November 28, 2012

VIA ELECTRONIC DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2012-P-1028 / Buprenorphine for Opioid Dependence

Dear Sir or Madam:

Actavis Inc. ("Actavis") submits these comments to the docket for the above-referenced Citizen Petition. The Citizen Petition, filed by Reckitt Benckiser Pharmaceuticals, Inc. ("Reckitt"), requests that the Food and Drug Administration ("FDA") refrain from approving any new drug application ("NDA") or abbreviated new drug application ("ANDA") for buprenorphine drug products unless certain conditions are met by the applicant. Among the conditions Reckitt seeks to impose is a requirement that each NDA/ANDA applicant include a targeted pediatric exposure education program as part of its application. The Citizen Petition also requests that FDA refrain from approving any buprenorphine/naloxone ANDA for addiction treatment until FDA determines whether the reference listed drug ("RLD") was discontinued for reasons of safety.

Other parties have submitted comments to the docket detailing why the Citizen Petition is without merit and should be denied.[1] We support those comments, and wish to supplement those filings by amplifying the factual and legal grounds on which FDA must dismiss the discrete requests cited above, which are of particular significance to those entities that have filed, or may in the future file, ANDAs for the RLD.[2] In sum, the requests made by Reckitt in its Citizen Petition are not based on any accurate, or even reasonable, interpretation of the applicable statutory and regulatory provisions. Rather, they are predicated on mischaracterizations and misuse of the applicable legal and administrative precedent, and would require FDA to adopt aberrant interpretations that would have far-reaching negative ramifications, not only on applications for buprenorphine drug products, but on *all* pending, future, and approved

---

1 In particular, we refer to the comments of Venable LLP, filed on behalf of Amneal Pharmaceuticals LLC ("Amneal Comments").

2 The Citizen Petition also requests that FDA deny approval to applications for buprenorphine drugs that lack child-resistant unit-dose packaging. Because the Citizen Petition directs this request at NDAs – Reckitt provides no rationale for the application of this request to ANDAs – our comments do not address this aspect of the Citizen Petition. We instead refer to and support the Amneal Comments, which detail the reasons why this request should also be denied.

Actavis Inc.
Actavis US Headquarters
60 Columbia Road, Building B
Morristown, NJ 07960
t 973 993 4500
f 973-993-4303
www.actavis.com

ANDAs. In short, Reckitt is asking FDA to invent new ANDA pre- and post-approval criteria, which the Agency may not lawfully do. Further, the Citizen Petition's request that FDA refrain from approving pending ANDAs for the RLD unless and until the Agency determines whether the product was withdrawn for reasons of safety represents a shameless and misleading attempt to block generic competition, as Reckitt *continues to market the RLD in the United States*. As a result, either Reckitt is engaged in a cynical ploy to delay FDA consideration of pending ANDAs, or it is intentionally putting patients at risk. In either case, FDA must immediately disregard and dismiss this aspect of the Citizen Petition.

I. The Citizen Petition Is a Contrived, Last-Ditch Attempt to Forestall Competition

Before proceeding with an analysis of the requests made in the Citizen Petition, we feel it is important to place the Citizen Petition within the broader context of Reckitt's longstanding strategy to protect its monopoly over sales of buprenorphine drug products. The Amneal Comments detail Reckitt's efforts to prevent and delay competition, most recently in connection with FDA's request that Reckitt collaborate with its potential competitors in the development of a single, shared REMS system ("SSRS"). The SSRS requirement, at least as applied to applicants with pending ANDAs, established a perverse incentive structure and allowed Reckitt to engage in the mischief described in the Amneal Comments. Indeed, imposing the SSRS requirement on generic applicants with *pending* ANDAs created, *as a condition of approval*, the need for applicants to obtain Reckitt's voluntary consent to enter into an SSRS under the terms of a commercial agreement governing the operation of that REMS. We are aware of no other context in which an NDA holder has been given direct control over the approvability of ANDAs for follow-on generic products.[3] It should therefore be no surprise that Reckitt would refuse to sign a shared REMS agreement upon commercially reasonable terms; nor should it be a surprise that Reckitt would view the SSRS requirement as an opportunity to proactively delay, if not prevent, generic competition. As documented in the Amneal Comments, that was and remains the strategy adopted by Reckitt.

