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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

On behalf of Covis Pharma Sàrl ("Covis" or "the Company"), the undersigned 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") and 21 C.F.R. § 10.20, § 10.30, and § 314.108 to request that the Commissioner of Food and Drugs confirm that Covis is entitled to three-year exclusivity for two never fully approved and never marketed dosage strengths of digoxin (Lanoxin® tablets) under new drug application ("NDA") 20-405 following approval of required chemistry, manufacturing, and control ("CMC") information and product labeling by the U.S. Food and Drug Administration ("FDA" or "the Agency").

FDA's complete administrative record for NDA 20-405 shows that the Agency only fully approved two of the six dosage strengths in that NDA. This fact is confirmed by the Agency's requirement that Covis submit a prior approval supplement ("PAS"), CMC dissolution data for the new strengths (0.0625 mg and 0.1875 mg), and draft labeling for the new strengths, and that FDA conduct a prior approval inspection. The FDA inspector also directed Covis to be in compliance with all blend uniformity testing requirements.

Final approval means that FDA has completed all of the required actions under the statute and regulations and the approved product can be marketed – but for the ministerial submission of final printed labeling ("FPL") or advertising and marketing materials, which are *post*-approval requirements. In the case of the two new strengths, Covis was required to do much more than simply submit FPL. It had to submit draft labeling and other critical *pre*-approval data for these dosages.

[1] *Codified at* 21 U.S.C. § 355(j).

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FDA determined that the original sponsor of NDA 20-405 was entitled to three years of marketing exclusivity for all six dosage strengths. However, without labeling and without the other contemporary CMC data that Covis had to perform, four of the strengths in that NDA could not have been fully approved and therefore not marketed. As a result, the exclusivity to which all six strengths were entitled did not run for these four strengths. Because Covis has only now supplied all the required data and information to FDA that permitted the Agency to complete the approval, Covis is entitled to a period of three-year exclusivity for the two never-marketed strengths (0.0625 mg and 0.1875 mg) that began running upon PAS approval.

Accordingly, we request that FDA confirm the following: (1) the Agency did not fully approve the 0.0625 mg and 0.1875 mg tablets on September 30, 1997 in NDA 20-405 because of: (a) the language in the administrative record; (b) the recently-required submission of draft labeling and CMC dissolution data for the two new dosage strengths; (c) the recently-required submission of a PAS; (d) the recent prior approval inspection; and (e) the FDA inspector's direction that Covis be in full compliance with all blend uniformity testing requirements; (2) three-year exclusivity was awarded but never began running for these two dosage strengths that have never been marketed under NDA 20-405, despite their listing in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book");[2] and (3) Covis is therefore entitled to a period of three-year marketing exclusivity for the 0.0625 mg and 0.1875 mg dosage strength products that began running upon PAS approval.[3]

A. *Action Requested*

Although FDA approved NDA 20-405 in 1997, four of the six strengths in that NDA have never been fully approved and therefore never marketed under the NDA. At the time of NDA approval, FDA determined that all six dosage strengths in NDA 20-405 should be awarded three-year exclusivity. However, the Orange Book erroneously implies that the exclusivity period expired for all six strengths.

In the present case, the awarded exclusivity did not begin running for the four never-marketed strengths. These four strengths could not have been fully approved in 1997 because FDA would not permit Covis to market the two new strengths before the Agency reviewed and approved new data and information. Covis has *only now* submitted a PAS with necessary labeling – an approval requirement for an NDA or an abbreviated new drug application ("ANDA"). Furthermore, Covis has *only now* submitted contemporary CMC dissolution data,

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

[3] The two strengths that have been marketed since NDA approval are 0.125 mg and 0.250 mg. Covis wants to begin marketing the 0.0625 mg and 0.1875 mg strengths, also part of NDA 20-405. The remaining two strengths that have never been marketed under NDA 20-405 are 0.375 mg and 0.500 mg. The 0.0625 mg and 0.1875 mg digoxin tablet dosage strengths are the only two products at issue in this Citizen Petition, and we primarily refer to them alone. However, Covis reserves the right to make these and other arguments in the future regarding the 0.375 mg and 0.500 mg strengths at such time as Covis determines that it wishes to begin marketing those two strengths as well.

another pre-approval requirement. These elements of approval, coupled with the prior approval inspection of Covis' contract manufacturer and FDA's direction that Covis comply with all appropriate blend uniformity testing requirements, confirm that this data and information are critical *pre*-approval and not post-approval requirements. This conclusion is confirmed by the Agency's administrative record for this NDA, particularly FDA's 1997 approval letter and the 2012-2013 communications between FDA and Covis regarding the new strengths.

Covis is therefore entitled to a period of three-year marketing exclusivity that began running upon approval of the PAS for these two new strengths. Only this outcome addresses the novel issue at stake here, to wit, the running of a three-year exclusivity period if a drug product is not fully approved and therefore not marketed. Furthermore, Covis' requested redress is consistent with the regulatory history of digoxin and the administrative record for NDA 20-405, the three-year exclusivity statutory and regulatory provisions, and the pre-approval requirements for an NDA.

Covis therefore respectfully requests that FDA take the following actions with respect to the Company's 0.0625 mg and 0.1875 mg strength digoxin tablets under NDA 20-405:

(1) Confirm that the Agency did not fully approve the 0.0625 mg and 0.1875 mg tablets on September 30, 1997 in NDA 20-405 because of: (a) the language in the administrative record; (b) the recently-required submission of draft labeling and CMC dissolution data for the two new dosage strengths; (c) the recently-required submission of a PAS; (d) the recent prior approval inspection; and (e) the FDA inspector's direction that Covis be in full compliance with all blend uniformity testing requirements;

(2) Confirm that three-year exclusivity was awarded but never began running for these two dosage strengths that have never been marketed under NDA 20-405, despite their listing in FDA's Orange Book; and

(3) Confirm that Covis is therefore entitled to a period of three-year marketing exclusivity for the 0.0625 mg and 0.1875 mg dosage strength products that began running upon PAS approval.

The bases for our requests are set forth more fully below.

