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Via e-mail: douglas.throckmorton@ fda.hhs.gov

Douglas C. Throckmorton, M.D.
Deputy Director for Regulatory Programs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Comment to the Docket on Behalf of ECI Pharmaceuticals LLC ("ECI") Regarding October 27, 2017 Request Submitted to FDA on Behalf of Virtus Pharmaceuticals OPCO II, LLC ("Virtus"), Request for Internal Agency Review of Decision under 21 C.F.R. § 10.75 Regarding the Regulatory Status of Librax.

Dear Dr. Throckmorton:

We represent ECI Pharmaceuticals LLC ("ECI") in the above-referenced matter. We are submitting the comments below in response to and in support of the October 27, 2017 request for Internal Agency Review of Decision under 21 C.F.R. § 10.75 submitted by Virtus Pharmaceuticals OPCO II, LLC ("Virtus" and "Virtus Request for Review").

In its Request for Review, Virtus requests that FDA review the Notice to the Docket issued by FDA's Center for Drug Evaluation and Research ("CDER") on May 23, 2016 (FDA Notice to Docket 1975-N-0336 Librax® DESI 10837 ("Notice")). The Notice stated that Librax was not subject to review under DESI because, as per a Stipulation for Dismissal entered into by FDA in 1973, FDA approved a new drug application for Librax on September 1, 1966 on the basis of *both* safety and efficacy. This 2016 Notice reversed approximately 40 years of both public pronouncements by FDA and FDA established practice, under which FDA both stated that Librax had not yet had a new drug application ("NDA") approved on the basis of efficacy (and that Librax therefore remained in DESI review), and under which FDA treated Librax and all Identical, Related and Similar ("IRS") drugs as being subject to DESI review.

We have reviewed the Notice, which consists of three sentences only. The sole basis provided by FDA for its reversal of its decades-long, established practice as to Librax's DESI status is a quote from the Stipulation for Dismissal in *Hoffman-La Roche, Inc. v. Richardson, et. al,* Civil Action 11-73 (D.N.J. Aug. 2, 1973):

> *A new drug application for Librax was approved by the Food and Drug Administration on September 1, 1966. At that time, pursuant to the 1962 New Drug Amendments, the Food and Drug Administration determined that Librax*

> *was safe and effective for the indications set forth in its labeling. As such, Librax is not subject to review under DESI.*

We strongly disagree with FDA's conclusions. The sole support which FDA cites for its statement that Librax is no longer subject to review under DESI is a single sentence in a stipulation dismissing litigation against FDA brought by Hoffman-LaRoche[1] that FDA had determined that Librax was safe and effective at the time that it approved an NDA for Librax on September 1, 1966. As discussed more fully below, the statement in the Stipulation for Dismissal is incorrect, as FDA did not approve a new drug application in 1966 for Librax, based on evidence of safety and efficacy. Rather, FDA *reinstated* Librax's previous, pre-1962 NDA, which had been based only on evidence of safety, not effectiveness. FDA's 1966 reinstatement of the Librax NDA was not based on any evidence of effectiveness; rather, it was based only on evidence addressing safety concerns which had arisen after its approval of the original NDA had been granted. Therefore, contrary to both the statement in the 1973 Stipulation for Dismissal and in the 2016 Notice, FDA has never approved Librax on the basis of effectiveness, and Librax remains in DESI review.

Moreover, as discussed more fully below, the regulatory history and docket relating to Librax confirms that Librax has never been approved on the basis of efficacy. During the entire 43-year period between the 1973 Stipulation for Dismissal and the 2016 Notice, FDA never stated or indicated anything other than that Librax remained in DESI review. Certainly, FDA never stated that Librax had been approved on the basis of effectiveness. Indeed, as recently as two months before it placed the 2016 Notice on the docket, FDA continued to represent to U.S. congressional staff that Librax remained in DESI review.

By contrast, the sole support for the May 23, 2016 Notice's statement that Librax is not subject to DESI review is the mistaken assertion in the 1973 Stipulation for Dismissal that the Librax NDA was approved in 1966 on the basis of efficacy. But this is far from the binding "authority" that FDA apparently considers it to be. First, Hoffman-LaRoche never submitted, and therefore FDA never considered, any evidence as to Librax's effectiveness; thus, the 1966 reinstatement of the Librax NDA *cannot* have been made on the basis of effectiveness. FDA had no power to stipulate to a determination which it had not made; indeed, to find that FDA is somehow bound to uphold a stipulation as to a determination of effectiveness which was never performed would undermine the laws which require FDA to protect consumers by assessing new drugs' effectiveness.

