CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211210Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 19, 2018

TO: Vivlodex (meloxicam) oral capsule, 5 mg and 10 mg (NDA 207233) File
Qmiiz ODT (meloxicam) orally disintegrating tablet, 7.5 mg and 15 mg (NDA 211210) File

FROM: CDER Exclusivity Board

SUBJECT: Whether the 3-year exclusivity for Vivlodex (meloxicam) oral capsule (NDA 207233) blocks the approval of Qmiiz (meloxicam) orally disintegrating tablet (NDA 211210)

This memorandum addresses whether the unexpired 3-year exclusivity recognized by the Food and Drug Administration (FDA or the Agency) for Vivlodex (meloxicam) oral capsules (NDA 207233) blocks the approval of Qmiiz (meloxicam) orally disintegrating tablets (ODT) (NDA 211210), submitted by TerSera Therapeutics LLC (TerSera). For the reasons discussed below, the Exclusivity Board (Board) within the Center for Drug Evaluation and Research (CDER) recommends that the approval of TerSera's 505(b)(2) application for Qmiiz should not be blocked by the unexpired 3-year exclusivity for Vivlodex.

I. Factual Background

A. Approved Single-Ingredient Meloxicam Products Containing the Active Moiety Meloxicam

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. Like other NSAIDs, the mechanism of action of meloxicam is thought to be related to inhibition of prostaglandin synthetase (cyclooxygenase). The Agency first approved a drug containing the active moiety meloxicam on April 13, 2000, under NDA 020938 for Mobic (meloxicam) immediate release (IR) oral tablets, 7.5 mg and 15 mg. Another dosage form of Mobic (meloxicam) was approved on June 1, 2004, under NDA 021530, in the form of oral suspension, 7.5 mg/15 ml.[1] Both these dosage forms of Mobic currently are approved for the relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis

[1] NDA 021530 is currently listed in the Discontinued Section of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

(RA), and pauci-articular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients who weigh ≥ 60 kg. There are also multiple generic IR oral tablet formulations of meloxicam available.

On October 22, 2015, the Agency approved NDA 207233 for Vivlodex oral capsules, 5 mg and 10 mg. Unlike the Mobic products which were approved, in part, for the "relief of the signs and symptoms of OA," Vivlodex was approved for the "management of OA pain," a different indication.[2] Vivlodex currently has unexpired exclusivity and is discussed in further detail below.

a. NDA 207233 for Vivlodex

NDA 207233 for Vivlodex (NDA 207233) is a 505(b)(2) NDA that relied for approval, in part, on FDA's finding of safety and effectiveness for Mobic tablets 7.5 and 15 mg (NDA 020938) and published literature. Vivlodex contains a single active ingredient, meloxicam, with a single active moiety, meloxicam. Vivlodex, the first IR oral capsule formulation of meloxicam, uses SoluMatrix Fine Particle Technology intended to reduce drug particle size with the goal of increasing the surface area-to-mass ratio and thereby facilitating enhanced meloxicam absorption in the gastrointestinal tract.[3] The (b) (4) Vivlodex capsules contain either 5 mg or 10 mg of meloxicam, (b) (4) which are available in 7.5 mg and 15 mg strengths.

To support approval of the application, the applicant Iroko Properties, Inc. (Iroko) conducted: a relative bioavailability (BA) study (MELl-12-04) compared to Mobic 15 mg tablets that also assessed dose proportionality (Vivlodex 5 mg and 10 mg), and food-effect; an adequate and well controlled Phase 3 efficacy and safety study (MEL3-12-02); and an open-label Phase 3 safety study (MEL 2-12-03).[4] Although Iroko, as noted above, developed Vivlodex to have a greater extent of absorption than Mobic, the BA study failed to demonstrate this to be the case. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP or Division) concluded that Vivlodex 10 mg capsules did not result in similar systemic exposure as and was not bioequivalent to Mobic 15 mg tablets.[5] When taken under fasted conditions, the Division found that the 33% lower dose of Vivlodex 10 mg capsules compared to Mobic 15 mg tablets resulted in equivalent (geometric mean) peak concentrations (Cmax), and 18 and 33% lower (geometric mean) AUC0-t and AUC0-∞, respectively. Since the 33% lower dose of Vivlodex resulted in 33% lower AUC0-∞ compared to Mobic, DAAAP concluded that the Vivlodex formulation did not improve the bioavailability of meloxicam over that of Mobic tablets.[6]

Because the BA study failed in meeting its objectives with Vivlodex showing lower exposures than expected, the Division determined that clinical data was needed to support the approval of the Vivlodex NDA. Iroko therefore submitted, among other things, a phase 3 efficacy and safety study, MEL3-12-02, which was conducted in subjects with OA pain of the knee or hip. Study MEL3-12-02 was a placebo-controlled, multicenter, randomized, double-blind study that

[2] See Vivlodex Labeling, Section 1.
[3] NDA 207233 Clinical Review at 10; see also NDA 207233 Division Director Review at 2.
[4] NDA 207233 Division Director Review at 2.
[5] NDA 207233 Division Director Review at 4.
[6] Id.

evaluated both Vivlodex 5 mg and 10 mg capsules. The primary efficacy endpoint of this trial was the change from baseline to Week 12 in the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) Pain Subscale Score. Based on the results of the primary endpoint analysis, both the 5 mg and 10 mg doses of Vivlodex demonstrated efficacy compared to placebo in subjects with OA of the hip or knee.[7] NDA 207233 for Vivlodex was approved on October 22, 2015, for the management of OA pain. According to the Division, management of OA pain (Vivlodex's approved indication) and relief of the signs and symptoms of OA (one of Mobic's approved indications) represent two different indications. The management of OA pain indication is supported by one primary endpoint that measures pain intensity (e.g., WOMAC pain subscale, numerical rating scale, visual analog scale) and the signs/symptoms indication is supported by three primary endpoints, which include pain intensity (WOMAC pain subscale, numeric rating scale, visual analog scale), function in OA (WOMAC function subscale), and patient global impression of change.

FDA determined that study MEL3-12-02 was a new clinical investigation essential to approval of the NDA and that the study was conducted by or for the applicant; thus, Vivlodex qualified for 3-year exclusivity, which expires on October 22, 2018.[8] The 3-year exclusivity is denoted in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) as "NP" (New Product) exclusivity.[9]

B. NDA 211210 for Qmiiz

TerSera filed a 505(b)(2) NDA on December 21, 2017, for Qmiiz (meloxicam) ODT, 7.5 mg and 15 mg, that relies on FDA's finding for safety and effectiveness for Mobic tablets and published literature.[10] TerSera is seeking approval of Qmiiz for the same indications as Mobic tablets, i.e., for relief of the signs and symptoms of OA, RA, and pauci-articular or polyarticular course JRA in patients who weigh ≥ 60 kg.[11] The ODT dosage form of meloxicam was designed for drug disintegration in the mouth shortly after oral administration to allow drug administration with or without liquid beverage.[12] The proposed dosing regimen for both strengths of Qmiiz is similar when compared to the relied-upon listed drug, Mobic tablets, which are dosed once daily. The Prescription Drug User Fee Act (PDUFA) goal date is October 21, 2018.