B. *Statement of Grounds*

I. BACKGROUND

A. Digoxin Regulatory History

Digoxin is one of several cardiac glycosides (referred to collectively as "digitalis") used to treat a number of cardiovascular conditions. Lanoxin tablets are indicated for (1) treatment of mild to moderate heart failure in adults; (2) the control of ventricular response rate in adults with chronic atrial fibrillation; and (3) increased myocardial contractility in children with heart failure. Digoxin is a narrow therapeutic index ("NTI") drug because therapeutic levels are only slightly lower than toxic levels. As a result, special care and consideration is required for determining the appropriate dosage, such as body weight, age, use of other medications, and renal function.[4] Safe use of the product requires monitoring for the signs and symptoms of both toxicity and clinical response, and dose adjustments based on toxicity, efficacy, and blood levels.[5]

Digoxin is a pre-1938 drug. According to the original holder of NDA 20-405 (Burroughs Wellcome), the company had manufactured and marketed a digoxin product in the U.S. since 1934[6]; indeed, "digitalis" is listed in The Dispensatory of the United States of America as far back as 1918.[7] Despite its long marketing history, FDA remains concerned about the potency and content uniformity of oral digoxin products, particularly because of digoxin's NTI drug status. In April 1970, FDA initiated a digoxin testing program on marketed tablet products to test them for potency. The outcome of this program was extensive product recalls. Later the same year, the Agency established a voluntary batch certification program. Under this program, manufacturers agreed that FDA could test batches of digoxin tablets to determine if they met the United States Pharmacopeia ("USP") content uniformity and potency requirements before being released.[8]

Because of these concerns, FDA determined that digoxin could not be considered generally recognized as safe and effective ("GRAS/E"). All digoxin products for oral use were

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[4] Lanoxin tablets labeling (rev. August 2012), at 2.

[5] Lanoxin tablets labeling (rev. August 2012), at 5.

[6] 65 Fed. Reg. 70573, 70573 (November 24, 2000).

[7] The Dispensatory of the United States of America, 20th ed. (Philadelphia and London: J.B. Lippincott Company, 1918), at 403-410.

[8] 39 Fed. Reg. 2471 (January 22, 1974).

therefore new drugs that required approved applications.[9] FDA issued a regulation outlining the conditions for marketing, including labeling language.[10] However, the Agency later stayed the time for the submission of ANDAs[11] until after labeling issues were further considered by FDA's Cardio-Renal Advisory Committee.[12] Public comments about the new drug status of oral digoxin products further delayed implementation of the ANDA filing requirements, but led to revised labeling for these products under 21 C.F.R. § 310.500.[13]

Twenty-four years later in November 2000 (with the stay on ANDA submissions still in effect[14]), FDA issued two notices – one reaffirming the new drug status of digoxin and outlining the conditions for marketing,[15] and one proposing to revoke the historical conditions for marketing established as part of the batch certification process.[16] The Agency took these actions because, as described immediately below, FDA had already approved NDA 20-405 for Lanoxin tablets in 1997. As a result, approval of ANDAs was possible and the need for batch certification was eliminated. Moreover, the dissolution requirements outlined in 21 C.F.R. § 310.500 became obsolete in light of the inclusion of dissolution requirements in the USP monograph for digoxin tablets.[17] In June 2002, FDA therefore revoked the historical regulation setting forth conditions for digoxin marketing.[18]

B. Lanoxin (NDA 20-405) History

The history of the Lanoxin NDA approval is central to the exclusivity arguments in this Citizen Petition. Therefore, we discuss this history at some length to illustrate why FDA never fully approved four of the six dosage strengths (including 0.0625 mg and 0.1875 mg) when it approved NDA 20-405 in 1997.

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[9] 39 Fed. Reg. 2471, 2472 (January 22, 1974) (proposed 21 C.F.R. § 130.51). FDA later extended the time for filing applications. 39 Fed. Reg. 9184 (March 8, 1974).

[10] 39 Fed. Reg. 2471, 2475 (January 22, 1974) (21 C.F.R. § 130.51).

[11] 39 Fed. Reg. 9184 (March 8, 1974).

[12] 39 Fed. Reg. 9219 (March 8, 1974).

[13] 41 Fed. Reg. 17755 (April 28, 1976) (now 21 C.F.R. § 310.500, formerly 21 C.F.R. § 130.51); 41 Fed. Reg. 43135 (September 30, 1976).

[14] 65 Fed. Reg. 70573, 70574 (November 24, 2000).

[15] 65 Fed. Reg. 70573 (November 24, 2000).

[16] 65 Fed. Reg. 70538 (November 24, 2000).

[17] 65 Fed. Reg. 70538, 70538-70539 (November 24, 2000).

[18] 67 Fed. Reg. 42992 (June 26, 2002).

1. *Original NDA Approval*

Burroughs Wellcome had manufactured digoxin 0.125 mg and 0.250 mg dosage strength tablets for decades, and since the 1970s at its facility in Greenville, NC. Despite this long manufacturing history, FDA had never approved an NDA for digoxin tablets. Therefore, FDA urged Burroughs Wellcome to submit an NDA, which it did in September 1993. This NDA contained published studies as well as two original clinical trials. The Agency presented digoxin labeling issues to the Cardiovascular and Renal Drugs Advisory Committee, which reviewed the labeling and also recommended that the results of a government-funded study on digoxin be submitted to the NDA and incorporated into the labeling.[19]

As submitted, the NDA included all six dosage strengths, and Burroughs Wellcome requested three years of market exclusivity.[20] In May 1997, the sponsor (then Glaxo Wellcome) supplied additional supplementary/updating information regarding the original exclusivity request "in response to the Division's invitation" (Division of Cardio-Renal Drug Products).[21] The company explained that its clinical trials met the criteria for three-year exclusivity because they were new clinical investigations conducted by or for the applicant that are essential to approval.

Glaxo's acquisition of Burroughs Wellcome in 1995 – *prior to approval* of the Lanoxin tablets NDA – added an additional level of complexity to the NDA review. The historical Glaxo manufacturing facility was located in Zebulon, NC, only a short distance from the historical Burroughs Wellcome manufacturing facility in Greenville, NC. As a result, the newly-formed Glaxo Wellcome submitted an amendment to its NDA to add the Zebulon facility as an alternate manufacturing site. As the company noted:

> LANOXIN® (digoxin) Tablets is currently marketed in the 0.125 and 0.25 mg tablet strengths. Upon completion of process validation in June 1997, production of LANOXIN® (digoxin) Tablets (*0.125 mg tablet strength only*) will be immediately transferred from Greenville, NC to Zebulon, NC. Following the approval of NDA 20-405, *the 0.25 mg strength* of LANOXIN® (digoxin) will also be transferred (emphasis added).[22]

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[19] 65 Fed. Reg. 70538, 70538 (November 24, 2000); 65 Fed. Reg. 70573, 70574 (November 24, 2000).

[20] Letter from Elizabeth Nies, Glaxo Wellcome, to Raymond Lipicky, FDA (May 5, 1997), at Attachment 1.

[21] Letter from Elizabeth Nies, Glaxo Wellcome, to Raymond Lipicky, FDA (May 5, 1997).

[22] Glaxo Wellcome amendment to NDA 20-405, submitted to Raymond Lipicky, FDA (April 30, 1997).