As that strategy began to unravel, Reckitt moved to the next step in its anti-competitive endgame strategy: the filing of a Citizen Petition that, among other requests, asks that FDA refrain from approving pending ANDAs for buprenorphine/naloxone products unless and until the FDA formally determines that this RLD was not withdrawn from the market for reasons of safety. Perhaps because (as detailed in the Amneal Comments) the generic sponsors of buprenorphine-containing drug products refused to countenance Reckitt's continued obfuscation and delay and sought a waiver from FDA of the SSRS requirement, the company moved too soon in including this request in its Citizen Petition. In the Citizen Petition, Reckitt asserts that it has discontinued sales of the RLD[4] and that the requested determination regarding the product's withdrawal is therefore ripe for review. But *Reckitt continues to sell the RLD in the United States*, and has publicly announced its intent to do so for a period of up to several months.[5]

Indeed, Reckitt's recent explanation for why the company continues to market the RLD despite its purported lack of safety is a quintessential example of its willingness to disregard its own

---

[3] Indeed, no other shared REMS has had this effect; in all other instances, the brand and generic members have been current, not potential, competitors.

[4] Reckitt Benckiser Pharmaceuticals Inc., Citizen Petition, Docket No. FDA-2012-P-1028 ("Citizen Petition"), at 44 (Sept. 25, 2012) (stating that "[i]n response to these findings [regarding pediatric exposure], [Reckitt] discontinued marketing of Suboxone tablets").

[5] Press Release, Reckitt Benckiser Pharmaceuticals Inc., Reckitt Benckiser Pharmaceuticals Inc. to Voluntarily Discontinue the Supply of Suboxone Tablets (buprenorphine and naloxone sublingual tablets) (Sept. 25, 2012), *available at* http://www.rb.com/site/RKBR/Templates/MediaInvestorsGeneral2.aspx?pageid=1328&cc=GB.

public statements and conduct in the service of protecting its monopoly. In the company's November 16, 2012 submission to the Citizen Petition docket, Reckitt chastises Amneal for questioning why the RLD remains on the market, stating that "Amneal seems unconcerned about the devastating effect on patients and the treatment community that would be caused by a precipitous removal, and ignores the mandatory 6-month notice period required under Section 506C of the FDC Act."[6] This explanation is risible for several reasons. First, Reckitt has failed to substantively address the point made by Amneal and these comments: the RLD remains on the market, so the issue of whether the drug was discontinued for safety reasons is not ripe for review. Neither the Food, Drug, and Cosmetic Act ("FDCA") nor the FDA regulations permit FDA to evaluate the basis for a discontinuance that has yet to occur. Second, it is not at all clear that Section 506C of the FDCA applies to the RLD, and that Reckitt has acted as such. Specifically, the RLD is not included on FDA's public list of drugs to be discontinued under this section of the FDCA and the associated FDA implementing regulation, suggesting that Reckitt did not, in fact, provide such a "mandatory" notice to FDA under Section 506C.[7] Moreover, it is patently disingenuous for Reckitt to state on the one hand that "precipitous removal" of the RLD would cause a "devastating effect on patients and the treatment community," while on the other hand stating in its Citizen Petition that the announced discontinuance is "[b]ased on the ready availability of safer alternatives for opioid dependence through Suboxone Film."[8] Indeed, as detailed in the Amneal Comments, Reckitt has engaged in a multi-year effort to transition patients from the RLD to its patent- and exclusivity-protected Suboxone Film. Finally, Reckitt fails to acknowledge that this same section of the FDCA provides FDA with the tools to mitigate the "devastating effect" of withdrawing the RLD: Section 506C(g) permits FDA to expedite ANDA reviews and approvals that may mitigate the impact of a potential drug shortage resulting from a discontinuance. However, in this case, Reckitt is making every effort to forestall, if not wholly prevent, such approvals, based on safety concerns. Simply put, Reckitt's own public statements illustrate its attempt to have it both ways: FDA may not approve ANDAs for the RLD because the drug presents "significant safety risks" and there are "readily availab[le] safer alternatives,"[9] but the company may otherwise continue to market the RLD for several weeks, if not months, due to the "devastating effect" on patients that would result from an immediate discontinuance and ensuing drug shortage.