In addition, to the degree that the stipulation arguably has any binding effect, it is well-settled that stipulations as to *issues* (as opposed to legal claims) have no binding effect at all outside of the litigation in which they were reached (i.e., stipulations as to factual issues have no collateral estoppel effect). The question of whether FDA's September 1, 1966 approval of the Librax NDA was based on both safety *and* efficacy is an issue of fact. Because this issue was never

[1] Hoffman-LaRoche is an entity which is no longer the owner of Librax, and which has no interest in the question of whether Librax is subject to DESI review.

litigated (FDA entered into a Stipulation for Dismissal in 1973 with Hoffman-LaRoche in lieu of filing an answer to Roche's complaint), the stipulation *cannot* bind FDA as to the question of whether the Librax NDA was approved on the basis of effectiveness (and therefore whether Librax remains in DESI review).

Finally, in its Request for Review and follow up comment, Virtus has demonstrated that the Notice was unlawfully issued, because FDA did not provide notice and an opportunity for comment prior to this significant change in its decades-old policy and otherwise failed to comply with the requirements of the Administrative Procedures Act ("APA"). We concur with and support Virtus's arguments.

We explain below.

I. Background and Regulatory History/Status of Librax Capsules and Identical, Related, or Similar (IRS) Drugs

The regulatory and administrative record related to Librax proves that Librax and those products that are identical, related, or similar to it ("IRS") remain under DESI review.

Librax was originally marketed by Roche Pharmaceuticals, Division of Hoffman-LaRoche, Inc., Nutley, New Jersey. Librax is currently marketed by Valeant Pharmaceuticals North America LLC, Bridgewater, New Jersey ("Valeant"). The following facts establish that FDA has not approved Librax for *both* safety *and* efficacy:

1. Librax was not included in the Orange Book in the more than three decades elapsing between its initial publication and the 2016 Notice.

The FDA's ***Approved Drug Products with Therapeutic Equivalence Evaluations*** (commonly known as the Orange Book) identifies drug products which have been approved on the basis of safety *and* effectiveness by FDA under the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act"). From the inception of the Orange Book, Librax was not included in its listings because Librax has never been the subject of an FDA-approved NDA for safety *and* effectiveness. In fact, for over 30 years, FDA's preface to the Orange Book made explicitly clear that Librax's omission from the Orange Book was not an oversight or error, but rather was the consequence of the fact that it was in DESI review: "[d]rugs on the market approved only on the basis of safety (covered by the ongoing [DESI] review [*e.g.*, Donnatal® Tablets and *Librax® Capsules*] or pre-1938 drugs [*e.g.*, Phenobarbital Tablets]) are not included in this publication."[2] Librax, in this regard, was the proverbial "poster child" of a drug still under DESI review and thus it and all drugs IRS to it could be marketed in spite of there being no FDA-approved NDA for efficacy. Further, the DailyMed website maintained by the National Institutes of Health affirmed for those many decades that Librax had not been approved on the basis of effectiveness,

[2] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf (*emphasis added*).

with a long-time statement that FDA has classified Librax as "possibly" effective as "adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis;" this statement was only deleted following FDA's May 23, 2016 Notice.

The Orange Book continued to omit Librax from the list of products approved on the basis of both safety and effectiveness, and to explicitly state that Librax had only been approved on the basis of safety and was therefore in DESI review, for more than three decades. Indeed, as recently as May 2, 2011, Lori Cantin, R.Ph. Pharm.D., CDR, USPHS, Division of New Drugs and Labeling Compliance, Office of Compliance, CDER in a May 2, 2011 stated in a presentation that Librax Capsules is not included in the Orange Book.[3] Librax was only included in the Orange Book after the errant 2016 Notice was issued.

2. FDA Compliance Policy Guide (CPG) 440.100)

The FDA in CPG 440.100 "Marketed New Drugs without Approved NDAs and ANDAs" also states that there are as many as several thousand drug products that are currently marketed without FDA approval. These include drugs that are subject to ongoing DESI proceedings and for which a final determination regarding their efficacy has not yet been made. This group includes unapproved products that are IRS to those products specifically reviewed by the NAS/NRC (*i.e.*, those products approved only for safety between 1938 and 1962). *See* 21 CFR 310.6. The FDA states in CPG 440.100 its longstanding policy that products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding.