Glaxo Wellcome provided data and information to demonstrate that digoxin tablets made at the Zebulon facility were equivalent to those made at the Greenville facility.[23]

The administrative record also reveals that Glaxo Wellcome had no intention of marketing four of the six strengths upon NDA approval, and FDA was well-aware of this fact. In February 1996, FDA wrote to Glaxo Wellcome that it had completed its review of the NDA with draft labeling, but the draft labeling was not in agreement with the 1994 approvable letter. FDA therefore requested that the FPL conform to the Agency's suggestions. FDA noted the following in its February 1996 letter:

> As you prepare final printed labeling, we ask that you consider marketing the 0.0625 mg dosage form of digoxin immediately upon approval and not wait until some future date to make that dosage form available. The other dosage forms that you wish to delay making available (0.1875 mg, 0.375 mg) seem reasonable to exclude.

FDA's rationale for its request was that the draft labeling indicated that patients over 70 years with impaired renal function should start at the 0.0625 mg/day dose.[24]

However, Glaxo Wellcome rejected FDA's request to market the 0.0625 mg strength immediately upon NDA approval. The company pointed out that FDA had essentially misread the draft labeling: the 0.0625 mg dosage strength is appropriate for patients with *marked* renal impairment, but patients over 70 years or those with *impaired* renal function should initiate treatment with a 0.125 mg dose. Therefore, Glaxo Wellcome stated to FDA that it "believe[d] that very few patients fall into this category and this is the basis for our decision to withhold marketing of the 0.0625 mg tablet at this time."[25]

Although draft labeling for all six dosage strengths does appear in the NDA administrative record, Glaxo Wellcome's decision to market only two strengths upon approval (0.125 mg and 0.250 mg) translated to the submission of additional revised draft labeling <u>for only those two strengths</u> in an NDA amendment on September 17, 1997. In that communication, Glaxo Wellcome stated the following:

> We trust that these changes accurately reflect the agreements made with the Division, and that we can move to approval of this pending NDA. *We understand that approval will include the six tablet strengths presented in the original NDA,*

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[23] Glaxo Wellcome amendment to NDA 20-405, submitted to Raymond Lipicky, FDA (April 30, 1997). Note that Glaxo Wellcome later sold the Greenville facility. It is today owned by DSM Pharmaceuticals, Inc. – the contract manufacturer that currently makes Lanoxin tablets for Covis.

[24] Letter from Raymond Lipicky, FDA, to Elizabeth Nies, Glaxo Wellcome (February 14, 1996).

[25] Letter from Elizabeth Nies, Glaxo Wellcome, to Raymond Lipicky, FDA (April 7, 1997).

> *even though the attached labeling includes only 2 strengths.* In addition, we have the agreement of the Division to a 90-day transition period from the date of NDA approval to allow a smooth change-over from the currently marketed Lanoxin Tablet product/labeling to the NDA approved product/labeling (emphasis added).[26]

It is clear that Glaxo Wellcome only intended to market two Lanoxin tablet dosage strengths upon approval, and that the Agency was well-aware of this fact and accepted it.

On September 30, 1997, FDA approved the Lanoxin NDA, and the approval letter specifically references all six dosage strengths. The approval letter does not mention the Greenville, NC manufacturing facility; however, with respect to the Zebulon facility, it stated the following:

> [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 (emphasis added).[27]

The Agency listed all six dosage strengths in the Orange Book.[28] The Orange Book indicated that all six products were awarded three-year exclusivity that ostensibly expired on September 30, 2000.[29]

In light of all of these facts, FDA's 1997 approval letter is not clear about the approval or manufacturing status of each of the six digoxin tablet strengths in the NDA. However, the administrative record discussed above reveals two important facts. First, only two strengths (0.125 mg and 0.250 mg) were historically manufactured in Greenville without an NDA, and only these two strengths were "approved to be manufactured" under the NDA in Zebulon as an alternate facility. Second, FDA only fully approved two of the six dosage strengths (0.125 mg and 0.250 mg) in the NDA because FDA did not review any draft labeling for the other four strengths immediately before approval. Despite Glaxo Wellcome's "understanding" that all six strengths would be approved, the fact remains that the complete draft labeling submitted only covered two dosage strengths, not all six.

This factual background is critical to Covis' argument that four of the dosage strengths in the NDA were not fully approved in 1997 and, as a result, the exclusivity that was awarded to

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[26] Letter from Elizabeth Nies, Glaxo Wellcome, to Raymond Lipicky, FDA (September 15, 1997).

[27] 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.

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

[29] Orange Book (20th ed.) (2000).

those particular strengths could not have run. This conclusion is confirmed by FDA's recent requirements and requests of Covis in conjunction with bringing the 0.0625 mg and 0.1875 mg dosages to market, as discussed below.

2. *Marketing the 0.0625 mg and 0.1875 mg Dosage Strengths*

In December 2011, Covis acquired the full commercial rights for Lanoxin in the U.S. and Puerto Rico from GlaxoSmithKline. Today, Covis still manufactures the only two dosage strengths that have ever been marketed under this NDA: 0.125 mg and 0.250 mg. Three generic drug sponsors currently have ANDAs for 0.125 mg and 0.250 mg digoxin oral tablets.[30] Two additional ANDAs were approved but are now listed as discontinued in the Orange Book.[31]

Covis has now begun manufacturing the 0.0625 mg and 0.1875 mg dosage strengths. The Company sought a waiver of testing requirements because the two new strengths are proportionately identical to the two marketed strengths (the only differences being tablet color and labeling). The Company initially believed that it could file either an annual report or a changes being effected in thirty days ("CBE-30") supplement to the NDA because any required data would fall within standard post-approval cGMP requirements and not be pre-approval requirements. Covis initiated conversations with FDA in April 2012 to discuss the required regulatory filing and to seek a waiver of any additional testing requirements.[32]

To Covis' surprise, FDA instead required the Company to file a PAS. FDA's requirement is not only a *de facto* denial of Covis' waiver request, but shows that FDA did not consider these two new strengths to be fully approved in 1997. The Agency required the PAS because, as the administrative record shows and as discussed above, FDA did not review and approve complete draft labeling for the 0.0625 mg and 0.1875 mg strengths at the time of NDA approval, and because these two dosages had never been commercially manufactured. Covis submitted a PAS in August 2012 with the required draft package insert and draft container labels, which FDA accepted. Approved draft labeling is a requirement for an approved application.

In January 2013, FDA conducted a prior approval inspection of the Lanoxin tablets contract manufacturer. During this inspection, the inspector raised concerns about the blend uniformity of these two new dosage strengths, and instructed Covis to be in compliance with all blend uniformity testing requirements. Indeed, the excipient to active pharmaceutical ingredient

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[30] ANDA 78-556 (Impax Labs; approved July 20, 2009); ANDA 76-268 (Jerome Stevens Pharmaceuticals, Inc.; approved July 26, 2002); ANDA 77-002 (West Ward, approved October 30, 2007).

[31] ANDA 76-363 (Caraco; approved January 31, 2003); ANDA 40-282 (Mylan; approved December 23, 1999).