II. Summary of Legal and Regulatory Background

Section 505(c)(3)(E)(iii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes which applications are eligible for 3-year exclusivity, as well as which 505(b)(2) NDAs will be barred or blocked from approval by another application's 3-year exclusivity. Under the Agency's interpretation of this statutory provision, for a single-entity drug to be potentially barred or blocked by 3-year exclusivity for another single-entity drug, the drug must contain the

[7] NDA 207233 Division Director Review at 10.
[8] NDA 207233 Exclusivity Summary.
[9] The Board notes generally that the scope of exclusivity should be determined by the nature of the clinical studies conducted to gain approval of the NDA, not by the exclusivity code that is used as shorthand to describe that approval in the Orange Book.
[10] NDA 211210 Clinical Review at 7.
[11] NDA 211210 Clinical Pharmacology Review at 3.
[12] NDA 21120 Clinical Review at 7.

same active moiety as the drug with 3-year exclusivity. As discussed in greater detail in Appendix A, 3-year exclusivity provides the holder of an approved NDA limited protection from new competition in the marketplace for the exclusivity-protected "conditions of approval," which FDA has interpreted to be the innovation represented by its approved drug product that is supported by new clinical investigations essential to approval. Thus, when a 505(b)(2) application for a single-entity drug seeks approval for the same drug (active moiety) to which exclusivity has attached, FDA will examine the conditions of approval supported by the new clinical investigations (other than bioavailability studies) that were essential to approval of the application with exclusivity.

If a pending 505(b)(2) application for a single-entity drug is seeking approval for the same drug for an exclusivity-protected condition of approval, the pending application will be blocked from approval until the exclusivity period expires. Exclusivity does not extend beyond the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential to approval. Therefore, 3-year exclusivity does not block approval of a pending 505(b)(2) application containing the same drug that is not seeking approval for an exclusivity-protected condition of approval for the prior NDA.

As explained in greater detail in Appendix A, the scope of 3-year exclusivity for a drug product may be affected by a previously approved drug product containing the same active moiety. The exclusivity protected condition of approval, and thus the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety. A drug product may, however, qualify for exclusivity for a condition(s) of approval that differs from the exclusivity-protected condition of approval of the earlier-approved drug product. In sum, because 3-year exclusivity generally covers only a different condition(s) of approval from a previously approved product, as a practical matter, a later-approved product is likely to have a narrower scope of exclusivity than the product approved previously with the same active moiety.

III. Discussion and Conclusion

At issue here is whether the unexpired 3-year exclusivity for Vivlodex blocks the approval of TerSera's 505(b)(2) application for Qmiiz. As explained below, consistent with the Agency's interpretation of the 3-year exclusivity statutory and regulatory provisions, the Board recommends that the unexpired 3-year exclusivity for Vivlodex should not block the approval of TerSera's NDA 211210 for Qmiiz.

Vivlodex and Qmiiz contain the same active moiety, meloxicam. As explained above and in Appendix A, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity. Because the products at issue contain the same single active moiety, the approval of TerSera's NDA 211210 for Qmiiz could potentially be barred by the unexpired 3-year exclusivity for Vivlodex that expires on October 22, 2018.

The Board must therefore consider whether for NDA 211210 for Qmiiz, TerSera is seeking approval for an exclusivity-protected condition of approval in the Vivlodex application. FDA

interprets the scope of exclusivity to be related to the scope of the underlying new clinical investigations that were essential to approval. As stated previously, the relative BA study demonstrated that Vivlodex 10 mg capsules had lower systemic exposures compared to and was not bioequivalent to the relied-upon listed drug, Mobic 15 mg tablets. Thus, the Division determined that clinical data was required to demonstrate the efficacy of Vivlodex. As discussed above, this clinical data was derived from study MEL3-12-02, which showed that Vivlodex demonstrated efficacy compared to placebo for the management of OA pain. Vivlodex is the first meloxicam product approved for this indication. Therefore, the scope of its exclusivity is limited to meloxicam for the management of OA pain. NDA 211210 is seeking approval of a meloxicam ODT product with strengths of 7.5 mg and 15 mg of meloxicam, for the relief of the signs and symptoms of OA, RA, and pauci-articular or polyarticular course JRA in patients who weigh ≥ 60 kg NDA211210 is not seeking approval for the management of OA pain. Therefore, TerSera is not seeking approval of Qmiiz for Vivlodex's exclusivity protected conditions of approval.

For these reasons, the Board recommends that the unexpired 3-year exclusivity for Vivlodex should not block the approval of TerSera's NDA 211210 for Qmiiz.

Appendix A: Legal and Regulatory Background for Exclusivity Determinations

I. Drug Approval Pathways Under the FD&C Act

Section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) new drug applications (NDAs), (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs).

A. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[13] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling, and it meets other applicable requirements.[14]

B. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[15] amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.[16] The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[17] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[18]

---

[13] See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include: a full list of the articles used as components of the proposed drug product; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. Id.

[14] See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

[15] Public Law 98-417 (1984).

[16] Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously-approved conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

[17] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[18] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the "full reports" requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[19] Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as: its own studies; published reports of studies to which the applicant has no right of reference; the Agency's findings of safety and/or effectiveness for one or more previously approved drugs; or a combination of these and other sources to support approval.[20]

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity (NCE),[21] and, in some instances, may describe a drug product with substantial differences from a listed drug.[22] When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can *bridge*[23] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability (BA)[24] of the two products, or other appropriate scientific information.

---

[19] Section 505(b)(2) of the FD&C Act provides for approval of an application:

> for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

See 21 CFR 314.3(b) (defining *right of reference or use*).

[20] See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA's transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

[21] See 21 CFR 314.108(a) (defining *new chemical entity*).

[22] In October 1999, the Agency issued a draft guidance for industry entitled "Applications Covered by Section 505(b)(2)" (505(b)(2) Draft Guidance) which states that "[a] 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference." 505(b)(2) Draft Guidance at 3, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

[23] The "bridge" in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

[24] Bioavailability data provide an estimate of the amount of the drug absorbed, as well as provide information related to the pharmacokinetics (PK) of the drug. See, e.g., FDA's Draft Guidance for Industry: "Bioavailability and

FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process, the 505(b)(2) Draft Guidance, and previous citizen petition responses.[25] FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. FDA's interpretation of section 505(b)(2) avoids requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval, with no corresponding benefit to the public health. In addition, the conduct of duplicative studies may raise ethical concerns because it could subject human beings and animals to medically or scientifically unnecessary testing. The 505(b)(2) pathway permits sponsors and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the drug on which the 505(b)(2) application seeks to rely.[26]

II. Three-Year Exclusivity Under the FD&C Act

A. General Framework

An application for a drug containing a previously approved active moiety (including a 505(b)(2) application) is generally eligible for 3 years of exclusivity if the statutory and regulatory standards are satisfied. The statute and regulations for 3-year exclusivity describe which original NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval by that exclusivity.