3. November 11, 1975, FDA Federal Register notice regarding *"Certain Drug Products Containing an Anticholinergic/Antispasmodic in Combination with a Sedative/Tranquilizer; Antispasmodic Drugs alone".*[4]

In a November 11, 1975 Federal Register notice, FDA conveniently recounted the approval history to that point for Librax Capsules, stating:

> A. The new drug application (NDA) for Librax® Capsules, containing clidinium bromide 2.5 mg and chlordiazepoxide 5 mg; Roche Laboratories, Division of Hoffman-La Roche, Inc., Nutley, NJ, was approved only based upon the drug safety regime prior to 1962. However, approval of the NDA was withdrawn by the FDA on January 26, 1966[5], following the occurrence of accentuated anticholinergic effects and the discovery that certain lots of the drug contained greater than usual amounts of impurities, which were analogues of clidinium.

[3] http://www.fda.gov/downloads/aboutfda/workingatfda/fellowshipinternshipgraduatefacultyprograms/pharmacystudentexperientialprogramcder/ucm253386.pdf
[4] 40 Fed. Reg. 52644 (Nov. 11, 1975).
[5] 31 Fed. Reg. 1015

In other words, Librax's NDA was not withdrawn because of the lack of evidence of effectiveness; rather, the NDA was withdrawn on January 26, 1966 due to safety concerns.

B. The Librax® new drug application was ***reinstated*** on September 1, 1966, after Roche submitted new data including new manufacturing procedures to decrease the amount of impurities. FDA continued in the November 1975 notice stating, "[h]owever, since this *reinstatement* approval *was not* based upon a complete review of the entire application and *did not constitute a determination that all claimed indications are supported by substantial evidence of effectiveness*, exclusion of Librax® from NAS-NRC review was *inappropriate*."[6]

Here it is clear FDA did not state the Librax® NDA was approved on September 1, 1966. The FDA merely reinstated the original NDA that was approved prior to 1962 for safety only. The reinstatement, therefore, placed Librax® back into DESI review status.

C. FDA continued in the November 1975 notice that the Agency had since reviewed the clinical data Roche included in the NDA and FDA concluded that the data do *not* provide substantial evidence of *effectiveness* of the fixed combination.[7]

D. Consequently, the FDA explicitly concluded that, as of November 11, 1975, "[a]ll identical, related, and similar ("IRS") drug products, not the subject of an approved new drug application, are covered by the applications reviewed and are subject to this notice (21 CFR 310.6)."[8]

E. FDA also added that, "[b]ecause of the importance in day-to-day practice of these drugs, the need to develop information on this widely used class of drugs, and the difficulty of planning and conducting studies of the common gastrointestinal disorders, these drugs are being permitted to remain on the market pending completion of scientific studies to determine effectiveness."[9]

F. FDA ordered that Class A drugs including the combination of clidinium bromide and chlordiazepoxide HCl shall be labeled as "*possibly effective* as adjunctive therapy in the treatment of peptic ulcer and as possibly effective and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis…."[10] (As noted above, Librax's labeling has now been changed, following the May 23, 2016 Notice.)

[6] *Id* at 52645-46 (*emphasis added*).
[7] *Id* at 52646.
[8] *Id.*
[9] *Id* at 52648.
[10] *Id at* 52649 (*emphasis added*).

4. January 16, 1981 Federal Register Notice

On January 16, 1981, FDA issued a Notice of Opportunity for Hearing (NOOH) to withdraw approval of the Librax NDA on the basis that the data submitted to FDA was inadequate and did *not* provide substantial evidence that Librax was *effective* for its intended uses.[11] In this January 16, 1981 *Federal Register* notice,[12] FDA stated that Roche Laboratories did not submit data from a clinical study in support of Librax. FDA also stated that Roche submitted data from an ongoing study of the prevalence of emotional factors in association with certain gastrointestinal disorders and the results of a medical marketing summary undertaken in August and September 1974 in which physicians were asked to indicate their preference concerning the use of anticholinergic/sedative drugs in various diseases. Roche also submitted the results of pharmacology studies in mice. FDA concluded in this notice that "[c]learly, none of these submissions fulfill the requirements that substantial evidence of effectiveness be shown by adequate and well-controlled studies."

5. July 14, 1981 Federal Register Notice

In the July 14, 1981 *Federal Register*, FDA published a notice withdrawing the approval for "Certain anticholinergics/Antispasmodics in Combination With a sedative, and Single-Entity Antispasmodic, in Conventional Dosage Form; Withdrawal of Approval." However, the FDA also stated that a hearing was requested for NDA 12-750 Librax® Capsules and other products, and that the requests were under review. The FDA concluded that marketing of those drug products for which hearing requests are under review, such as those covered by NDA 12-750 Librax® Capsules, *may continue pending a ruling on the requests*.[13]

6. July 24, 2012 Federal Register Notice[14]

A. The FDA published a notice in the July 24, 2012 *Federal Register* offering an opportunity to affirm *outstanding* hearing requests pertaining to several dockets including Docket No. FDA-1975-N-0336, (Formerly75N-0184) (DESI 10837).[15]

B. FDA noted that in response to the January 1981 notice, Roche Laboratories (now part of Genentech, Inc.) filed a timely hearing request. The FDA also stated that it had sent a letter to Genentech in November 2010 requesting (Genentech) either withdraw or affirm its outstanding hearing request under this docket within thirty (30) days.[16]

[11] 46 Fed. Reg. 3977.
[12] 46 Fed. Reg. 3977
[13] *See id* at 36248.
[14] 77 Fed. Reg. 43337.
[15] *See Id* at 43338.
[16] *See Id* at 43341.