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

("API") ratio is 800:1 for the 0.0625 mg strength and 490:1 for the 0.1875 mg strength, making digoxin the quintessential NTI drug.[33]

Following the inspection, FDA issued a Complete Response letter in February 2013. To support approval of the two never-marketed dosage strengths, FDA requested dissolution profiles with f2 statistical testing comparing both new strengths to the two existing strengths using the approved dissolution method. The Agency also required the Company to submit draft labeling.[34] Covis submitted additional draft labeling as well as dissolution data in April 2013. FDA approved the PAS, thereby allowing Covis to begin manufacturing and marketing the 0.0625 mg and 0.1875 mg dosage strengths, on October 17, 2013.

C. Preapproval Requirements

An NDA or an ANDA sponsor must meet all applicable requirements before FDA will approve the application. These requirements include, among others, submission of CMC data, submission of draft labeling, and completion of a prior approval inspection when warranted. If any one of these requirements is not met, then FDA cannot approve the application. As the administrative record here shows, the original NDA sponsor did not have a full approval for four of the six dosages in the Lanoxin tablets NDA, including the newly-approved 0.0625 mg and 0.1875 mg tablets, because these elements were not reviewed by the Agency.

1. *CMC Data, Including Dissolution and Blend Uniformity Testing, is Necessary for Approval*

Current good manufacturing practices ("cGMPs") are essential for the production 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. Furthermore, within this core of CMC requirements, dissolution and blend uniformity data are critical for NTI drugs such as digoxin. All of these requirements are integrally related and essential for both product approval and manufacturing. Without these data and information, a drug product cannot be approved or marketed. FDA's request for CMC dissolution data in the Complete Response letter is, therefore, illustrative of the fact that the Agency did not grant full approval of these non-marketed dosage strengths in 1997. Furthermore, the FDA inspector's statement that Covis must be in compliance with all

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[33] *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; 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.

[34] Letter from Norman Stockbridge, FDA, to Aziza Johnson, Covis Pharma Sàrl (February 28, 2013).

appropriate blend uniformity testing requirements demonstrates the critical nature of this data to drug manufacturing.

cGMPs cover many aspects of drug production,[35] including personnel; facilities; equipment; reports and records; controls for components, containers, and closures; controls for production and processing; and controls for packaging and labeling. Compliance with cGMPs is essential not only for approved drug products, but also for approval of new applications and FDA therapeutic equivalence evaluation decisions. To be listed as therapeutically equivalent to a reference listed drug ("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.[36]

FDA requires that both NDAs[37] and ANDAs[38] contain specific CMC information about a drug substance and a drug product.[39] For drug *substances*, this information includes process controls used for manufacturing and packaging, as well as specifications used to ensure the identity, strength, quality, and purity of the drug substance. For drug *products*, sponsors must provide data and information that describes (1) the components (and the components' specifications) used to manufacture the product; (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 pre-approval cGMP requirements.

Also central to CMC data is dissolution and blend uniformity testing. FDA recognized the complexity of ensuring bioavailability ("BA") and potency from proper dissolution and blend uniformity 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

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[35] 21 C.F.R. Part 211.

[36] 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).

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

[38] 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)].

[39] 21 C.F.R. § 314.105(c).

> vary in bioavailability, the Commissioner has determined that immediate actions must be taken to assure better uniformity of all digoxin products for oral use.[40]

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.[41]

In the ensuing decades, FDA recognized the evolution of digoxin production and testing methods. As a result, the Agency reassessed its labeling and other testing requirements. For example, FDA 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.[42] 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 digoxin USP monograph was later amended to include a dissolution requirement.[43] Our companion Citizen Petition addresses the NTI drug status of digoxin and the high excipient to API ratio in Lanoxin 0.0625 mg and 0.1875 mg tablets as these factors impact the approval of generic digoxin products.[44]

2. *Draft Labeling Versus Final Printed Labeling*

NDAs and ANDAs must contain draft labeling as a requirement for approval.[45] On the other hand, FPL is submitted after approval. FPL generally includes all final product information such as approval date, national drug code number, and complete formatting. The Agency recognizes the distinction between these two types of labeling in several official documents.[46] Most importantly, a request for labeling prior to approval of the application is a

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[40] 39 Fed. Reg. 2471, 2472 (January 22, 1974).

[41] 39 Fed. Reg. 2471, 2472 (January 22, 1974).

[42] 41 Fed. Reg. 17755, 17756 (April 28, 1976).

[43] 65 Fed. Reg. 70573, 70573 (November 24, 2000); 65 Fed. Reg. 70538, 70539 (November 24, 2000).

[44] Citizen Petition submitted by Edward John Allera, Barbara Binzak Blumenfeld, and Tina Hu (October 21, 2013).

[45] 21 C.F.R. § 314.50(l)(1)(i) [NDAs]; 21 C.F.R. § 314.94(d)(1)(ii) [ANDAs].

[46] *See, e.g.,* Form FDA 356h, "Application to Market a New or Abbreviated New Drug or Biologic for Human Use" (expires December 31, 2013), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf (requiring an applicant to check, if included in the documentation, either "draft labeling" or "final printed labeling"); *see also, e.g.,* FDA, "Draft Guidance for Industry: PET Drug Applications – Content and Format for NDAs and ANDAs" (March 2000), *available at*

request for draft labeling; after approval, FPL must be submitted. These labeling differences are clearly distinguished by the Lanoxin tablets NDA 1997 approval letter and the 2013 Complete Response letter.

> For example, the 1997 approval letter states that:
>
> The final printed labeling (FPL) must be identical to the enclosed draft labeling....Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed....Approval of this submission by FDA is not required before the labeling is used.[47]

In contrast, the Agency only requested draft labeling in the 2013 Complete Response letter:

> Submit draft labeling that incorporates revisions in the attached labeling....To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes,....The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.[48]

Therefore, providing draft labeling in the NDA and during the NDA review process is a critical *pre*-approval requirement. On the other hand, FPL is submitted after approval of an application as a *post*-approval requirement. FDA requested Covis to submit draft labeling, which is indicative of the fact that the two new dosage strengths were not fully approved in 1997. If they had been, only FPL would have been required.

3. *Prior Approval Inspections*[49]

FDA has established a risk-based approach for determining if a prior approval inspection is necessary before an application is approved. These inspections are performed to demonstrate, to FDA's satisfaction, that a particular manufacturing facility is able to manufacture a particular drug product(s). These inspections may be discretionary or mandatory. In the case of ensuring compliance with the CMC section of an application, FDA often (though not always) will conduct

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077238.pdf, at 14 ("Once the FDA approves your NDA, you will need to submit 12 copies of the final printed labeling (also known as FPL) to the FDA as part of your official records. Copies of the final printed labeling are sent to various FDA offices as part of the approval process.").