FDA should therefore conclude that Reckitt's statements in the Citizen Petition, which are belied by the facts, are a brazen and misleading attempt to subject pending and future ANDAs to another protracted administrative proceeding before becoming eligible for approval. Further, even if Reckitt had actually discontinued the product as of the date of its Citizen Petition, as detailed below, the circumstances associated with Reckitt's forthcoming withdrawal of the RLD clearly support the conclusion that the company is not seeking to withdraw the product for reasons of safety, as detailed below. FDA should therefore immediately deny the Citizen Petition, in whole or with respect to its request for a determination regarding the basis for the withdrawal of the RLD from the market, in accordance with Section 505(q)(1)(E) of the FDCA.[10]

---

6 Reckitt Benckiser Pharmaceuticals Inc., Comment, Docket No. FDA-2012-P-1028 ("Reckitt Comments"), at 4, note 5 (Nov. 16, 2012).

7 FDA, Drugs to be Discontinued, http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050794.htm (last updated Nov. 21, 2012).

8 Citizen Petition, at 26.

9 *Id.*

10 Section 505(q)(1)(E) states in pertinent part that if FDA "determines that a petition . . . was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid scientific or regulatory issues, the Secretary may deny the petition at any point based on such determination."

II. FDA Is Not Lawfully Permitted to Grant the Requests Made in the Citizen Petition

The Citizen Petition asserts that FDA must deny any ANDA seeking approval of a buprenorphine drug product for opioid dependence that lacks "targeted educational interventions on pediatric exposure risks" because such applications (1) fail to contain the "same labeling" as the RLD, and (2) lack the "same risk-benefit profile" as the RLD.[11] As detailed below, Reckitt bases each of these requests on invented statutory and regulatory approval criteria, or no legal criteria at all. As such, the requests should be rejected outright by FDA.

A. FDA May Not Grant Reckitt's "Same Labeling" Request

With respect to the labeling of generic drugs, the Citizen Petition correctly states that FDA may not approve an ANDA that does not include the same labeling as the RLD.[12] The Citizen Petition claims that that Reckitt's so-called "comprehensive pediatric exposure education campaign with specific interventions targeted to educate providers on pediatric exposure risks" constitutes labeling under the FDCA, based on the broad definition set forth in FDA's prescription drug advertising regulations:

> Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug . . . .[13]

The Citizen Petition asserts that, based on this definition of labeling, "there can be little question that [Reckitt's] educational campaign would be considered part of the labeling of its buprenorphine products."[14] We agree that Reckitt's educational campaign would indeed be considered "labeling" for certain purposes under the FDCA – but Reckitt's suggestion that it applies in the context of the ANDA "same labeling" requirement is wrong, and, if accepted by FDA, would have vast consequences on both approved and future ANDAs.

Simply, Reckitt fails to acknowledge the well-understood distinction between FDA-approved labeling and advertising and promotional labeling. It is the former, not the latter, category of labeling that applies in the context of ANDA approvals, as articulated in the statutory and regulatory provisions that Reckitt itself cites.[15] Section 505(j)(4)(G) of the FDCA requires FDA to deny approval of an ANDA if the proposed generic's labeling is not the "same as the labeling *approved for the listed drug* referred to in the application."[16] Similarly, under 21 C.F.R. § 314.127(a)(7), FDA will refuse to approve an ANDA if the labeling for the proposed generic is not the "same as the labeling *approved for the listed drug* referred to in the [ANDA]." Therefore, the question is not whether Reckitt's educational campaign constitutes "labeling" under the FDCA, but rather whether it constitutes "labeling approved for the listed drug." The answer is clearly and indisputably "no."