For NDAs, section 505(c)(3)(E)(iii) of the FD&C Act states:

> *If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant*, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under

Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" (March 2014) (BA/BE NDA/IND Draft Guidance), at 3.

[25] See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

[26] 21 CFR 314.54(a) states that a 505(b)(2) application "need contain only that information needed to support the modification(s) of the listed drug."

> subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[27]

The first clause (italicized) in section 505(c)(3)(E)(iii) of the FD&C Act, often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. FDA has interpreted the term "active ingredient" in the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean active moiety. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for single-entity drugs that are not eligible for 5-year NCE exclusivity (because they contain an active moiety "that has been approved in another application")[28] are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA's implementing regulations interpret certain aspects of the statutory language regarding 3-year exclusivity. Among other things, they define the terms *clinical investigation*,[29] *new clinical investigation*,[30] *essential to approval*,[31] and *conducted or sponsored by the applicant.*[32]

The second clause in section 505(c)(3)(E)(iii) of the FD&C Act (underlined), often referred to as the bar clause, describes which 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity. The Agency's interpretation of the bar clause and thus a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) involves two steps. One step of the scope inquiry focuses on the drug at issue. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause. The term "drug" in the eligibility clause refers to "a drug, which includes an active ingredient (including any ester or salt of the

---

[27] See Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4)(iv).

[28] The longest and most protective period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity. See section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act. A 5-year exclusivity period is provided for a drug "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [section 505(b)]." For single-entity drugs, this exclusivity generally has been interpreted to prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug. Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

[29] "Clinical investigation" is defined as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects." 21 CFR 314.108(a).

[30] "New clinical investigation" is defined, in relevant part, as "an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 CFR 314.108(a).

[31] "Essential to approval" means "with regard to an investigation, that there are no other data available that could support approval of the NDA." 21 CFR 314.108(a).

[32] "Conducted or sponsored by the applicant" is defined, in relevant part, as "that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation." 21 CFR 314.108(a).

active ingredient) that has been approved in another application," that is, the drug which includes a previously approved active moiety. Thus, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity.

The second step of the scope inquiry focuses on the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant determines the "conditions of approval" for which certain subsequent applications are barred.

Although neither the statute nor the regulations defines the phrase *conditions of approval* for purposes of determining the scope of 3-year exclusivity,[33] the preamble to FDA's proposed rule governing exclusivity (1989 Proposed Rule)[34] provides the Agency's interpretation. It makes clear FDA's view that 3-year exclusivity covers the innovative change that is supported by the new clinical investigations:

> Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.[35]

FDA thus interprets the scope of exclusivity to be related to the scope of the underlying *new clinical investigations* that were essential to the approval. Exclusivity does not extend beyond the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential. Courts have upheld FDA's view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year exclusivity.[36]

---

[33] 21 CFR 314.108(a) and 314.108(b)(4)(iv).

[34] See generally, Abbreviated New Drug Application Regulations, 54 FR 28872 (July 10, 1989) (1989 Proposed Rule).

[35] 1989 Proposed Rule at 28896-97.

[36] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 115-24 (D.D.C. 2015); *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement'"); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) ("[T]he Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . ."). Although the latter two cases involved the parallel statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.

Thus, in the case of an application submitted for a single-entity drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval (i.e., the conditions of approval for which new clinical investigations were essential).

B. Effect of Previously Approved Drug Products on Scope of 3-Year Exclusivity

Generally speaking, the scope of 3-year exclusivity for a drug product may be affected by a previously approved drug product containing the same active moiety. In practice, where two single-entity drug products that have the same active moiety are sequentially approved, the result may be that the scope of exclusivity of the second drug product is limited – often narrower in scope – relative to any exclusivity recognized for the first drug product. This "narrowing" concept, and its statutory and regulatory basis, is described below.

As stated above, 3-year exclusivity provides the holder of an approved NDA limited protection from new competition in the marketplace for the exclusivity-protected "conditions of approval," which FDA has interpreted to be the ***innovation represented by its approved drug product*** that is supported by new clinical investigations essential to approval.[37] Exclusivity is recognized only for new clinical investigations that are "essential to approval," which "means, with regard to an investigation, that there are no other data available that could support approval of the NDA."[38] Exclusivity does not cover aspects of the drug product for which new clinical investigations were not essential.

This link between the scope of exclusivity and the new clinical investigations essential to approval means that, in assessing the scope of 3-year exclusivity for a single-entity drug product containing the same active moiety as a previously approved single-entity drug product, the Agency looks at the innovative change(s) represented by the later-approved drug product relative to the previously approved drug product. Exclusivity for the later-approved drug product cannot cover any condition of approval for which "new clinical investigations" were not "essential." If an earlier-approved drug product was approved for a particular condition of approval, new clinical investigations would not be considered "essential" to support the same condition of

[37] 1989 Proposed Rule at 28896-97.

[38] 21 CFR 314.108(a). *See* 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994) ("The phrase 'essential to the approval' suggests that the clinical investigations that warrant exclusivity must be vital to the application or supplement . . . '[T]o qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective.'" (internal citations omitted)); 1989 Proposed Rule at 28900 ("In addition, there must not be an already approved drug product for which the applicant could submit an ANDA or 505(b)(2) application. . . . A study will not be considered essential to approval merely because it was necessary for the applicant to conduct the study to avoid the exclusivity of the pioneer and obtain an immediate effective date of approval.").

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 18, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 211210
Product Name and Strength:	Qmiiz ODT (meloxicam) orally disintegrating tablets; 7.5 mg and 15 mg
Applicant/Sponsor Name:	TerSera Therapeutics
FDA Received Date:	10/16/2018
OSE RCM #:	2018-94-3
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

DAAAP requested that we review the revised labels and labeling for Qmiiz ODT (Appendix A) to determine if they are acceptable from a medication error perspective. The labels and labeling were revised to replace the placeholder, "Trade name", with the proprietary name, Qmiiz ODT,[a] that was recently found conditionally acceptable.

2 CONCLUSION

The revised labels and labeling for Qmiiz ODT are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Johnson, C. Proprietary Name Review for Qmiiz ODT (NDA 211210). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 2. RCM No.: 2018-25544259.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 16, 2018.