[47] 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.

[48] Letter from Norman Stockbridge, FDA, to Aziza Johnson, Covis Pharma Sàrl (February 28, 2013).

[49] FDA also refers to these as "pre-approval inspections."

a prior approval inspection. However, if the drug has a narrow range (*i.e.,* is an NTI drug), then the inspection will be deemed "priority."[50]

Digoxin is an NTI drug, and FDA stated that it was conducting the inspection because the two new strengths had never before been manufactured – not because the contract manufacturer had not been inspected in more than two years.[51] These are key indications that FDA considered the inspection to be a *prior* approval inspection, and not a post-approval routine inspection.

4. *FDA "Approval"*

Although FDA legally approves "applications,"[52] in reality the Agency approves the individual drug product(s) in the application. This is confirmed by the fact that each individual drug product in a single approved application has its own Orange Book listing with unique patent, exclusivity, and RLD information included.[53] Therefore, each approved drug product in an application is considered separately in matters of patent certifications, exclusivity time periods, and RLD status.

D. Three-Year Exclusivity

The Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Amendments")[54] provided that NDA holders would receive marketing exclusivity against any ANDA applicant for certain periods of time in a number of circumstances. For example, if the application that was submitted under FFDCA § 505(b) includes an active ingredient approved in another § 505(b) application but contains reports of new clinical investigations that are essential

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[50] FDA, Compliance Program Guidance Manual ("CPG") 7346.832, "Pre-Approval Inspections" (issued April 12, 2010), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/UCM071871.pdf, at 2-3.

[51] Electronic mail message from Teshara Bouie, FDA, to Aziza Johnson, Covis (January 23, 2013).

[52] 21 C.F.R. § 314.3(b) (an application is the collective information referred to in 21 C.F.R. § 314.50, including amendments and supplements); Lanoxin Tablets approval letter ("[a]ccordingly, the *application* is approved effective on the date of this letter." (emphasis added)).

[53] 57 Fed. Reg. 17950, 17954 (April 28, 1992) ("In some instances, such as the submission of an ANDA for a product with multiple strengths, there may be more than one reference listed drug. In these instances, FDA considers each strength to represent a different drug product...."); 21 C.F.R. § 314.3(b) ("the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application"). Furthermore, FDA has designated the 0.250 mg Lanoxin tablets product as the RLD because it is the highest dosage strength marketed under the NDA. *See* Orange Book (33rd ed.) (2013), *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm; *see also* Drugs@FDA, *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[54] Pub. Law No. 98-417 (September 24, 1984).

to approval that the sponsor conducted, then FDA may not approve another § 505(b) or § 505(j) application for the same conditions for three years from the date of approval.[55]

Three-year exclusivity therefore serves as "limited protection from new competition in the marketplace" as a result of the efforts undertaken by the NDA holder.[56] The preambles to FDA's regulations have addressed the requirements for three-year exclusivity,[57] and the Courts have vetted many of these issues.[58] Nevertheless, the matter of whether a three-year exclusivity period awarded to all individual drug products within a single NDA does not begin running for one or more of those individual drugs that is not fully approved and therefore never marketed is a novel one. Authorization to market is central to the 180-day exclusivity period for certain generic drug products,[59] but no such requirement is explicitly set forth in the exclusivity provisions of the Act or the implementing regulations.

II. ARGUMENT – COVIS IS ENTITLED TO THREE-YEAR EXCLUSIVITY FOR THE NEVER-MARKETED 0.0625 MG AND 0.1875 MG DOSAGE STRENGTHS

A. FDA's Administrative Record Shows that the Agency Did Not Fully Approve the Never-Marketed 0.0625 mg and 0.1875 mg Dosage Strengths, and the Exclusivity Period for these Strengths Therefore Never Began Running

FDA has never clearly and consistently referred to the approval status of the Lanoxin tablets NDA or the individual dosage strengths in that NDA. For example, in the Agency's November 2000 *Federal Register* notice reaffirming digoxin tablet's new drug status, FDA stated that "*FDA approved NDA 20-405* for Lanoxin Tablets (62.5, 125, 187.5, 250, 375, and

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[55] FFDCA § 505(c)(3)(E)(iii), *codified at* 21 U.S.C. § 355(c)(3)(E)(iii); FFDCA § 505(j)(5)(F)(iii), *codified at* 21 U.S.C. § 355(j)(5)(F)(iii); 21 C.F.R. § 314.108.

[56] 54 Fed. Reg. 28872, 28896 (July 10, 1989) (proposed rule for ANDAs).

[57] 59 Fed. Reg. 50338, 50356-50358 (October 3, 1994) (addressing public comments on the phrases "essential to the approval," "substantial support," and "new clinical investigation").

[58] *See, e.g.,* ViroPharma, Inc. v. Hamburg, 916 F.Supp.2d 76 (D.D.C. 2013) (acknowledging that FDA's administrative records show that studies relied upon for three-year exclusivity were not essential to approval of labeling changes); AstraZeneca Pharmaceuticals LP v. FDA, 872 F.Supp.2d 60 (D.D.C. 2012) (noting that FDA has interpreted the statutory provision as requiring a relationship between the "new clinical investigations," the change to the product, and the scope of exclusivity), *aff'd*, AstrZeneca Pharmaceuticals LP v. FDA, 713 F.3d 1134 (D.C.Cir. 2013); Zeneca Inc. v. Shalala, 1999 WL 728104, at *12 (D.Md. 1999) ("[t]he exclusivity extends only to the 'change approved in the supplement.' Zeneca's NDA supplement sought authority to add EDTA to Diprivan....Thus, the exclusivity applies to propofol products including EDTA, not to propofol products with other preservatives."), *aff'd*, Zeneca Inc. v. Shalala, 213 F.3d 161 (4th Cir. 2000).

[59] FFDCA § 505(j)(5)(D)(i)(I), *codified at* 21 U.S.C. § 355(j)(5)(D)(i)(I) (defining "forfeiture event" for purposes of 180-day exclusivity, in part, as the failure of the first generic drug applicant to market the drug by the later of 75 days after the date on which the approval of the first applicant's application is made effective, or 30 months after the date of submission of the first applicant's application).