C. FDA reported that Genentech informed FDA on February 4, 2011 that it was no longer interested in pursuing the hearing request filed by Roche Laboratories, but noted that Genentech had sold the rights of the product to Valeant Pharmaceuticals International, Inc.

D. It is our understanding that the NDA holder affirmed the hearing request for Librax® Capsules on August 12, 2012. Valeant did not withdraw its request for almost four years (until after FDA issued its mistaken May 23, 2016 Notice).

7. Information Provided by FDA Staff to Congress (U.S. House of Representatives, Energy and Commerce Committee)

FDA continued to take the position that Librax was subject to DESI review well into 2016. Less than two months before it issued the May 23, 2016 Notice, the FDA provided information to the Majority Staff of the House Energy and Commerce Committee. The Majority Staff had submitted questions to FDA about the DESI program. In response, on March 8, 2016 and March 28, 2016, FDA staff stated, in writing, that approximately 3,400 drug products intended for use in humans were reviewed under the DESI program. The FDA staff also stated that these prescription (Rx only) drugs had been approved for safety only and fewer than a dozen DESI proceedings remain open or "pending."

The FDA staff report identified Librax, in particular, as one of the drugs still subject to DESI review, stating:

> **"Chlordiazepoxide hydrochloride and clidinium bromide (Librax); (Docket No. FDA-1975-N-0336, formerly 75N-0184); DESI 10837**
> This proceeding remains pending with an open hearing request."

II. FDA's May 23, 2016 Notice, and the Underlying 1973 Stipulation for Dismissal and September 1, 1966 Letter Reinstating Librax's NDA

Notwithstanding its consistent, 43-year history of treating Librax as a drug which had not been approved for effectiveness and as therefore subject to DESI review, on May 23, 2016, FDA placed the subject Notice on the Librax DESI docket stating that Librax was no longer subject to DESI review. The entire three-sentence body of the Notice reads as follows:

> As set forth in the Stipulation for Dismissal in Hoffman-La Roche, Inc. v. Richardson, et. al, Civil Action 11-73 (D.N.J. August 2, 1973), "[a] new drug application for Librax was approved by the Food and Drug Administration on September 1, 1966. At that time, pursuant to the 1962 New Drug Amendments, the Food and Drug Administration determined that Librax was safe and effective for the indications set forth in its labeling." As such, Librax is not subject to review under DESI.

The record is silent as to why, not two months after informing congressional staff that Librax was subject to the DESI process, FDA suddenly decided to reverse its four-decades long policy of adjudging Librax subject to DESI review. We note that not one of the Notice's three authors initialed it, which is highly unusual in an official FDA notice to the docket. Of greater import, we also note that FDA placed the Notice on the docket without any prior notice to the public and without publishing it in the *Federal Register* or providing any opportunity for public comment.

As discussed above and as is clear from the body of the Notice, the sole "authority" upon which the Notice's assertion that Librax is not subject to DESI review rests is a single sentence which was apparently excerpted from the 1973 Stipulation for Dismissal of litigation between Hoffman-LaRoche (the original owner of Librax) and FDA. We have contacted the District Court for the District of New Jersey to obtain a copy of the entire Stipulation for Dismissal; however, the Court has informed us that it has been unable to locate a copy of this document. We have also attempted to obtain a copy of the stipulation from FDA, which has similarly informed us that it has been unable to obtain this document. Moreover, while Virtus quoted from the Stipulation for Dismissal in its Request for Review and apparently attached it to its Request as an exhibit, it is not available in the version of Virtus's Request for Review, which has been placed on the Librax DESI docket. Therefore, we cannot comment specifically upon the contents of that stipulation, including the context for its apparent assertion that FDA's September 1, 1966 Librax approval was based upon both safety and efficacy. We note, however, that as per Virtus's Request for Review, the statement as to FDA's approval of the Librax NDA apparently contained in the Stipulation was explicitly made subject to FDA's right to "review its above-referenced approval of the new drug application for Librax." In addition, Roche retained its right to "interpose procedural or substantive objections to any subsequent Agency action bearing on Librax."