7.5 mg Blister pack label

15 mg Blister pack label

7.5 mg professional sample carton label 10-count

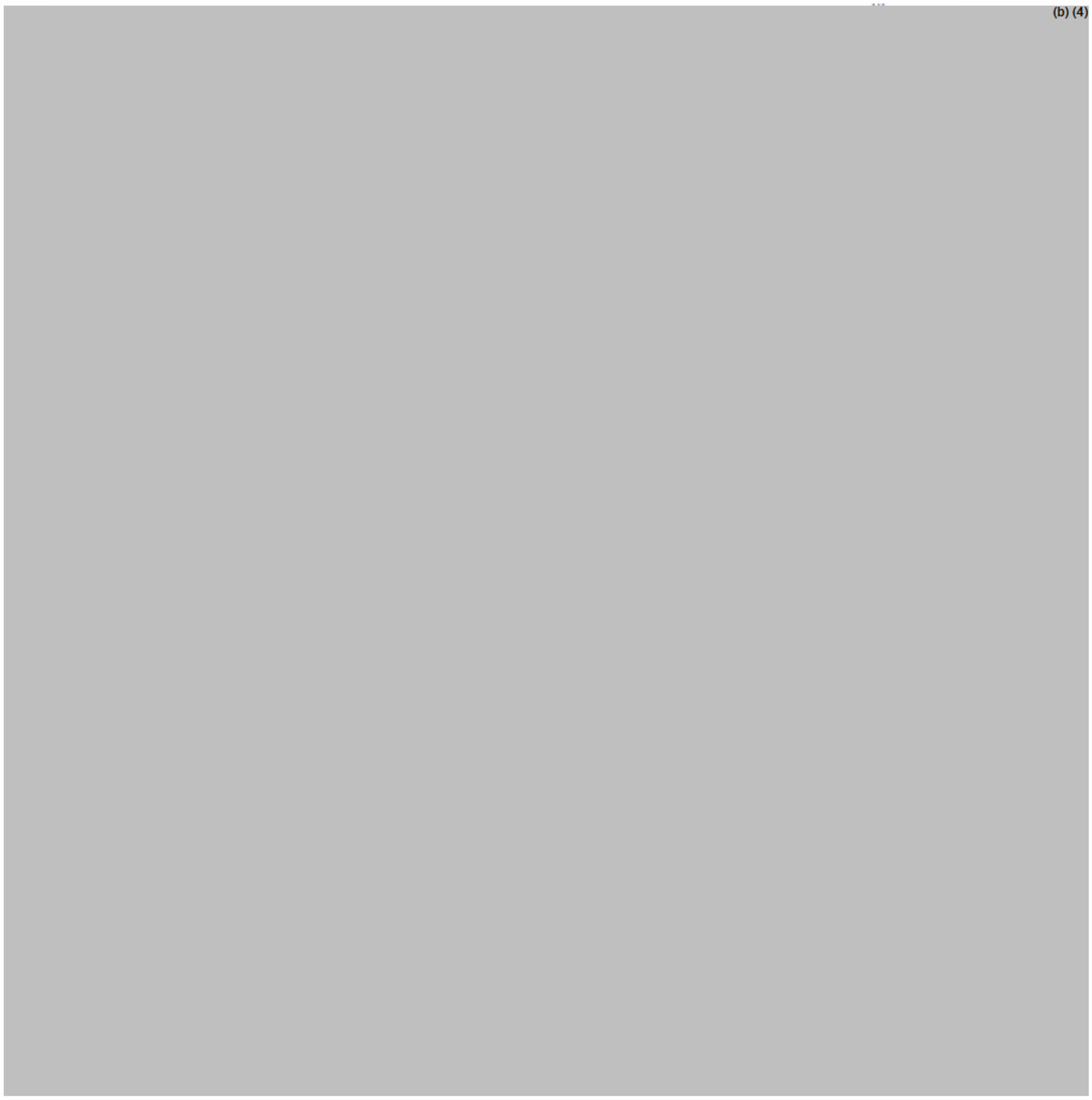
(b) (4)

15 mg professional sample carton label 10-count

7.5 mg carton labeling 30-count

15 mg carton labeling 30-count

7.5 mg carton labeling 90-count



15 mg carton labeling 90-count

Prescribing Information (Image not shown)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAMERON D JOHNSON
10/18/2018

OTTO L TOWNSEND
10/18/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 25, 2018
To:	Sharon Hertz, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Koung Lee, RPh, MSHS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	TRADENAME (meloxicam) orally disintegrating tablet (ODT), for oral use
Application Type/Number:	NDA 211210
Applicant:	TerSera Therapeutics LLC

1 INTRODUCTION

On December 21, 2017, TerSera Therapeutics LLC, submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 211210 for TRADENAME (meloxicam) orally disintegrating tablet (ODT), for oral use. The Reference Listed Drug (RLD) is MOBIC (meloxicam) tablets, NDA 020938. The Applicant has developed a new ODT dosage form of meloxicam for once daily (QD) administration for the relief of signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA) pauci-articular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients who weigh greater than or equal to 60 kg.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on February 9, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (meloxicam) orally disintegrating tablet (ODT), for oral use.

2 MATERIAL REVIEWED

- Draft TRADENAME (meloxicam) orally disintegrating tablet (ODT), for oral use MG received on December 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 19, 2018.
- Draft TRADENAME (meloxicam) orally disintegrating tablet (ODT), for oral use Prescribing Information (PI) received on December 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 19, 2018.
- Approved MOBIC (meloxicam) tablets comparator labeling dated June 30, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

5 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN W REDWOOD
09/25/2018

KOUNG U LEE
09/25/2018

BARBARA A FULLER
09/25/2018

LASHAWN M GRIFFITHS
09/25/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 21, 2018

To: Christina Fang, M.D.
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Taiye Ayoola, Pharm D
Regulatory Health Project Manager, DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Samuel Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for (b) (4) (meloxicam) orally disintegrating tablet (ODT) for oral use

NDA: 211210

In response to the Division of Anesthesia, Analgesia, and Addiction Products' consult request dated February 9, 2018, OPDP has reviewed the proposed prescribing information (PI) and carton and container labeling for the original NDA submission for (b) (4) (meloxicam) orally disintegrating tablets (ODT).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on September 19, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 30, 2018, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Koung Lee at (301) 402-8686 or Koung.lee@fda.hhs.gov.

44 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KOUNG U LEE
09/21/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 13, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 211210
Product Name and Strength:	Meloxicam orally disintegrating tablet, 7.5 mg and 15 mg
Applicant/Sponsor Name:	TerSera Therapeutics
FDA Received Date:	September 11, 2018
OSE RCM #:	2018-94-2
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

DAAAP requested that we review the revised blister pack labels for meloxicam (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised blister pack labels for meloxicam are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Johnson, C. Label and Labeling Review for Meloxicam NDA 211210. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 31. RCM No.: 2018-94-1.

