UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

TAKEDA PHARMACEUTICALS U.S.A., INC., Plaintiff, v. SYLVIA BURWELL, Secretary of Health and Human Services, *et al*., Defendants. and HIKMA PHARMACEUTICALS PLC AND WEST-WARD PHARMACEUTICAL CORP., Intervenors-Defendants.	Civil Action No. 1:14CV1668 (KBJ)

DEFENDANTS' SUPPLEMENTAL BRIEF

Pursuant to this Court's Minute Entry dated November 5, 2014, FDA files this supplemental brief to address some issues raised by Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") in its reply brief ("Takeda Reply"). As explained below, in FDA's prior brief, and in oral argument before this Court, Takeda has wholly failed to demonstrate that FDA acted in an arbitrary and capricious, or otherwise unlawful, manner when it approved West-Ward Pharmaceutical Corp.'s ("West-Ward") colchicine product, Mitigare. As a result, judgment should be entered in FDA's favor, and this case should be dismissed.

I. Reference Drugs are Chosen by the Sponsor, Not by FDA

Takeda raises several new arguments in its reply brief. Those arguments include the assertion that West-Ward was required to reference Colcrys because FDA requires 505(b)(2) sponsors to choose the "most appropriate" listed drug to reference. Takeda Reply at 12. The citizen petition response on which Takeda relies for this assertion (the "Suboxone CP response") belies Takeda's contention. The Suboxone CP response explains:

> The Fenofibrate CP response[1] describes a suggested approach intended to enhance the efficiency of a prospective 505(b)(2) applicant's development program. An applicant choosing to rely on FDA's finding of safety and/or effectiveness for a listed drug very similar to the proposed product submitted in the 505(b)(2) application would generally need to submit less additional data to support the differences between the proposed product and the listed drug for approval in the 505(b)(2) application. However, as stated in the Fenofibrate CP response, this suggested approach does not reflect a statutory or regulatory requirement. Further, the determination of which listed drug is "most similar" to a proposed product may be difficult (except in cases in which a pharmaceutical equivalent previously has been approved) and dependent on the sponsor's approach to its development program. Accordingly, a sponsor interested in submitting a 505(b)(2) application that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs should determine which listed drug(s) is most appropriate for its development program.

Takeda Reply Ex. C at 7. Ultimately, the sponsor of a 505(b)(2) application "should determine which listed drug(s) is most appropriate for its development program[.]" *Id.* at 3. As FDA noted in the Suboxone CP response, applicants who plan "to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs" are "routinely advised" that they "must establish that reliance on the listed drug(s) is scientifically appropriate and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s)." *Id.* at 8.

[1] The Fenofibrate citizen petition response was discussed in the Suboxone CP response. *See* Takeda Reply Ex. C at 4, n.12 .

As the above makes clear, so long as a sponsor provides the necessary data and information to support the difference(s) between the reference drug and its proposed drug, and so long as the proposed drug is not an exact duplicate of the reference drug, a sponsor is free to choose the listed drug that *it* deems "most appropriate" for reliance in its 505(b)(2) application. "Most appropriate" does not mean "most similar," despite Takeda's (unsupported) attempts to attribute that meaning to the term. *See* Takeda Reply at 12-13. Here, FDA concluded that Mitigare is safe and effective, based on West-Ward's reliance on FDA's prior safety and effectiveness finding for Col-Probenecid, as well as data and information submitted in West-Ward's application. *See* AR at 119-120, 97-98. West-Ward determined that Col-Probenecid was in fact the "most appropriate" reference listed drug for Mitigare, and Takeda has not provided, and cannot provide, any authority for its contention that West-Ward was required to reference Colcrys in the Mitigare 505(b)(2) application.

II. West-Ward Did Not Rely on Colcrys in Seeking and Obtaining Approval for Mitigare

The Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(b)(2), permits a sponsor to rely on information required for approval that comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference or use (*i.e.*, published literature or FDA's prior finding of safety and/or effectiveness for one or more listed drugs). That provision discusses information "relied upon by the applicant for approval of the application," 21 U.S.C. § 355(b)(2), rather than information relied upon by FDA in approving an application. Yet Takeda claims that because *FDA* discussed Colcrys' data during its review of the Mitigare application, West-Ward was required to name Colcrys as the reference listed drug,

and FDA's purported failure to require West-Ward to reference Colcrys was arbitrary and capricious. *See* Takeda Reply at 14-17.

Takeda's contention begins with a misunderstanding of the statutory provision,[2] which does not address the data and information on which FDA is permitted to rely but rather the information on which *an applicant* is permitted to rely when seeking approval. *See* 21 U.S.C. § 355(b)(2). Here, West-Ward relied on published literature as well as FDA's safety and effectiveness findings for Col-Probenecid. AR at 108. Despite Takeda's exhaustive cites to instances in the administrative record where FDA mentioned Colcrys in reviewing the Mitigare application, Takeda has not provided any authority for the purported requirement that a 505(b)(2) applicant name a particular product as its reference listed drug if FDA "relies" on data from that product's application during the agency's review of the 505(b)(2) application. Indeed, because the results of West-Ward's drug-drug interaction studies differed from the results of Takeda's studies, it would have been unreasonable for FDA *not* to consider what led to those different results before approving Mitigare. FDA's scientific conclusions are well-documented and supported by the administrative record, and Takeda has failed to demonstrate that FDA acted in an arbitrary and capricious manner by not prohibiting West-Ward from referencing Col-Prebenecid as the listed drug in the Mitgare application.