We can and must comment, however, upon the September 1, 1966 letter itself, as it is the sole source material for the Stipulation's (apparent) assertion that FDA approved Librax for both safety and efficacy in 1966. As discussed more fully above, the original Librax NDA approval was given prior to the 1962 amendments to the Act, which required a showing of effectiveness as well as safety in new drug applications. As such, the original NDA was approved solely on the basis of safety. Subsequent to this approval, issues as to Librax's safety – not its effectiveness – led FDA to withdraw its approval of Librax. FDA then reinstated its approval to Librax once again via a letter to Hoffman – La Roche dated September 1, 1966; however, as FDA explicitly stated in its November 11, 1975 *Federal Register* notice, 40 *Fed. Reg.* 52644, this approval did not take the form of a new NDA as if it were divorced from the NDA that had gone before. Rather, the original, safety-only pre-1962 Librax NDA was ***reinstated*** on September 1, 1966, after Roche submitted new safety data, including new test procedures to detect the amount of impurities. As stated in FDA's November 11, 1975 *Federal Register* notice, "this *reinstatement* approval *was not* based upon a complete review of the entire application and *did not constitute a*

determination that all claimed indications are supported by substantial evidence of effectiveness . . . ."[17]

Moreover, the September 1, 1966 letter itself conclusively establishes that the approval which FDA granted to Librax in FDA's 1966 was confined solely to Librax's safety, and did not address the question of Librax's effectiveness. The letter acknowledges receipt of Roche's "supplemental new drug application" for Librax on May 17, 1966, and specifies that the supplemental application provides for the following areas/topics: "revised labeling, revised synthesis for clidinium bromide, revised manufacturing and control procedures, and for [information redacted] as a supplier of crude clidinium bromide raw material." Each one of these listed areas or topics addresses safety issues only and does not address effectiveness. The letter concludes with a statement that "[a]pproval of this new drug application, as supplemented, is *reinstated*." Thus, the pre-1962 NDA for Librax, which was based solely on safety, was reinstated as supplemented by data addressing the safety concerns that had arisen after the original approval had been given.

III. Valeant's Repeated False Assertions that Librax Has Been Approved for Effectiveness

Both before and after FDA placed its May 23, 2016 Notice on the Librax DESI docket, Valeant has routinely – and falsely – asserted that FDA approved Librax for *both* safety *and effectiveness* in 1966. Curiously, although Valeant is the owner of the rights to Librax and presumably has access to the entire file and documentary history of this drug, Valeant has *never* cited to nor provided in support of these assertions any FDA approval letters, evidence of data supporting the effectiveness of Librax submitted to FDA, etc., to support its claim that FDA has fully approved Librax for both safety and effectiveness.

For example, on July 30, 2015, Valeant sent a cease and desist letter to ECI, asserting that "A new drug application for Librax was approved by the Food and Drug Administration ("FDA") on September 1, 1966. At that time, pursuant to the 1962 New Drug Amendments, FDA determined that Librax was safe and effective for the indications set forth in its labeling. As a result, Librax is an FDA-approved drug." Valeant provided no documents or other evidentiary basis whatsoever for this assertion. Based on this false assertion, Valeant demanded that ECI cease and desist selling its lawful chlordiazepoxide hydrochloride 5 MG, clidinium bromide 2.5 MG oral capsules. Curiously again, although Valeant sent the July 30, 2015 cease and desist letter to ECI almost a year prior to FDA's issuance of its May 23, 2016 Notice, the 3-sentence wording of Valeant's false claim that Librax was approved for effectiveness in 1966 is almost identical to the 3-sentence wording which makes up the body of the FDA's May 2016 Notice.[18]

[17] *Id* at 52645-46 (*emphasis added*).
[18] As quoted above, FDA's 2016 Notice states: "As set forth in the Stipulation for Dismissal in Hoffman-La Roche, Inc. v. Richardson, et. al, Civil Action 11-73 (D.N.J. August 2, 1973), '[a] new drug application for Librax was approved by the Food and Drug Administration on September 1, 1966. At that time, pursuant to the 1962 New Drug

After FDA issued its May 23, 2016 Notice, Valeant sent another letter to ECI dated June 15, 2016, again demanding that ECI cease selling its chlordiazepoxide hydrochloride 5 MG, clidinium bromide 2.5 MG oral capsules. Relying solely upon FDA's mistaken May 23, 2016 Notice, Valeant again falsely asserted that Librax was approved for safety and effectiveness on September 1, 1966 and is therefore not subject to DESI review.