APPENDIX A. IMAGES OF LABELS RECEIVED ON SEPTEMBER 11, 2018

Blister pack labels

7.5 mg

15 mg

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAMERON D JOHNSON
09/13/2018

OTTO L TOWNSEND
09/13/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 31, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 211210
Product Name and Strength:	Meloxicam orally disintegrating tablet, 7.5 mg and 15 mg
Applicant/Sponsor Name:	TerSera Therapeutics
FDA Received Date:	August 29, 2018 and August 30, 2018
OSE RCM #:	2018-94-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

DAAAP requested that we review the revised blister pack labels and carton labeling for meloxicam (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised blister pack labels are unacceptable from a medication error perspective. The proprietary name (indicated as "trade name") and established name lack prominence and the expiration date format has not been defined.

[a] Johnson, C. Label and Labeling Review for (b) (4) ODT NDA 211210. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 08. RCM No.: 2018-94.

3 RECOMMENDATIONS FOR TERSERA

We recommend the following be implemented prior to approval of this NDA:

A. The proprietary name (indicated as "trade name") and established name lack prominence on the blister pack labels. The proprietary name, established name, and strength should be the most prominent information on the PDP to prevent product selection errors.[b] To increase the prominence of this important information consider either increasing the font size of the proprietary and established name (meloxicam) or decreasing the font size of the manufacturer, Rx only statement, NDC (National Drug Code), lot number and expiration date. Furthermore, please ensure that while revising the labels that the established name is at least half the size of the proprietary name to comply with 21 CFR 201.10(g)(2).

B. We note you indicated that you will use the expiration date format, MMM-YYYY, for your carton labeling. However, it is unclear if you intend to use the same format on the blister pack labels. We recommend using the same format, (i.e., MMM-YYYY) for the blister pack labels.

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON AUGUST 29, 2018

Blister pack labels

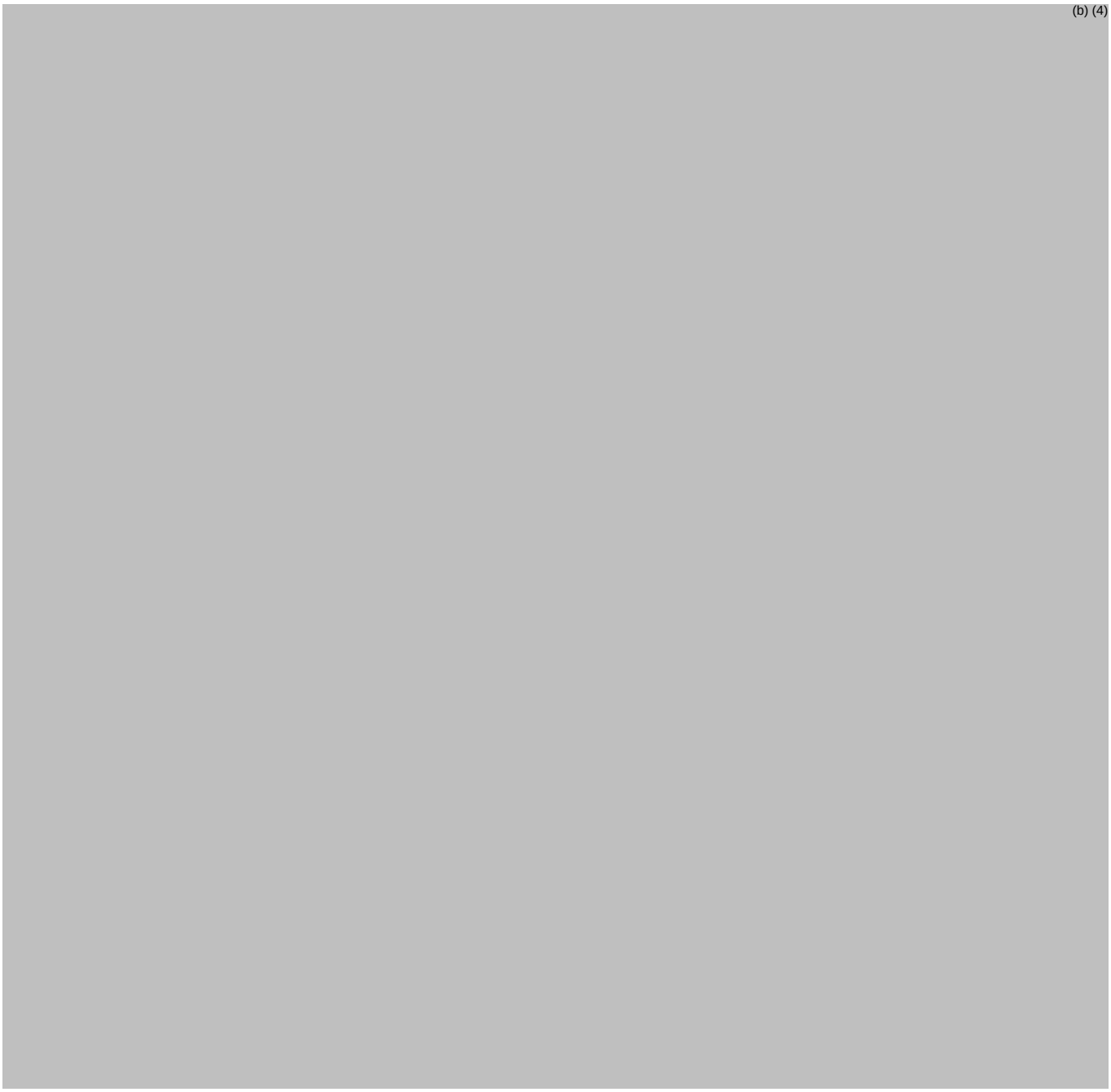
7.5 mg

15 mg

Carton labeling

7.5 mg professional sample carton 10- count

15 mg professional sample carton 10- count



7.5 mg carton 30-count

15 mg carton 30-count

7.5 mg carton 90-count

15 mg carton 90-count


(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAMERON D JOHNSON
08/31/2018

OTTO L TOWNSEND
08/31/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: August 29, 2018 **Date consulted:** February 9, 2018

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Drug: Meloxicam Orally Disintegrating Tablet (ODT)

Drug Class: NSAID

NDA: 211210

Applicant: TerSera Therapeutics, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication: For the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis and also for the relief of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis.

Materials Reviewed:

- DPMH consult request dated February 9, 2018 in DARRTS (Reference ID: 4219860)
- Applicant's submission for NDA 211210, a 505(b)(2) application, December 21, 2017 and the Prescribing Information (PI) for Meloxicam ODT
- US Prescribing Information (USPI) provided on December 21, 2017 and March 20, 2018.

Consult Question:

DAAAP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections to comply with the Pregnancy and Lactation Labeling (PLLR) format.