---

11 Citizen Petition, at 34, 36.

12 Citizen Petition, at 34 (citing 21 C.F.R. § 314.127(a)(4)). We note that Reckitt likely intended to cite subparagraph (a)(7), rather than (a)(4), of this regulation.

13 21 C.F.R. § 202.1(l)(2), Citizen Petition, at 29–31.

14 Citizen Petition, at 31.

15 *Id.* at 34, note 83 (citing 21 U.S.C. § 355(j)(4)(G), 21 C.F.R. § 314.127(a)(4)). As noted above, Reckitt likely intended to reference subsection (a)(7) of the applicable regulation.

16 21 U.S.C. § 355(j)(4)(G) (emphasis added).

When submitting an ANDA, an applicant is required to provide a copy of the proposed label and labeling for the product.[17] The applicable regulations clarify that "[l]abeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the [RLD]," with limited enumerated exceptions.[18] This "approved labeling" for the RLD is publicly available on the Drugs@FDA website, which is the primary resource for identifying and locating the labeling to be used as the basis for comparison in an ANDA submission.[19] With respect to the RLD that is the subject of the Citizen Petition, the Drugs@FDA website includes the current label for the product, a copy of the approved REMS, and the medication guide distributed by Reckitt – but no references to or information on the "educational campaign" described by Reckitt in its Citizen Petition.

Importantly, if Reckitt truly believes that its "several critical educational interventions," including the development of websites and other promotional materials, constitute "approved labeling" under the applicable ANDA approval laws and regulations, Reckitt would have amended its NDA to include these materials as "approved labeling." For instance, FDA regulations require that a supplemental NDA be filed if the NDA holder changes the labeling for the product, including changes intended to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product."[20] However, a review of the history for the RLD confirms that Reckitt made no such filings.[21] Therefore, one is left to question whether Reckitt is confused as to what it believes to be legal noncompliance or, more likely, it is again manufacturing issues to delay competition. Along these same lines, it is noteworthy that the single example Reckitt cites in support of its "same labeling" argument – the fact that FDA ostensibly required that "all generic manufacturers of Accutane . . . adopt all of the essential elements of Accutane's risk-management measures" – is qualified by a footnote confirming that the NDA holder "had submitted certain educational materials for its risk management program for Accutane as part of a labeling supplement."[22]

Further, FDA regulations clearly distinguish between "approved labeling" and "promotional labeling and advertising." Juxtaposed against the requirement to amend "approved labeling" through a supplemental NDA is the regulatory requirement that an "applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with [an NDA supplement]."[23] While the FDA regulations recognize this distinction, Reckitt seems to do so only when it serves a business purpose: it must have been Reckitt's position that its websites and promotional materials were *not* approved labeling when disseminated (as evidenced by the lack of supplemental NDAs), but, now that generic competition is imminent, they are.

---

17 21 C.F.R. § 314.94(a)(8)(ii).

18 *Id.* at § 314.94(a)(8)(iv).

19 *See* Drugs@FDA: FDA Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

20 21 C.F.R. § 314.70(c)(6)(iii)(C).

21 Reckitt has submitted two labeling amendments since first obtaining approval of the RLD; one to "[i]ncrease the prominence of the strength on the Suboxone labels to be commensurate with the size of the proprietary name" (NDA 20-733/S-003, approved October 4, 2006), and one to incorporate Reckitt's approved REMS and a revised package insert (NDA 20-733/S-007 & S-008, approved December 22, 2011). *See* S-003 Approval Letter (Oct. 4, 2006), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/020732s002,020733s003LTR.pdf; S-007 & S-008 Approval Letter (Dec. 22, 2011), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020733s007,s008ltr.pdf.

22 Citizen Petition, at 35, note 87.

23 21 C.F.R. § 314.70(a)(4).