Valeant has not confined its false claims to letters to ECI. On June 2, 2016, Valeant sent a letter to Thomas Cosgrove, J.D., and Kathleen Anderson, Pharm D., Office of Compliance, CDER. Pointing solely to FDA's mistaken May 23, 2016 Notice, Valeant stated that it was withdrawing its NOOH hearing request for Librax because FDA had "formally acknowledged" that the Librax NDA had been "fully approved on the basis of both safety and effectiveness." Once again, Valeant provided no evidence or documentation to support this claim whatsoever, other than FDA's May 2016 Notice.

Finally, Valeant repeated its false claims as to FDA's approval of Librax in its opposition to Virtus's Request for Review of FDA's May 23, 2016 Notice. In a letter to Douglas C. Throckmorton, M.D. dated September 26, 2017, Valeant stated that "FDA approved the Librax NDA on the basis of safety and effectiveness on September 1, 1966." Valeant cites to no NDA approval letter or other documentation whatsoever that establishes that any evidence as to Librax's effectiveness was submitted to FDA in connection with that September 1, 1966 approval (or indeed, ever), much less that FDA's September 1, 1966 approval was based upon Librax's effectiveness. Relying upon this false assertion, Valeant then urged FDA to "initiate enforcement action" to remove products which are IRS to Librax from the market.

Valeant submitted another letter to Douglas C. Throckmorton, M.D. dated November 22, 2017, in response to Virtus's October 27, 2017 comments on its Request for Review. Valeant again falsely asserts that FDA "fully approved [Librax] on the basis of safety and effectiveness in September 1966," and again pushes FDA to remove all other drugs which are IRS to Librax from the market. Again, however, Valeant neither references nor attaches any documentation whatsoever actually demonstrating that FDA's September 1, 1966 reinstatement of Librax's pre-1962 NDA approval was based on any evidence or findings as to Librax's effectiveness.

As discussed more fully above, Valeant's consistent assertions that FDA's September 1, 1966 reinstatement of Librax's pre-1962 NDA approval was based upon both safety and effectiveness are belied by FDA's September 1, 1966 letter itself, which makes no mention of any evidence of or findings as to Librax's effectiveness. They are also belied by FDA's prior *Federal Register* notices and FDA's decades-long course of conduct both before and after the 1973 Stipulation for Dismissal.

Amendments, the Food and Drug Administration determined that Librax was safe and effective for the indications set forth in its labeling.' As such, Librax is not subject to review under DESI."

Finally and significantly, they are belied by the fact that until January of 2017, Valeant itself acknowledged that Librax has not been approved effective for all indications covered by the drug's NDA, because Valeant's own labeling for Librax included less than effective indications as required by FDA in its November 11, 1975 Federal Register notice.[19] Until January of 2017, Valeant's labeling for Librax and that of other IRS products (such as ECI's product) included the following statement in the "Indications and Usage" section identical declarations:

> Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications as follows: 'Possibly' effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis. Final classification of the *less-than-effective indications* requires further investigation.

For FDA to grant a new drug approval under section 505 of the FFDCA, FDA must find the product to be safe *and effective* for all of its labeled indications. Until January of 2017, Valeant's Librax labeling consistently bore less-than-effective indications, which directly contradicted Valeant's repeated assertions that FDA had found that Librax was effective for all labeled indications on September 1, 1966, and further reveal the error in FDA's May 23, 2016 Notice to Docket that Librax is FDA-approved for safety and efficacy. In fact, the only obvious conclusion is that FDA has never approved Librax Capsules for safety and efficacy and FDA is mistaken in its May 2016 Notice.

FDA has taken this same view in multiple public venues, not the least of which was that until 2016, the Orange Book did not include Librax as an FDA approved drug under the 1962 Amendments (including safety and effectiveness).

IV. Even Assuming that FDA Has Concluded that Librax Has Been Approved for Effectiveness and that Librax is No Longer Subject to DESI Review, FDA Has Not Made Any Determination that Drugs Which Are IRS to Librax Are Unapproved and/or Unlawful for Sale

The regulatory "status" or significance of FDA's May 23, 2016 Notice to Docket is, at best, highly ambiguous. Unlike FDA's prior actions during the long period of regulatory history regarding Librax's DESI status, FDA did not publish the Notice to Docket in the *Federal Register*, nor did it provide notice or opportunity for public comment.

However, even assuming for the sake of argument that FDA has decided via its May 2016 Notice that Librax has now been fully approved for both safety and effectiveness, FDA's decision is limited to just that – a determination as to Librax itself. FDA's May 23, 2016 Notice

[19] *See* 40 Fed. Reg. 52644 (Nov. 11, 1975).

to Docket states only that Librax is not subject to DESI review, and cites to the 1973 Stipulation for Dismissal as its sole support for this conclusion. It is completely silent as to anything other than Librax, including drugs that are IRS to Librax, and makes no finding or ruling whatsoever that such IRS drugs are unapproved or otherwise unlawful for sale.