INTRODUCTION

This is an original 505(b)(2) application for Meloxicam ODT, submitted on December 21, 2017 for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis and also for the relief of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis. This NDA relies on the FDA's previous findings of safety and efficacy of listed drug (RLD) Mobic (meloxicam) tablets, NDA 020938 by Boehringer Ingelheim Pharmaceuticals, Inc. Human pharmacokinetic data from four Phase 1 studies designed to establish bioequivalence between meloxicam ODT and United States (US) brand are provided. It also relies on relevant safety and efficacy results from the published literature. No new efficacy or safety studies have been conducted by the applicant. The applicant has provided labeling which is similar to the labeling for Mobic.

DAAAP consulted DPMH on February 9, 2018, to provide input for appropriate labeling of the *Pregnancy* and *Lactation* subsections of meloxicam ODT to comply with the PLLR.

Regulatory History

The RLD, Mobic Tablets, was approved on April 13, 2000, for the:

- Relief of the signs and symptoms of osteoarthritis
- Relief of the signs and symptoms of rheumatoid arthritis
- Relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients who weigh ≥60 kg

Drug Characteristics[1]

- Meloxicam is metabolized to 4 biologically inactive metabolites that are excreted via the urine and feces to an equal extent. All four metabolites are known to have no *in vivo* pharmacological activity.
- The molecular weight of meloxicam is 351.403 Daltons
- The mean plasma half-life of meloxicam is about 20 hours
- Oral meloxicam is almost completely absorbed and is bound to plasma proteins (≈99.5%)
- Meloxicam is neither genotoxic, mutagenic nor clastogenic

Current RLD Labeling

The current labeling for Mobic (meloxicam) was approved on June 30, 2016, and is in Physician Labeling Rule (PLR), and in PLLR format[2]. It states[1]:

> Meloxicam is an non-steroidal anti-inflammatory drug (NSAID) that should not be used after 30 weeks (third trimester) because it can cause closure of the fetal Ductus Arteriosus (DA)…Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma. There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for

[1] Mobic labeling of June 30, 2016, Sections 11, 12 and 13 and applicant's proposed USPI

[2] Mobic was updated to PLLR format on May 9, 2016. DPMH did not participate in this conversion. DPMH had been consulted on December 6, 2011 in regards to the addition by the applicant labeling revisions to the full prescribing information for Mobic Tablets in the USE IN SPECIFIC POPULATIONS and the PATIENT COUNSELING INFORMATION sections to include statements regarding the potential delay in ovulation with meloxicam and effects on fertility. See DARRTS consult of December 7, 2011, Reference ID: 3054635

MOBIC and any potential adverse effects on the breastfed infant from the MOBIC or from the underlying maternal condition. NSAIDs, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women.

REVIEW

PREGNANCY

Animal Data

The applicant did not perform any studies and depends on FDA's findings on Mobic. No additional information was identified by the applicant. Published literature states that placental transfer of meloxicam or its metabolites have been demonstrated in the rat.[3]

Review of Literature

Applicant's Review

The applicant did not provide any published information in reference to the proposed labeling, rather depending entirely on the existing Mobic labeling in PLLR.

Reviewer comment

The Mobic labeling, in addition to NSAID class labeling, were adapted to create the applicant's proposed labeling text, as no data from studies of meloxicam in pregnant women or animals have become available since the approval of the Mobic labeling.

Pharmacovigilance Review

No pharmacovigilance review was provided by the applicant.

DPMH Review

DPMH conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for meloxicam and use in pregnancy. No additional human data publications were identified. . The Reprotox and Shepard's databases also report no published human data found on use of meloxicam in pregnancy. GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation report

> …it is not known if meloxicam crosses the human placenta, but it does cross the rat placenta.[4] Because of meloxicam's low molecular weight, it is expected to cross the human placenta. NSAIDs and specifically those with greater COX-2 affinity have a lower risk of developmental toxicity than aspirin. There is a positive association between meloxicam and spontaneous abortions.[5,6]

NSAIDs use in Pregnancy and Oligohydramnios

Oligohydramnios associated with NSAIDs use during pregnancy is well recognized in the

---

[3] Oiwa Y, Shibata T, Senda C, Kuritani M, Nagakura A, Matsumura R, Kobayashi S. [Metabolic fate of 14C-meloxicam 2. Placental transfer in rats]. Yakubutsu Dotai 1997;12:118-20

[4] Levin DI. Effects of inhibition of prostaglandin synthesis on fetal development, oxygenation, and the fetal circulation. Semin Perinatol 1980;4:35-44

[5] Tassinari MS, Cook JC, Hurt ME. NSAIDs and developmental toxicity: Birth defects.Res B. Dev Reprod Toxicol 2003;68:3-4

[6] Nielsen GI, Sorensen HT, Larsen H, Pederson I. Risk of adverse birth outcomes and miscarriage in pregnant users of NSAIDs; population based observational study and case-control study. Br Med J 2001;322:266-70

obstetric community for many years and has been documented in the medical textbook of Williams Obstetrics. Impairment of kidney function, and in consequence, reduced amniotic fluid, has been reported as fetotoxic effects of NSAIDs in late pregnancy.[7] Oligohydramnios is associated with risks to fetal development and can affect lung and renal development.

Considering the mechanism of action of NSAIDs, the plausible mechanism for NSAID-associated oligohydramnios is the inhibition of prostaglandin synthesis in the fetal kidney, which lowers renal blood flow and tubular function, resulting in a reduction of fetal urine production.[8] Oligohydramnios has been described in association with use of several NSAIDs, including diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, niflumic acid, nimesulide, and piroxicam.[9,10] Oligohydramnios is usually reversible within 6 days from the day the drug is discontinued.

The most serious cases of oligohydramnios were documented after week 30 of gestation, but in rare cases, oligohydramnios has been reported before week 28. However, Hickok *et. al.* published a case of oligohydramnios after seven days treatment with indomethacin at week 21[11] and Schernec *et. al.* reported pathological findings of oligohydramnios that were detected at gestational weeks 22 and 23 after long-term diclofenac exposure of at least 150 mg per day.[12]

Summary

No new animal data apart from what is reported in labeling for Mobic was identified. Review of the literature has failed to produce any human literature on meloxicam use in pregnancy, and therefore, no meloxicam-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes has been identified. Published literature reports that use of NSAIDs during the second and third trimesters of pregnancy increases the risk of oligohydramnios and premature closure of the fetal ductus arteriosus. DAAAP is conducting ongoing review of the association of oligohydramnios with NSAID use in pregnancy and discussing the potential for a class-wide safety labeling change. Language consistent with the current NSAID class labeling includes a Warning and Precaution on premature closure of the fetal ductus arteriosus and will be included in the Meloxicam ODT labeling. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first trimester of pregnancy are inconclusive.