500 micrograms) (emphasis added)" and that "an ANDA should use Glaxo's NDA 20-405 as the reference listed drug."[60] On the other hand, during recent communications between Covis and FDA about the two new dosage strengths, FDA stated that *"[c]urrently we do not see approval of the two mentioned doses.* You will need to submit a PAS" (emphasis added).[61] Finally, the February 2013 Complete Response letter contains conflicting internal statements, including "[t]his supplemental new drug application proposes *addition of two previously approved but never marketed doses* (62.5 and 187.5 mcg)" (emphasis added) and *"[t]o support the approval of the proposed 187.5 mcg and 62.5 mcg un-scored tablets,...*" (emphasis added).[62]

Despite FDA's confusing and inconsistent position on the approval status of the individual dosage strengths in NDA 20-405, FDA's administrative record for NDA approval[63] is clear: although FDA approved the application on September 30, 1997, the Agency did not fully approve all six dosage strengths that are listed in the NDA. This conclusion is based upon the complete NDA 20-405 administrative record; the recently-submitted complete draft labeling in the PAS and in response to FDA's Complete Response letter; the recent request for CMC dissolution data; the recent prior approval inspection; and the FDA inspector's instruction that Covis must be in compliance with all applicable blend uniformity testing requirements. Only Covis' interpretation – that the four never-marketed dosage strengths were not fully approved and that exclusivity could not therefore have run – is borne out by all of these facts. Post-hoc explanations and rationalizations are legally invalid.

1. *The Lanoxin Tablets Administrative Record Demonstrates that FDA did not Fully Approve Four of the Six Dosage Strengths in NDA 20-405*

We have discussed in great detail the administrative record of NDA 20-405. In light of the entire history, the Agency was clearly aware when it approved the NDA that Glaxo Wellcome was only going to market two of the six dosage strengths. As a result, FDA did not fully approve the remaining four strengths. Instead, the Agency used the following language in its 1997 approval letter:

> We note that you have decided not to market the 62.5, 187.5, 375, and 500 mcg tablet strengths at this time. *Only the 125 mcg and 250 mcg tablet strengths are*

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[60] 65 Fed. Reg. 70573, 70575 (November 24, 2000).

[61] Electronic mail message from Alexis Childers, FDA, to Todd Phillips, Beckloff Associates, Inc. (U.S. agent for Covis Pharma Sàrl) (July 2, 2012).

[62] Letter from Norman Stockbridge, FDA, to Aziza Johnson, Covis Pharma Sàrl (February 28, 2013).

[63] The administrative record comprises the documents in the administrative file of a particular administrative action the Commissioner relies on to support an administrative action.

> *approved to be manufactured* at your Zebulon, North Carolina facility (emphasis added).[64]

This language is critical because, prior to NDA approval, only the 0.125 mg and 0.250 mg dosage strengths were historically manufactured at the Greenville facility and, as indicated in the approval letter, only these same two strengths were approved for manufacturing at the Zebulon facility. There was no mention in the letter at all about the other four strengths.

Furthermore, FDA's choice of wording in the Lanoxin approval letter is distinct from that language used in a different drug's approval letter. In that case, the Agency approved multiple dosage strengths under one NDA and awarded exclusivity for all strengths regardless of marketing status.

FDA approved Seroquel XR® extended-release tablets (50 mg, 200 mg, 300 mg, and 400 mg) on May 17, 2007 (NDA 22-047). The approval letter singled-out the 50 mg dosage strength, noting:

> We recognize that, *although we have approved the 50 mg dosage strength*, you do not plan to market the product at this time and it is not included in the attached labeling.[65]

FDA awarded three-year exclusivity to all four Seroquel XR dosage strengths (including 50 mg), as reflected in the Orange Book.[66]

The result of FDA's different approaches in the Seroquel XR and Lanoxin tablets approval letters to describe the approval status of the non-marketed strengths leads to two different results. In the case of Seroquel XR, FDA approved all four of the strengths (including 50 mg). Although the sponsor would have been required to submit FPL, the product was otherwise ready to be marketed. It is of no consequence that the Seroquel XR sponsor chose not to market the 50 mg strength product; the sponsor received approval for the 50 mg product and could have marketed it if it chose to do so. FDA correctly listed three-year exclusivity for all Seroquel XR strengths in the Orange Book. The exclusivity ran upon NDA approval, and has now expired.

In contrast, FDA only fully approved two of the six strengths in the Lanoxin tablets NDA. Final approval means that a product can immediately launch but for submission of such documentation as FPL or advertising and marketing materials, which are *post*-approval

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[64] 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.

[65] Letter from Thomas Laughren, FDA, to Gerald Limp, AstraZeneca Pharmaceuticals LP (May 17, 2007), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/022047Orig1s000ltr.pdf.

[66] Orange Book (28th ed.) (2008).

requirements. Covis had to do much more than simply submit this type of information. At FDA's insistence, the Company had to submit necessary *pre*-approval CMC dissolution data. It also required a pre-approval inspection, as well as submission of complete draft labeling (not FPL). Because FDA required this CMC data and other information *before* marketing, and because CMC data is essential to application approval, the Agency could not have completely approved the four strengths in 1997. If the four strengths were not marketed because they were not approved, then no applicant could submit ANDAs for these particular dosage strengths, either. As a result, exclusivity could only run for the two strengths approved and marketed (0.125 mg and 0.250 mg).

Simply stated, the exclusivity period for the remaining four Lanoxin tablet dosage strengths could not have run because they were never fully approved and therefore never marketed. Rather, the awarded three-year exclusivity period for these strengths should begin to run after full approval, *i.e.,* after FDA approves Covis' PAS for the 0.0625 mg and 0.1875 mg strengths.

2. *FDA's Request for Draft Labeling, not FPL, Indicates that the Two New Dosage Strengths were not Previously Fully Approved*

We have also discussed at length above the fact that Glaxo Wellcome submitted complete draft labeling for only the two dosage strengths that it intended to market immediately upon NDA approval (0.125 mg and 0.250 mg). It does not matter that Glaxo Wellcome stated in its September 15, 1997 amendment with completed draft labeling that it was under the impression that NDA approval would encompass all six strengths. Legally speaking, Glaxo Wellcome was only half-right: the NDA approval did cover all six strengths, but the missing information that is central to NDA approval meant that FDA had not fully approved those strengths that were missing this information. Only now, sixteen years later, has Covis submitted complete draft labeling covering the two new strengths. Without this information in 1997, FDA did not have all necessary elements of an NDA to grant approval. Therefore, exclusivity could not have run for the 0.0625 mg and 0.1875 mg dosages at that time.

3. *The Required PAS and CMC Dissolution Data, the Prior Approval Inspection, and the FDA Inspector's Direction to Comply with Blend Uniformity Testing Requirements Confirm that these were Critical Pre-Approval Activities before Marketing Could Begin*

Prior to acquisition of the Lanoxin brand in late 2011, Covis believed that only an annual report or, at most, a CBE-30 would be required to begin marketing the 0.0625 mg and 0.1875 mg strengths, as is the normal course to bring a new but previously-approved dosage strength to market. As the record shows, the Agency disagreed. FDA had not reviewed the completed draft labeling for these two strengths at the time of NDA approval, and the two strengths had never been marketed.