FDA similarly failed to state or find in any way that drugs which are IRS to Librax are unapproved or otherwise unlawful for sale in its only public pronouncement regarding the May 2016 Notice, which is an August 18, 2016 letter to Hyman, Phelps & McNamara, P.C. (Virtus's counsel). As in the Notice itself, FDA's discussion in this letter is confined solely to the issue of whether Librax is subject to DESI review. While FDA does mention the fact it did not object to the entry of drugs which are IRS to Librax prior to the 2016 Notice, it mentions this fact solely in the context of "acknowledging" that its entire prior regulatory course of conduct (including its treatment of drugs which are IRS to Librax) is inconsistent with the Notice; it does not state that IRS drugs are now unapproved, unlawful, etc., nor does it make any statements or conclusions as to the regulatory status of any drug other than Librax.

Nineteen months have now elapsed since FDA issued the May 23, 2016 Notice regarding Librax. During this entire period, FDA has neither issued any announcement or opinion that drugs which are IRS to Librax are now unapproved or unlawful for sale nor taken any enforcement action against sellers of IRS drugs – notwithstanding Valeant's continued urgings to do so. Therefore, the only conclusion which can be drawn from FDA's writings and lack of action is that FDA has not "ruled" or determined that drugs which are IRS to Librax are unapproved or otherwise unlawful to sell in the United States.

V. Virtus's Request for Internal Agency Review and ECI's Conclusions in these Comments

On July 7, 2017, Virtus filed its Request for Internal Agency Review of FDA's determinations that Librax has had a current valid NDA since September 1, 1966 for both safety and effectiveness and therefore is not subject to the DESI review process, and that Librax is therefore not subject to a Notice of Opportunity for Hearing ("NOOH") that has been outstanding since January 16, 1981.

In its Request, Virtus asserts that Librax has not been approved on the basis of effectiveness, because the September 1, 1966 NDA approval was not made on the basis of effectiveness, and/or because even if it were, FDA subsequently in effect withdrew that finding in 1975 when it determined that the effectiveness of the fixed combination of chlordiazepoxide HCl and clidinium bromide had not been established. Virtus further asserts that the 1970 Stipulation for Dismissal does not bind FDA to a finding that Librax has been approved for both safety and effectiveness, because the stipulation expressly reserved FDA's right to review its approval of Librax, which it subsequently did when it found that Librax did not satisfy the effectiveness requirements for a combination product. Virtus also argues that even if FDA had approved

Librax's NDA on the basis of both safety and effectiveness, this would not prevent it from being subject to DESI review, as FDA's position is that if a drug has been found to lack substantial evidence of effectiveness for any of its claims, FDA may place the drug on DESI review, regardless of the approval status of that product. Finally, Virtus argues that FDA's actions are unlawful as a matter of law because they violate the due process rights of Virtus and others without providing the right to a public hearing, and because they violate the Administrative Procedure Act and FDA's own regulations by failing to provide notice and an opportunity for public comment.

ECI agrees with and supports all of Virtus's claims, and adopts them here by reference. Clearly, FDA is obligated by law to continue to observe its longstanding policy permitting drugs subject to DESI Review and those that are IRS to such drugs to be marketed without an FDA-approved NDA. Valeant's assertion that Librax is approved for safety and efficacy is false and FDA's statement in the recent Notice to Docket that Librax is approved for safety and efficacy is mistaken.

When FDA reinstated the Librax NDA on September 1, 1966, only one approval existed to be reinstated: the pre-1962 Roche NDA, which FDA approved based upon safety data alone. Moreover, FDA reiterated in the *Federal Register* subsequent to both the September 1, 1966 letter and the 1973 Stipulation for Dismissal with Roche that Librax had not been found effective. Neither Roche nor Valeant has an FDA-approved NDA for Librax that has been considered on the basis of *both* safety *and* effectiveness. And until it abruptly abandoned decades of administrative practice in the May 2016 Notice, FDA has repeatedly taken the view that Librax remains in DESI status as well.

The FDA has no legal basis for issuing the "Notice to Docket" asserting that the FDA approved Librax in 1966 for safety and efficacy. As discussed more fully above, the sole support which FDA cites for its conclusion in its May 23, 2016 Notice that Librax has been approved for both safety and efficacy is the 1973 Stipulation for Dismissal of the litigation filed against FDA by Hoffman La-Roche. In fact, FDA asserts in its August 18, 2016 letter to Virtus that it is bound by the 1973 Stipulation for Dismissal, because it was signed by the Commissioner of Food and Drugs.