And, moreover, Reckitt asks FDA to reach this same conclusion without acknowledging the vast implications of requiring a generic applicant to demonstrate "sameness" with any and all materials associated with the RLD that meet the broad definition of labeling under FDA's drug advertising regulations. It appears that Reckitt would have generic applicants demonstrate, in order to obtain ANDA approval, sameness with all websites, promotional materials, brochures, mailings, price lists, and other materials used by the NDA holder for the RLD. Further, as changes in RLD labeling generally necessitate changes in the labeling of ANDAs referencing the RLD,[24] Reckitt's interpretation of the "same labeling" requirement would require generic manufacturers to continually monitor all "labeling" disseminated by the NDA holder – whether or not submitted to FDA in a supplemental NDA – and adjust their own labeling accordingly.

These potential outcomes underscore the outlandish nature of this Citizen Petition request. FDA must account for the fact that Reckitt has essentially requested the Agency to invent a new pre- and post-approval ANDA requirement, and deny the request accordingly.

B. FDA May Not Grant Reckitt's "Same Risk-Benefit Profile" Request

Similar to the "same labeling" request, the Citizen Petition asserts that FDA must deny ANDAs that lack pediatric exposure educational interventions because such applications would lack the same risk-benefit profile as the RLD.[25] In the section of the Citizen Petition detailing this argument, Reckitt fails to cite a single statutory or regulatory provision supporting its assertion; rather, the company cites a generic description of the "sameness" standard found on FDA's website. Elsewhere in the Citizen Petition, Reckitt does cite provisions of the FDCA and FDA's implementing regulations that would ostensibly support this request in the Citizen Petition, but a review of these provisions demonstrates that Reckitt has mischaracterized their meaning in the service of an equally extreme and unprecedented request.

In its "Legal Background" section, Reckitt lays the groundwork for the request by noting that "FDA's regulations indicate that an ANDA product is unsafe, and may not be approved, if there is a 'reasonable basis' to conclude that the ANDA raises serious questions of safety."[26] Reckitt then asserts that "FDA has also indicated that the ANDA disapproval standards are consistent with the ANDA withdrawal standards, and FDA may withdraw an ANDA 'whenever there is a reasonable basis to conclude that a drug is unsafe even if the agency lacks proof that the drug is unsafe.'"[27] Finally, Reckitt claims that "FDA has indicated that an ANDA sponsor must demonstrate that the generic drug has the same risk-benefit profile as the RLD, by stating that those drugs have comparable safety risks."[28] Based on this interpretation of the legal and regulatory standards for ANDA approval, Reckitt concludes that "[i]f the safety risks of a generic and innovator must be the same as the RLD, then FDA cannot conclude that buprenorphine marketed without targeted interventions concerning pediatric exposure is the same as buprenorphine marketed with such interventions."[29] Reckitt's request is therefore predicated on obtaining FDA's acceptance of two conclusions outlined in the Citizen Petition: first, that FDA possesses the overarching authority to independently assess the safety of a proposed generic based on whatever data

---

[24] *See, e.g.*, FDA, Guidance for Industry, "Revising ANDA Labeling Following Revision of the RLD Labeling" (May 2000).

[25] Citizen Petition, at 36–38.

[26] *Id.* at 26–27.

[27] *Id.* at 27.

[28] *Id.* at 36.

[29] *Id.* at 37.

and information the agency sees fit to consider; and, second, that FDA must therefore deny approval to buprenorphine ANDAs based on ill-defined "targeted interventions" conducted by the innovator that are not included in the RLD's approved labeling. In each case, the conclusions are the result of self-serving mischaracterizations of the generic drug approval laws and regulations.