Instead, FDA determined that Covis could not begin marketing the 0.0625 mg and 0.1875 mg dosage strengths until the Company submitted and the Agency approved CMC dissolution data (as well as draft labeling). The Agency also considered a prior approval inspection necessary because, as FDA stated, "the inspection is being conducted because the 0.0625 and 0.1875 strengths have never been manufactured, not because an inspection has not been conducted in the last two years. The last inspection occurred in April 2012."[67] Furthermore, even though Covis was not required to submit blend uniformity data, the FDA inspector made the point clear that compliance with all required blend uniformity testing was essential.

All of FDA's actions support the conclusion that the Agency considered this data and information to be critical to the approval process. FDA has asked Covis to produce and/or submit the data that the original sponsor did not provide. If these two new strengths were previously approved, then Covis should have been able to submit a CBE-30 or an annual report simply indicating that it was now marketing these two dosages. FDA's PAS requirement, therefore, is a *de facto* recognition that these two strengths (as well as the 0.375 mg and 0.500 mg strengths) were not fully approved in 1997.

Upon PAS approval, the application requirements for the 0.0625 mg and 0.1875 mg strengths were completed. Exclusivity for these two strengths therefore legally began running upon that full approval. As the current NDA holder, Covis has now completed the requirements necessary for marketing, and deserves to market with a period of three-year exclusivity.

B. Marketing and Exclusivity Information in the Orange Book is Not Dispositive of a Drug's Marketing Status or the Tolling of Exclusivity

Upon approval, FDA listed all six dosage strengths in NDA 20-405 in the Orange Book with three years of marketing exclusivity for each strength. Today, the Orange Book lists the four never-marketed strengths as "discontinued." These listings are not factually accurate[68] and are not dispositive of the actual marketing and exclusivity status of Lanoxin tablets.

Since 1980, FDA has maintained a document containing a list of all prescription drug products approved for safety and efficacy, as well as therapeutic equivalence decisions. The Agency decided to formalize such a list as a result of numerous State requests in the 1970s for FDA to provide information about permissible drug substitutions. Enactment of the Hatch-Waxman Amendments in 1984 required FDA to maintain a list of approved drug products (and

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[67] Electronic mail message from Teshara Bouie, FDA, to Aziza Johnson, Covis (January 23, 2013).

[68] Covis notes that FDA's Orange Book, as well as its Drugs@FDA database, list the four never-marketed strengths as "discontinued." In both cases, FDA uses "discontinued" to include products that have never been marketed, although the "discontinue" label can clearly cause legal confusion. Orange Book preamble, at vi; FDA, "Drugs@FDA Glossary of Terms" (last updated February 2, 2012), *available at* http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#D.

monthly supplements), and the Agency deemed its pre-existing list to satisfy this Congressional requirement.[69]

The statutory requirement for maintaining this drug list requires only certain minimal information, including (1) the official and proprietary name of each drug; (2) the application number and approval date; and (3) whether *in vitro* or *in vivo* BE studies are required.[70] FDA has expanded the content of the Orange Book beyond the statutorily-mandated content requirements to include exclusivity and therapeutic equivalence evaluations as well. As FDA has stated, it will, "[a]s a general rule,...use the list and its supplemental updates as the primary means of announcing information regarding patent status, exclusivity, type of bioequivalence ["BE"] study needed, and eligibility for consideration in an ANDA."[71] Even today, the Agency notes that sponsors do not receive letters regarding the grant of exclusivity; rather, "[t]he Orange Book is the official vehicle for dissemination of this information."[72]

For years the Agency has taken the stance that its maintenance of individual patent listings in the Orange Book is ministerial. The Courts have upheld this position[73] by recognizing that FDA does not have the same expertise as the U.S. Patent and Trademark Office to determine whether a patent should have been listed in the Orange Book as required by the FFDCA and regulation. FDA derives this position from the Act[74] and from regulations[75] which only make reference to the correctness of *patent* listings in the Orange Book, not *exclusivity* listings in the Orange Book.

Unlike patent listing decisions, FDA's exclusivity decisions are based on its own expertise and the Agency's role in these decisions is more than ministerial. But FDA's role in

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[69] Orange Book (33rd ed.) (2013), at iv-v.

[70] FFDCA § 505(j)(7)(A)(i)(I)-(III), *codified* at 21 U.S.C. § 355(j)(7)(A)(i)(I)-(III).

[71] 54 Fed. Reg. 28872, 28876 (July 10, 1989).

[72] FDA, "Frequently Asked Questions on Patents and Exclusivity" (last updated December 5, 2012), *available at* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm#How is an NDA holder notified if their application is granted exclusivity by the FDA?.

[73] For a list of cases addressing FDA's ministerial role, *see* 68 Fed. Reg. 36676, 36683 (June 18, 2003).

[74] FFDCA § 505(j)(7)(A)(iii), *codified at* 21 U.S.C. § 355(j)(7)(A)(iii) ("[w]hen patent information submitted under subsection (b) or (c) respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.").

[75] 21 C.F.R. § 314.53(f) ("Correctness of patent information errors") (a person disputing the accuracy of patent listing information in the Orange Book must first contact FDA in writing, and FDA will request the NDA holder to confirm the correctness of the listed patent information; however, "[u]nless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list.").

exclusivity determinations should not be confused for infallibility. The publication of exclusivity information in the Orange Book is not dispositive of the correctness of these exclusivity decisions, nor of the published information about them.

The Orange Book by its nature is subject to change so that it can remain an effective and current tool for drug sponsors and the Agency alike. For example, products may be moved between the "discontinued" list and other lists in the Orange Book as necessary,[76] and patent holders can request that FDA correct inaccurate patent information in the Orange Book.[77] The Agency notes that changes or corrections to the Orange Book should be reported, even though "[e]very effort is made to ensure the Annual Edition is current and accurate."[78] However, FDA is not infallible, and the Orange Book cannot be presumed to be entirely accurate at all times, as Courts have concluded. However, as the cases cited below indicate, the litigated issue of Orange Book accuracy has previously extended only to patent listings, not exclusivity listings.

For example, in Ben Venue Laboratories, Inc. v. Novartis Pharmaceutical Corp., the Court noted that "[a]lthough the FDA's listing of a patent may be entitled to some deference, since the FDA has refused to list patents in the past,...the Court concludes that *the FDA's listing should not create any presumption that the patent was correctly listed*" (internal citation omitted; emphasis added).[79] This position was echoed by the Court in Bayer Schera Pharma AG v. Sandoz, Inc.,[80] which stated that "[a] number of courts have recognized, however, that the Orange Book and the patents listed therein do not reliably indicate what uses of a drug are FDA-approved, in part because the FDA takes the NDA-holders at their word as to which patents claim FDA-approved uses....Accordingly, *listings in the Orange Book are not a reliable indicator of what uses of a drug have received FDA approval* (emphasis added)."[81] Although these litigated cases have involved Orange Book patent listings, FDA and the Courts have clearly

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[76] 57 Fed. Reg. 17950, 17953 (April 28, 1992).