FDA's apparent beliefs as to the binding effect of its 1973 Stipulation for Dismissal are incorrect as a matter of law. The Supreme Court has held that while consent judgments (which would include cases dismissed pursuant to Stipulations for Dismissal) have *res judicata* (claim preclusion) effect, they *do not* have collateral estoppel (issue preclusion) effect in any proceeding other than the one in which they were reached: "In most circumstances, it is recognized that consent agreements ordinarily are intended to preclude any further litigation on the claim presented but are not intended to preclude further litigation on any of the issues presented. Thus consent judgments ordinarily support claim preclusion but not issue preclusion." *See Arizona v. California*, 530 U.S. 392, 395 – 96 (2002) (*quoting* 18 C. Wright, A. Miller, & E. Cooper,

Federal Practice and Procedure § 4443, p. 384- 85 (1981)). This is because "In the case of a judgment entered by confession, consent, or default, none of the issues is actually litigated. Therefore, the rule of this Section [describing issue preclusion's domain] does not apply to any issue in a subsequent action." *See id.* at 396 (*quoting Restatement (Second) of Judgments* § 27, p. 250 (1982)). The reason for this rule is clear: giving collateral estoppel effect to a "fact established in prior litigation not by judicial resolution but by stipulation" would "discourage parties from compromising and narrowing issues because of the possible future preclusive effect of their actions." *See, e.g., United States v. Young*, 804 F.2d 116, 118 (Eighth Cir. 1986). *Accord CSX Transp., Inc. v. Clark*, 2012 U.S. Dist. LEXIS 103028 (D. Minn. 2012).

Here, FDA appears to believe that it is bound by the provision in the 1973 Stipulation for Dismissal stating that "A new drug application for Librax was approved by the Food and Drug Administration on September 1, 1966. At that time, pursuant to the 1962 New Drug Amendments, the Food and Drug Administration determined that Librax was safe and effective for the indications set forth in the labeling." This language is a stipulation as to a factual *issue* (whether the Librax NDA had been approved for both safety and effectiveness), not a *claim.* Because FDA and Roche entered into the Stipulation for Dismissal before FDA even filed an answer to Roche's complaint, the issue of whether FDA's 1966 NDA approval for Librax was based on both safety and effectiveness was never actually litigated or adjudicated. Therefore, the statement in the Stipulation that the Librax NDA was approved for both safety and effectiveness in 1966 is not binding on anyone, including the FDA.[20]

More importantly, even if the 1973 Stipulation could be construed as arguably having some sort of binding effect on its face (which it does not), it would be completely against public policy and an abrogation of FDA's statutory responsibilities to find that FDA is bound by a stipulation that it completed a statutorily required action which it did not in fact perform. FDA claims in its August 18, 2016 letter to Virtus that the "Stipulation for Dismissal is the controlling legal document on the question of whether Librax is subject to DESI review." That assertion is wrong, as the "controlling legal document" on the subject of whether Librax has been approved for effectiveness and hence is or is not subject to DESI review is the September 1, 1966 letter reinstating the pre-1962 Librax NDA. As discussed more fully above, the September 1, 1966 letter makes clear that Librax has never been approved for effectiveness. FDA could not legally

[20] The Supreme Court noted that while settlements generally do not give rise to issue preclusion, there may be exceptions where it is "clear" that the parties to the settlement intend their agreement to have such an effect. *See Arizona v. California, supra,* 530 U.S. at 395 – 96. Here, the terms of the Stipulation itself make clear that FDA and Roche did not intend for the Stipulation to preclude all future question or examination of whether Librax was fully approved for both safety and efficacy. As discussed more fully in Virtus's Request for Review, the Stipulation contained a provision explicitly stating that the declaration in the Stipulation that the FDA had determined that Librax was "safe and effective for the indications set forth in the labeling" in 1966 was "without prejudice to whatever rights the Food and Drug Administration may have to review its above-referenced approval of the new drug application for Librax. Similarly, plaintiff retains whatever rights it has to interpose procedural or substantive objections to any subsequent Agency action bearing on Librax."

stipulate to a necessary administrative proceeding (approval of a Librax NDA for effectiveness) which had not in fact occurred.

Finally, as discussed more fully in Virtus's Request for Review, the Notice is unlawful because it was issued without notice and opportunity for public comment. Therefore, it cannot serve to change FDA's well-established, over forty-year practice of treating Librax as a drug subject to DESI review.

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If you have any questions regarding the foregoing, please feel free to contact me directly at 410-220-2800 or blengland@fdaimports.com.

Sincerely,

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