First, Reckitt's claim that FDA may deny approval to an ANDA if there is a "reasonable basis" to conclude that an ANDA "raises serious questions of safety" is simply wrong. As FDA has consistently acknowledged, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic product in order to obtain approval.[30] Rather, the applicant relies upon FDA's previous finding that the RLD is safe and effective and, to that end, submits data demonstrating that its proposed generic is the "same" as the RLD with respect to the drug's active ingredient, conditions of use, route of administration, dosage form, strength, and (with limited exceptions) labeling.[31] The regulation Reckitt cites in support of its proposition is limited to FDA's required assessment of safety issues presented by the use of different *inactive ingredients* in proposed generic products, as, generally speaking, the inactive ingredients in a generic product need not match those in the RLD.[32] Reckitt therefore (and improperly) seeks to characterize this regulation, which applies solely to permitted differences in inactive ingredients, as a general approval standard for ANDAs. Similarly, Reckitt's attempt to equate the ANDA approval and withdrawal standards by stating that FDA has "indicated" as much is another gross misrepresentation.[33] FDA did nothing of the sort. Rather, FDA engaged in a comparison of the ANDA approval and withdrawal standards only when describing the standard of proof necessary to support a conclusion that an ANDA should not be approved under FDCA Section 505(j)(4)(H), which is based on the safety (or lack thereof) of the *inactive ingredients* in a proposed generic product.[34] As such, Reckitt is again attempting to generalize a discrete statutory and regulatory approval criterion in an effort to inject a broad safety assessment into the generic drug approval process that lacks any grounding in the applicable laws and regulations.

Reckitt's effort to invent a general standard for ANDA approval based on an assessment of whether a proposed generic product shares the same "risk-benefit" profile as the RLD therefore must be dismissed. There is no support for such a standard in the FDCA or FDA's implementing regulations, despite Reckitt's misleading attempt to argue otherwise. Because, as discussed above, Reckitt's "educational interventions" are not part of the RLD's "approved labeling" for purposes of generic approval, FDA has no lawful grounds on which to consider these activities when reviewing ANDAs for generic versions of the RLD.

---

30 *See* FDA Response to ISTA Pharmaceuticals Citizen Petition, Docket Nos. FDA-2008-P-0368 and FDA-2011-P-0128, at 2 (May 11, 2011)

31 *Id.* at 2–3 (citing 21 U.S.C. §§ 355(j)(2)(A), 355(j)(4)).

32 *Id.* at 3 (citing 21 U.S.C. § 355(j)(4)(H), 21 C.F.R. § 314.127(a)(8)(i)).

33 Citizen Petition, at 27.

34 *See* Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17969 (Apr. 8, 1992). Reckitt cites this source, but, as with other sources, fails to place it in context.

C. Reckitt Intends to Withdraw the RLD For Business, Not Safety, Reasons

As noted above, Reckitt currently markets the RLD in the United States, while at the same time asserting in a public Citizen Petition that the product is unsafe. As explained above, this fact alone prevents Reckitt from compelling FDA to issue a determination regarding whether the RLD was withdrawn for reasons of safety, as the Citizen Petition seeks to do. Moreover, the facts associated with Reckitt's purported withdrawal of the RLD uniformly support the conclusion that the move has little, if anything, to do with the safety concerns Reckitt cites. As a result, even if FDA were required to issue a determination on whether the RLD was withdrawn for safety reasons before approving an ANDA for the RLD, FDA would be required to find that the RLD was indeed not withdrawn for such reasons.

In support of its request, Reckitt states that "Suboxone Tablet is . . . less safe than Suboxone Film, and [Reckitt] discontinued marketing it for that reason."[35] However, Reckitt's claim regarding its intent in withdrawing the RLD is belied by the facts, which include, among others:

- Reckitt continues to market and distribute the RLD in the United States over two years following approval of Suboxone Film, the "safer alternative";[36]
- The RLD was, and remains, safe and effective when used as directed on the product's labeling; and
- Reckitt marketed the RLD for several years, despite its recognition that the drug was subject to misuse resulting in accidental pediatric exposure.

Indeed, Reckitt's public statements before and concurrent with the approval of the film dosage form confirm that the company's priority was market share and profits, not patient safety. For example, at the time the film was launched, Reckitt noted in its Annual Report that the "patent-protected and consumer preferred Suboxone film" was launched to "mitigate the potential impact" of generic competition.[37] Only now, as that generic competition is imminent, does Reckitt claim that it is discontinuing the RLD in favor of the film for reasons of safety.