[2] Takeda's statement that "FDA has made it clear that a 505(b)(2) applicant must reference another product if the agency relies on studies or data relating to that product in approving the applicant's application," Takeda Reply at 14, is simply not true. Takeda cites a FDA draft guidance document as support for its statement, *see* Compl. Ex. 11, but that document is devoid of any statement that FDA's review of data will bind an applicant to referencing a particular listed drug.

III. Mitigare's Labeling Does Not Need to Include Information on an Unapproved Use

Takeda claims that a FDA regulation requires drug product labeling to include information about risks raised by unapproved uses. *See* Takeda Reply at 4. Takeda is wrong. The regulation Takeda cites, 21 C.F.R. § 201.57(c)(6), provides that a "specific warning relating to a use not provided for under the "Indications and Usage' section *may be* required by FDA." 21 C.F.R. § 201.57(c)(6) (emphasis added). FDA did not require West-Ward to include information about acute gout flares on its labeling, a decision that was within the agency's discretion. *See* 21 C.F.R. § 201.57(c)(6). Other than misreading the relevant regulation, Takeda offers no support for its contention that the Mitigare labeling must contain information about an unapproved use.

Takeda also continues to assert that FDA's 2011 citizen petition response mandated inclusion of low-dose options for treatment of acute gout flares on all single-ingredient colchicine products, including those approved only for prophylaxis of gout. Takeda Reply at 4. But as FDA explained in its prior brief, *see* FDA Br. at 15-16, Takeda misinterprets the one sentence from FDA's letter that it cites. Moreover, because Mitigare is not approved for the treatment of acute gout flares, the labeling explicitly notes this fact and cautions patients to talk to their healthcare provider in the event they experience a gout flare while taking Mitigare. AR at 33-34, 40, 42-44. Takeda has once again failed to show that FDA erred in not requiring Mitigare to include information in the labeling about a use for which the product is not approved.

IV. CONCLUSION

For the foregoing reasons, judgment should be entered in favor of FDA.

Of Counsel:

WILLIAM B. SCHULTZ
General Counsel

ELIZABETH H. DICKINSON
Associate General Counsel
Food and Drug Division

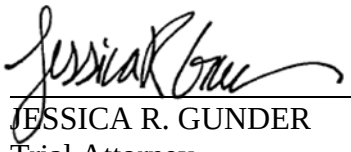
ANNAMARIE KEMPIC
Deputy Chief Counsel, Litigation

SHOSHANA HUTCHINSON
Associate Chief Counsel, Litigation
U.S. Dept. of Health & Human Services
Office of the General Counsel
10903 New Hampshire Ave.
White Oak 31, Room 4560
Silver Spring, MD 20993-0002
301-796-8566

Respectfully submitted,

JOYCE R. BRANDA
Acting Assistant Attorney General

MICHAEL S. BLUME
Director



JESSICA R. GUNDER
Trial Attorney
Consumer Protection Branch
Civil Division
U.S. Department of Justice
P.O. Box. 386
Washington, D.C. 20044
202-532-4719
Jessica.R.Gunder@usdoj.gov

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CERTIFICATE OF SERVICE

I certify that on November 14, 2014, I caused a true and correct copy of the above-entitled DEFENDANTS' SUPPLEMENTAL BRIEF to be served via the Court's Electronic Case Filing system to counsel for the plaintiff and intervenors as follows:

Jessica L. Ellsworth
HOGAN LOVELLS US LLP
555 13th Street NW
Washington, DC 20004
(202) 637-5886
jessica.ellsworth@hoganlovells.com

Susan Margaret Cook
HOGAN LOVELLS US LLP
555 13th Street, NW
Washington, DC 20004
(202) 637-6684
susan.cook@hoganlovells.com

Catherine E. Stetson
HOGAN LOVELLS, US LLP
555 13th Street, NW
Washington, DC 20004-1109
(202) 637-5491
cate.stetson@hoganlovells.com

Charles Bennett Klein
WINSTON & STRAWN, LLP
1700 K Street, NW
Washington, DC 20006
(202) 282-5977
cklein@winston.com

Elaine H. Blais
GOODWIN PROCTER LLP
53 State Street
Boston, MA 02109
(617)-570-1205
eblais@goodwinprocter.com

Jovial Wong
WINSTON & STRAWN LLP
1700 K Street, NW
Washington, DC 20006
(202) 282-5867
jwong@winston.com

Samuel S. Park
WINSTON & STRAWN LLP
35 W. Wacker Drive
Chicago, IL 60601
(312)-558-7931
spark@winston.com

William G. James
GOODWIN PROCTER, LLP
901 New York Avenue, NW
Washington, DC 20001
(202)-346-4046
wjames@goodwinprocter.com

s/ JESSICA R. GUNDER
JESSICA R. GUNDER