[77] *See, e.g.,* Merck Sharp & Dohme Corp. v. Sandoz Inc., 2013 WL 591976 (D.N.J. 2013), at *2 ("[h]owever, upon approval of the NDA for the 150 mg dose, only the '336 patent was listed in the Orange Book. Any reference to the '942 patent was excluded. The omission was corrected in April 2012, shortly before the filing of this lawsuit, but after submission of Defendants' ANDAs."); In re Androgel Antitrust Litigation (No. II), 687 F.Supp.2d 1371 (N.D.Ga. 2010), at 1373-1374 ("[i]n June 2003, Solvay requested that the PTO correct certain mistakes that it made in the patent....The FDA accepted Solvay's submission and listed the '894 patent in the Orange Book.").

[78] Orange Book (33rd ed.) (2013), at xxiii.

[79] 10 F.Supp.2d 446, 456 (D.N.J. 1998).

[80] We believe that the correct company name here is "Bayer Schering." However, as the court case lists the company name as "Bayer Schera," we retain the use of that name in this document.

[81] 741 F.Supp.2d 541, 552 (S.D.N.Y. 2010).

recognized that mistakes will be made in the Orange Book. There is no reason to conclude that mistakes with respect to exclusivity listings will not also occur.[82]

Covis recognizes that GlaxoWellcome, its predecessor in interest regarding NDA 20-405, did not contest the running or expiration of the three-year exclusivity for the four never-marketed digoxin tablet dosage strengths because FDA was forcing the Company to go through the steps of obtaining at least some approval under FFDCA § 505(b) so that the agency could approve generic competition. As documented in the administrative record and discussed herein, that company chose only to market two of the six strengths. However, Covis is not prohibited from arguing that the Company, as the current NDA holder, is entitled to three-year exclusivity. Cases involving exclusivity and final Agency action have involved matters of a competitor attempting to force FDA to make a decision on another party's entitlement to exclusivity,[83] as well as requests for FDA decisions on the forfeiture of 180-day exclusivity.[84] These cases are clearly different from the current situation because Covis is the successor in interest to the original exclusivity awardee. Therefore, these exclusivity rights are Covis' to assert. It is Covis that submitted the additional dissolution and draft labeling information to FDA, that underwent a prior approval inspection, and that was instructed to comply with blend uniformity testing requirements. Therefore, Covis completed the information the Agency required to be able to market the 0.0625 mg and 0.1875 mg strengths, and the Company has the right to enforce the previously-awarded exclusivity.

FDA's Orange Book exclusivity listings for NDA 20-405 were inaccurate. If four of the strengths were never fully approved, then the exclusivity – while correctly awarded to all six strengths – could not have run. If exclusivity did not run, then it did not expire. Only this result accords with the purpose of three-year exclusivity to protect products from competition in the marketplace. If a drug is not in the marketplace, it cannot be protected from competition, and the Congressional purpose of exclusivity is not realized. More importantly, if a drug cannot legally be marketed because it is lacking complete data and information that precludes a full approval, then the benefits of being awarded exclusivity are further eviscerated.

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[82] In one case, Alphapharm Pty Ltd. v. Thompson, 330 F.Supp.2d 1 (D.D.C. 2004), a third party challenged FDA's refusal to list a patent that the party believed claimed the drug. When the third party wrote to FDA, the Agency forwarded the request to the application holder and asked the application holder to provide FDA with "'any corrections that need to be made to the patent *and exclusivity information*'" in the Orange Book (emphasis added). *Id.* at 4. However, the entire case involved the correctness of the patent listing, not the exclusivity listings.

[83] *See, e.g.,* Mylan Pharmaceuticals Inc. v. FDA, 789 F.Supp.2d 1, 13 (D.D.C. 2011) (stating that "[i]f a plaintiff cannot seek judicial review of the FDA's failure to decide the plaintiff's *own* entitlement to exclusivity by a certain time, Plaintiffs in this case, who seek to enforce an FDA decision on a *competitor's* entitlement to exclusivity, certainly cannot present a claim that is fit for review" (emphasis in original).).

[84] *See, e.g.,* Hi-Tech Pharmacal Co., Inc. v. FDA, 587 F.Supp.2d 1, 8 (D.D.C. 2008) (in a case involving the potential forfeiture of 180-day exclusivity, noting that "Hi-Tech is not entitled to judicial review of the interpretation and application of the exclusivity forfeiture provisions of the Medicare Modernization Act until the FDA itself first interprets and applies those provisions with respect to Hi-Tech's ANDA – i.e., until there is final agency action.").

III. CONCLUSIONS

Covis requests FDA to confirm that, based upon the Agency's administrative record for approval of NDA 20-405, the Company is entitled to three years of marketing exclusivity for two never-marketed digoxin dosage strengths (0.0625 mg and 0.1875 mg) upon approval of a required PAS. These strengths have never been marketed under the NDA. Although FDA determined that all six strengths were deserving of three-year exclusivity at the time of NDA approval in 1997, this exclusivity could not have run for the four never-marketed strengths because they were never fully approved. This fact is confirmed by the Agency's requirement that Covis submit draft labeling, CMC data, and a PAS. It is also confirmed by the Agency's prior approval inspection of Covis' contract manufacturer, as well as by the FDA inspector's instruction that Covis must be compliant with all blend uniformity requirements. These are all *pre*-approval requirements.

As a result of submitting this data and information, Covis should receive the benefit of the three-year exclusivity period originally awarded in 1997 that began running upon PAS approval. Only this outcome is consistent with the regulatory history of digoxin and the NDA 20-405 administrative record, the three-year exclusivity statutory and regulatory provisions, and the pre-approval requirements for an NDA.

Covis therefore respectfully requests that FDA take the following actions with respect to the Company's 0.0625 mg and 0.1875 mg strength digoxin tablets under NDA 20-405:

(1) Confirm that the Agency did not fully approve the 0.0625 mg and 0.1875 mg tablets on September 30, 1997 in NDA 20-405 because of: (a) the language in the administrative record; (b) the recently-required submission of draft labeling and CMC dissolution data for the two new dosage strengths; (c) the recently-required submission of a PAS; (d) the recent prior approval inspection; and (e) the FDA inspector's direction that Covis be in full compliance with all blend uniformity testing requirements;

(2) Confirm that three-year exclusivity was awarded but never began running for these two dosage strengths that have never been marketed under NDA 20-405, despite their listing in FDA's Orange Book; and

(3) Confirm that Covis is therefore entitled to a period of three-year marketing exclusivity for the 0.0625 mg and 0.1875 mg dosage strength products that began running upon PAS approval.

If you require further information regarding these issues, please contact either Edward Allera or Barbara Binzak Blumenfeld 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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