Reckitt also fails to provide a legal or regulatory basis on which FDA may reach the determination requested in the Citizen Petition. Reckitt cites administrative precedent that ostensibly supports the proposition that FDA may base its determination on the comparative safety of the RLD to other formulations of the drug, such as Suboxone Film. However, a review of this precedent shows that, if it applies to the current proceeding at all, it supports a conclusion opposite to the one Reckitt would have FDA make. For instance, in support of its claim that FDA must employ a comparative analysis in determining whether an RLD was withdrawn for reasons of safety, Reckitt cites the proceeding for the drug Chloromycetin (chloramphenicol). What Reckitt fails to acknowledge is the fact that the discontinued version of the drug that was the subject of the proceeding was originally approved to help address a "significant unmet medical need," and that the label limited use of the product to "treat only serious infections for which less potentially dangerous drugs are ineffective or contraindicated."[38] It

---

35 Citizen Petition, at 45.

36 Reckitt Comments, at 4, note 5 (acknowledging that Reckitt continues to market Suboxone Tablet).

37 Reckitt Benckiser Annual Report and Financial Statements 2010, at 2 (released Mar. 29, 2011), *available at* http://www.rb.com/Investors-media/Investor-information.

38 Determination that Chloromycetin (Chloramphenicol) Capsules, 250 Milligrams, Were Withdrawn from Sale for Reasons of Safety or Effectiveness, 77 Fed. Reg. 41412, 41412 (July 13, 2012).

therefore stands to reason that FDA's cited basis for its determination that the drug was withdrawn for safety reasons – "approval of additional therapies with less severe adverse drug effects" – would alter the balance between the drug's benefits and the significant risks identified on its label.[39] Moreover, in its ruling, FDA noted that, if the discontinued version of the drug were to be reintroduced, a REMS would be required to ensure that the benefits of the drug outweigh the risks – an exact reflection of the SSRS process currently underway for buprenorphine drugs, which will address precisely the risk (pediatric exposure) cited by Reckitt in the Citizen Petition.[40]

Similarly, FDA's determination in the proceeding for the drug Brevibloc (esmolol hydrochloride) was based principally on the adequacy of the withdrawn product's labeling, not a comparison of the withdrawn product to another formulation.[41] Reckitt asserts that this proceeding demonstrates that FDA may account for "alternative presentations" of a product in assessing the safety of a withdrawn formulation.[42] However, a review of that determination shows that the primary basis on which FDA concluded that the product was withdrawn from the market for reasons of safety was the inability of the NDA holder to address the risks of the product through labeling. Specifically, FDA determined that the "latest approved labeling . . . is inadequate to reduce medication errors to an acceptable level," and that additional studies of the product in the typical practice setting would be required in order to reintroduce the product.[43] Here, again, it bears repeating that the SSRS requirement imposed by FDA for buprenorphine drugs is intended to, through labeling, address precisely the safety risks cited by Reckitt in its Citizen Petition.

Finally, Reckitt mischaracterizes the statements made by FDA in resolving a citizen petition associated with the withdrawal of Xibrom (bromfenac ophthalmic solution 0.09%). Reckitt cites this proceeding in support of the proposition that "a risk-benefit comparison to alternative products can inform FDA's determination of the reasons a product has been discontinued for sale," and quotes statements to this effect from the FDA decision letter.[44] However, the statements Reckitt quotes relate to something else entirely; they are drawn from a paragraph in which FDA discusses the innovator's mischaracterization of the *drug approval* process, not the criteria for determining the reasons a product was withdrawn from the market.[45] Indeed, with respect to those criteria, FDA concluded that "we have found no information . . . to indicate that the product was withdrawn from sale for reasons of safety or effectiveness."[46] More to the point, not a single sentence in the FDA decision letter (as it relates to the determination regarding the reason for Xibrom's withdrawal) is directed at an actual "risk-benefit

---

39 *Id.*

40 *Id.* at 41,413.

41 *See* Determination that Brevibloc (Esmolol Hydrochloride) Injection, 250 Miligrams/Mililiter, 10-Mililiter Ampule, Was Withdrawn from Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 24710, 24711 (May 5, 2010).

42 Citizen Petition, at 44, note 105.

43 75 Fed. Reg. at 24711. The fact that an "alternative presentation" of the product was available was noted, but not relied upon, in making this determination.

