alabama addressed a question certified to it by the U.S. District Court for the Middle District of Alabama, answering that the brand manufacturer of a drug can be liable for fraud or misrepresentation based on the brand drug's labeling statements even if the patient was injured by the generic version of the brand drug. In Weeks, the plaintiff was injured after long-term use of a drug that caused a severe neurological disorder. The plaintiff admitted that he had not taken any brand name drug product, but sued several manufacturers of brand name drug on the theory that the brand drug manufacturers did not warn the plaintiff's physician of the dangers of long-term drug use.[89] According to the Court:

> In the context of inadequate warnings by the brand-name manufacturer placed on a prescription drug manufactured by a generic-drug manufacturer, it is not fundamentally unfair to hold the brand-name manufacturer liable for warnings on

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[86] The Pliva Court also rejected plaintiffs' argument that the generic companies could have issued "Dear Doctor" letters to provide additional warnings about the drug product. FDA considers "Dear Doctor" letters to constitute labeling; therefore, such a letter containing new information would be inconsistent with the approved labeling, and would imply that the branded and the generic products were not therapeutically equivalent. Pliva, 131 S.Ct. at 2576.

[87] *See, e.g.,* Foster v. American Home Products Corp., 29 F.3d 165 (4th Cir. 1994) (holding in a pre-Wyeth and pre-Pliva case that, under Maryland law, a brand name manufacturer had no duty of care in its own drug representations when patients were given the generic equivalent of the branded drug); *but see, e.g.,* Conte v. Wyeth, Inc., 168 Cal.App.4th 89 (Cal. App. 1 Dist. 2008) (holding in another pre-Wyeth and pre-Pliva case that, in declining to follow Foster, a branded company has a duty to use due care in formulating product warnings and this duty extends to patients who receive generic versions of the drug; the court noted that it departed from the majority of cases that have considered the issue).

[88] 2013 WL 135753 (Ala. 2013).

[89] Weeks, 2013 WL 135753 at *1.

> a product it did not produce because the manufacturing process is irrelevant to misrepresentation theories based, not on manufacturing defects in the product itself, but on information and warning deficiencies, when those alleged misrepresentations were drafted by the brand-name manufacturer and merely repeated by the generic manufacturer.[90]

The Weeks court also addressed existing case law across the country on this issue, noting a divergence of opinions not only within the State of Alabama,[91] but also among several other jurisdictions as well.[92]

These various cases (some of which were decided post-Wyeth and Pliva) signal the fact that a brand drug sponsor such as Covis can be held liable, at least in some jurisdictions, for injuries caused by the patient's use of a generic digoxin tablet product. In light of all of the known information about digoxin, particularly its NTI drug status and the high excipient to API ratio in Lanoxin, Covis urges FDA to ensure that ANDA sponsors meet the same testing and validation standards that Covis was required to meet prior to marketing. The Agency should not permit ANDA sponsors to bypass these standards by waiving any testing requirements. Granting waivers or otherwise not requiring ANDA sponsors of digoxin tablet products to ensure the dissolution and blend uniformity of their drugs will place Covis at substantial market risk, including product liability for injuries sustained that are not a result of using Lanoxin. It will also place patients at risk because of the serious medical ramifications associated with dosing this drug product.

III. CONCLUSION

Covis requests that FDA require all generic sponsors of 0.0625 mg and 0.1875 mg dosage strengths that use Lanoxin as the RLD to perform the same validation testing that the Agency required Covis to perform. Covis requested a waiver of testing requirements through filing either a CBE-30 or annual report to the Lanoxin NDA, but FDA instead required submission of a PAS. Covis was required to submit contemporary dissolution data, and the FDA inspector also instructed Covis to be in compliance with appropriate blend uniformity testing requirements (the Company has such supporting data). This Agency response amounted to a *de facto* denial of Covis' waiver request. This CMC data is critical to any 0.0625 mg and 0.1875 mg digoxin drug product, regardless of whether the application is an NDA or an ANDA. FDA must therefore deny any waiver requests from generic drug sponsors, just as the Agency denied Covis' waiver request.

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[90] Weeks, 2013 WL 135753 at *19.

[91] Weeks, 2013 WL 135753 at *1 (citing the cases that have created an "intrastate split" in Alabama).

[92] The Weeks Court compared Foster v. American Home Products Corp. with Conte v. Wyeth, *supra* note 87. The Weeks Court also discussed Kellogg v. Wyeth, 762 F.Supp.2d 694 (D.Vt. 2010) (holding that a brand manufacturer has a duty to use reasonable care to avoid injury to patients who are prescribed the generic drug). All of these cases are discussed in Weeks, 2013 WL 135753 at *11-*14.

Covis therefore respectfully requests that FDA take the following actions with respect to the 0.0625 mg and 0.1875 mg strengths of Lanoxin tablets:

(1) Require all sponsors of generic 0.0625 mg and 0.1875 mg strength digoxin tablets relying upon Lanoxin as the RLD to conduct and pass the same validation testing that Covis has conducted at the Agency's request – namely, dissolution and blend uniformity testing; and

(2) Deny any requests from generic drug sponsors to waive these tests for the 0.0625 mg and 0.1875 mg strengths.

If you require further information regarding these issues, please contact Edward Allera, Barbara Binzak Blumenfeld, or Tina Hu at the contact information listed below.

C. *Environmental Impact*

A categorical exclusion is claimed in accordance with 21 C.F.R. § 25.31(a). Therefore, an environmental impact analysis is not required.

D. *Economic Impact*

An economic impact statement will be provided upon request.

E. *Certification*

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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