44 Citizen Petition, at 44–45.

45 *See* FDA Response to ISTA Pharmaceuticals Citizen Petition, at 16. Bromday was approved "as a new bromfenac product" via a supplement to the Xibrom NDA; the statements Reckitt quotes in its Citizen Petition are drawn from a paragraph addressing "the events leading to Bromday's approval" prior to Xibrom's withdrawal and are wholly inapplicable here. *Id.* at 14, 16.

46 *Id.*

comparison" to an alternative product. Simply, Reckitt has cherry-picked FDA statements in support of an invented proposition regarding "risk-benefit comparisons."

If a lesson can be drawn from the administrative precedent cited by Reckitt in the Citizen Petition, it is that FDA will consider the adequacy of a withdrawn product's labeling when determining whether to permit reintroduction to the market. Such a conclusion is consistent with other administrative precedent that is more relevant to the current proceeding. In particular, the FDA's review of the withdrawal of "original" Zosyn from the market is cogent and instructive.[47] In that proceeding, generic applicants sought a determination from FDA that Wyeth did not withdraw the original formulation of the product for reasons of safety or effectiveness. Wyeth asserted that it had reformulated the product due to concerns regarding the formation of particulate matter, and that reformulation also resulted in a change to product's compatibility profile with respect to Lactated Ringer's Solution ("LRS") and certain aminoglycoside antibiotics.[48] In challenging FDA's ability to grant the requested determination and approve generic versions of the original Zosyn formulation, Wyeth cited (among other potential safety issues) the risks associated with approving a generic product that exhibits a different compatibility profile than the currently-marketed brand product. FDA dismissed the argument, noting that "[t]he *approved labeling* informs health care providers about the generic product's compatibility (or lack thereof) . . . . [and the] generic [product] is as safe and effective as Wyeth's reformulated Zosyn under the labeled conditions of use."[49] In response to Wyeth's claim that it withdrew the original formulation for safety reasons, FDA found that *facts* such as "Wyeth marketed the original Zosyn formulation for nearly 13 years," "[b]oth the original Zosyn formulation and reformulated Zosyn were on the market simultaneously for some period of time," and Wyeth's announcement, upon approval of reformulated Zosyn, that the "safety profile" of the product had not changed, were determinative.[50]

In the case of Reckitt's RLD, the same facts that led FDA to dismiss Wyeth's arguments exist: Reckitt marketed the RLD and Suboxone Film concurrently for more than two years,[51] it marketed the product for several years after first learning of the pediatric exposure issues, and its public statements indicate that the withdrawal occurred primarily, if not solely, for business, not safety, reasons. Moreover, FDA's institution of a SSRS requirement on applicants seeking to market generic versions of the RLD indicates that the agency believes that the risks cited by Reckitt (pediatric exposure) can in fact be adequately addressed through the product's labeling. At bottom, neither the facts nor the law and administrative precedent support a conclusion that Reckitt's plan to withdraw the RLD from the market is based on safety concerns.

---

47 *See* FDA Consolidated Response to Sandoz Inc., Wyeth Pharmaceuticals, Rakoczy Molino Mazzochi Siwik LLP, and Orchid Healthcare Citizen Petitions, Docket Nos. FDA-2005-P-003, FDA-2006-P-0019, FDA-2006-P-0331, and FDA-2006-P-0391 (Sept. 15, 2009).

48 *Id.* at 2.

49 *Id.* at 6 (emphasis added).

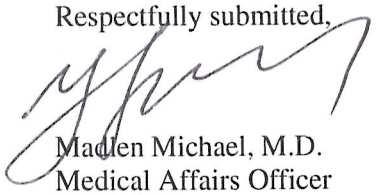
50 *Id.* at 9.

51 We note that, in the case of Zosyn, Wyeth marketed both formulations for a period of months, not years.

* * * *

For the reasons set forth herein and by other commenters to the above-referenced docket, we respectfully request that FDA deny Reckitt's Citizen Petition in full.

Respectfully submitted,



Madlen Michael, M.D.
Medical Affairs Officer
Actavis Inc.