LACTATION

Animal Data

No additional animal data about lactation is provided by the applicant. As per approved

---

[7] Antonucci R, Zaffanello M, Puxeddu E, Porcella A, Cuzzolin L, Pilloni D, Fanos V, Use of non-steroidal anti-inflammatory drugs in pregnancy: impact on the fetus and newborn, Curr. Drug Metab. 13 (2012) 474–490.

[8] Abou-Ghannam G, Usta IM, Nassar AH. Indomethacin in Pregnancy: Applications and safety. Am J Perinatol 2012;29(3):175-86.

[9] Magann E. The amniotic fluid index, single deepest pocket, and two-diameter pocket in normal human pregnancy. Am J Obstet Gynecol 2000;182:1581–8.

[10] Momma K, Takeuchi H, Constriction of fetal ductus arteriosus by non-steroidal anti-inflammatory drugs, Prostaglandins 26 (1983) 631–643

[11] Hickok DE, Hollenbach KA, Reilley SF, Nyberg DA, The association between decreased amniotic fluid volume and treatment with nonsteroidal anti-inflammatory agents for preterm labor, Am. J. Obstet. Gynecol. 160(1989) 1525–1530.

[12] Scherneck S, Schöpa FL, Entezami M, Kayser A, Weber-Schoendorfer C, Schaefer C. Reversible oligohydramnios in the second trimester of pregnancy in two patients with long-term diclofenac exposure. Reproductive Toxicology, 58,61-64;2015

Mobic labeling, meloxicam was present in rat milk.

Review of Literature
Applicant's Review
The applicant did not provide any literature search. Therefore, no clinical information on lactation is provided by the applicant.

Reviewer Comment
The Mobic labeling, in addition to NSAID class labeling, were adapted to create the applicant's proposed labeling text, as no data from studies of meloxicam in breastfeeding women or animals have become available since the approval of the Mobic labeling.

DPMH Review
DPMH conducted a literature search in PubMed, Embase and the LactMed databases for meloxicam and use in lactation as well as in GG Briggs and RK Freeman Drugs in Pregnancy and Lactation and Hale TW Medications and Mother's Milk.

LactMed states that

> No information is available on the use of meloxicam during breastfeeding. Therefore, other agents may be preferred, especially while nursing a newborn or preterm infant.

No relevant information was identified about maternal and infant levels of meloxicam in association with breast feeding (presence of meloxicam in breast milk) or the effects of meloxicam on the breastfed infant or on milk production.

Hale TW in Medications and Mother's Milk[13] states

> There are no data for transfer of the drug to human milk. Meloxicam was present in rodent milk…because of the long half-life and high bioavailability, another NSAID would be preferred during breastfeeding.

Briggs GG & Freeman RK in Drugs in Pregnancy and Lactation also did not identify any publications/reports of the use of meloxicam during breastfeeding. They conclude that because of "the low molecular weight (351 Daltons), meloxicam should be present in breast milk". The American Academy of Pediatrics[14] classifies piroxicam, a similar drug, as compatible with breastfeeding.

Summary
There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. Meloxicam was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Animal Data

[13] Hale WT. Medications & Mothers' Milk. 2017, Seventh Edition. Springer Publishing Co., NY, NY
[14] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk.Pediatrics 2001,;108:776-84

On March 18, 2015, DPMH produced a PLLR Labeling Memorandum after a request by DAAAP to assist in updating the class labeling template for NSAID labeling (see DARRTS, March 18, 2015, Reference ID: 3715387). In that memorandum, DPMH proposed the following language regarding 8.3 Females and Males of Reproductive Potential, Infertility, Females:

> Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including Tradename, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including meloxicam in women who have difficulties conceiving or who are undergoing investigation of infertility.

This DPMH recommendation is based on review of the NSAIDs data and literature described in prior DPMH reviews that are available in DARRTS (PMHS-MHT consult review dated April 10, 2013 and PMHS-MHT Memorandum dated August 21, 2014). Additionally, DPMH provided review and content for the Drug Safety Communication on the possible risks of pain medicine use during pregnancy issued January 9, 2015.

Summary
Meloxicam is not mutagenic or genotoxic, and is not associated with major birth defects. Therefore, there is no need for pregnancy testing or contraception during treatment with meloxicam. The above statement on Infertility should be included in the Meloxicam ODT labeling, Subsection 8.3 as per the current template for NSAIDs labeling.

CONCLUSIONS
Meloxicam labeling has been edited to comply with the PLLR. DPMH revised subsections 8.1, 8.2, and 8.3 and section 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

The *Pregnancy*, *Lactation,* and *Females and Males of Reproductive Potential* subsections of Meloxicam ODT labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**
  - The "Pregnancy" subsection of Tradename labeling was formatted in the PLLR format to include: "Risk Summary", "Clinical Considerations" and "Data" headings.
- **Lactation, Subsection 8.2**
  - The "Lactation" subsection of Tradename labeling was formatted in the PLLR format to include the "Risk Summary" heading.
- **Females and Males of Reproductive Potential, Subsection 8.3**
  - Females and Males of Reproductive Potential subsection of Tradename labeling was formatted in the PLLR format to include the "Infertility" subheading.
- **Section** 17 **PATIENT COUNSELING INFORMATION**

RECOMMENDATIONS

DPMH has the following recommendations for Tradename labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1).

----------USE IN SPECIFIC POPULATIONS----------

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of Tradename in women who have difficulties conceiving (8.3)

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

FULL PRESCRIBING INFORMATION: CONTENTS

5 WARNINGS AND PRECAUTIONS

Meloxicam may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including tradename, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published literature reports that use of NSAIDs, including Tradename, after 30 weeks gestation increases the risk of premature closure of the fetal ductus arteriosus. Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimester of pregnancy are inconclusive. Avoid use of NSAIDs, including Tradename in pregnant women starting at 30 weeks of gestation (third trimester) (*see Clinical Considerations, Data).*

In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.32 and 3.24-times the maximum recommended human dose (MRHD) of 30 mg of meloxicam based on body surface area (BSA). Increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 39-times the MRHD of 30 mg of meloxicam. In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.04-times the MRHD of 30 mg of meloxicam No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 1.3 and 13-times the MRHD of 30 mg of Tradename *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Premature Closure of the Fetal Ductus Arteriosus: Avoid use of NSAID's in pregnant women after 30 weeks gestation because NSAIDs, including Tradename, can cause premature closure of the fetal ductus arteriosus (see Data).

Data
Animal Data
Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (1.3-fold greater than the MRHD of 30 mg of meloxicam based on BSA comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (39-fold greater than the MRHD of 30 mg of meloxicam based on BSA comparison). The no effect level was 20 mg/kg/day (13-fold greater than the MRHD of 30 mg of meloxicam based on BSA conversion). In rats and rabbits, embryo-lethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.32 and 3.24-fold greater, respectively, than the MRHD of 30 mg of meloxicam based on BSA comparison) when administered throughout organogenesis.

Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (0.04-times the MRHD of 30 mg of meloxicam based on BSA comparison).

8.2 Lactation

Risk Summary
There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma. The concentration of the drug in animal milk does not necessarily predict the concentration of drug in human milk. However, when a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tradename and any potential adverse effects on the breastfed infant from the Tradename or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Infertility
Females
Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including Tradename, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including Tradename, in women who have difficulties conceiving or who are undergoing investigation of infertility

17 PATIENT COUNSELING INFORMATION

Female Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including Tradename may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)]*.

Fetal Toxicity
Advise pregnant women to avoid use of Tradename after 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. Advise females of reproductive potential to contact their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.1).]*

Appendix:

Mobic approved labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of MOBIC in women who have difficulties conceiving (8.3)

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION: CONTENTS

Meloxicam may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including MOBIC, in pregnant women starting at 30 weeks of gestation (third trimester) *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including MOBIC, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including MOBIC, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Warnings and Precautions (5.10)*]. There are no adequate and well-controlled studies of MOBIC in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss.

In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5-times the maximum recommended human dose (MRHD) of MOBIC. Increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 78-times the MRHD. In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.08-times MRHD of meloxicam. No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.6 and 26-times the MRHD *[see Data]*.

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors, such as meloxicam, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of MOBIC during labor or delivery. In animal studies, NSAIDs, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Animal Data

Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2.6-fold greater than the MRHD of 15 mg of MOBIC based on BSA comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA conversion). In rats and rabbits, embryolethality occurred at oral meloxicam doses of 1

mg/kg/day and 5 mg/kg/day, respectively (0.65and 6.5-fold greater, respectively, than the MRHD based on BSA comparison) when administered throughout organogenesis.

Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (0.08-times MRHD based on BSA comparison).

8.2 Lactation

Risk Summary

There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MOBIC and any potential adverse effects on the breastfed infant from the MOBIC or from the underlying maternal condition.

Data

Animal Data

Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including MOBIC, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including MOBIC, in women who have difficulties conceiving or who are undergoing investigation of infertility.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
08/29/2018

TAMARA N JOHNSON
08/29/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 8, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 211210
Product Name and Strength:	(b) (4) ODT (meloxicam) orally disintegrating tablets 7.5 mg, 15 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	TerSera Therapeutics LLC
FDA Received Date:	5/18/2018
OSE RCM #:	2018-94
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for (b) (4) ODT (meloxicam) orally disintegrating tablet, 7.5 mg and 15 mg, the Division of Anesthesia, Analgesia, and Addiction Products requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anesthesia, Analgesia and Addiction Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Highlights of Prescribing Information and Full Prescribing Information (FPI)			
1.	In the Dosage and Administration and Indications and Usage	This symbol may result in misinterpretation and	Replace the symbol, "≥", with its intended meaning, "greater than or equal to", to

	sections of the Highlights and the FPI, the symbol "≥" is used (e.g. ≥ 60 kg).	confusion which could lead to a medication error.[a]	prevent misinterpretation and confusion.
2.	In the Dosage Forms and Strengths section of the Highlights and FPI, the dosage form is abbreviated as "ODT".	The use of abbreviations can lead to misinterpretations and confusion.	For these sections, include the intended meaning for "ODT" such as "(b) (4) ODT (meloxicam) orally disintegrating tablets".
Full Prescribing Information			
1.	The Dosage and Administration section, subsection 2.4 contains the statement: (b) (4)	(b) (4)	Revise the statement (b) (4) (b) (4)
2.	The available strengths are not given in the How Supplied section.	Per 21 CFR 201.57(c)(17), the strength of the dosage form should be included in the How Supplied Section.	Include the 7.5 mg and 15 mg strengths in the How Supplied section.
3.	The How Supplied section does not include the number of tablets	Per 21 CFR 201.57(c)(17)(ii), the How Supplied section should include "The units in which the dosage form is	Include a net quantity statement that describes the number of tablets contained in each blister pack.

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 JUL 10]. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf

[b] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

	available in each blister pack.	ordinarily available for prescribing by practitioners (e.g., bottles of 100)".	For example, "Carton containing 3 blister packs of 10 tablets each, for a total of 30 tablets"
4.	The How Supplied section does not include information pertaining to the imprinting, shape, color, or coating for each dosage strength available.	This information facilitates product identification in a case of a mix-up between tablets of different strengths and to prevent wrong strength errors.	To comply with 21CFR 201.57(c)(17)(iii), include information on the imprinting, shape, color, and coating for each dosage strength in the How Supplied section.
5.	The How Supplied section does not contain a National Drug Code (NDC) for each of the package configurations that are available.	Per 21 CFR 201.57(c)(17)(iii), the How supplied section should include "Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number;".	We have provided a recommendation in Table 3 below for the Applicant to include NDC's on each package configuration.

Table 3: Identified Issues and Recommendations for TerSera Therapeutics LLC (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Blister pack labels and carton labeling			
1.	The strength lacks prominence on the 7.5 mg blister pack label and the 7.5 mg carton labeling.	The strength should be easily identifiable and prominently displayed on the labeling.	To comply with 21 CFR 201.15(a)(6), increase the prominence of the strength on the 7.5 mg blister pack label and the 7.5 mg carton labeling.
2.	The strength on the 7.5 mg and 15 mg blister pack labels and carton labeling does not have a space between the numeral and the unit of measurement.	Including a space between the numeral and unit of measurement improves the readability of the product's strength.	Place adequate space between the numeral and the unit of measurement (e.g. change 7.5mg to 7.5 mg).

3.	The 7.5 mg and 15 mg strength statements on the blister pack labels and carton labeling are not clearly differentiated.	(b) (4) [redacted]	There is inadequate differentiation between the 7.5 mg and 15 mg strengths. Consider the use of different colors, boxing, or some other means to provide adequate differentiation between the strengths.
4.	On all blister pack labels and carton labeling the dosage form following the established name is abbreviated as "ODT".	The dosage form should be spelled out because the use of abbreviations can lead to misinterpretations and confusion.	Change the dosage form following the established name from "ODT" to its intended meaning, "orally disintegrating tablets".
Blister pack label			
1.	For the 15 mg blister pack label and the 15 mg carton labeling, (b) (4) [redacted]	(b) (4) [redacted]	Revise (b) (4) [redacted]
2.	The blister pack label does not contain the name of the manufacturer, packer or distributor of the drug.	Per 21 CFR 201.10(i), the minimum amount of information that is required includes the manufacturer, packer or distributor of the drug.	Revise the blister pack labels to include the manufacturer, packer or distributor of the drug.
3.	The blister packs do not contain a linear barcode on each individual blister cell.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to each individual blister cell of each blister pack as required per 21 CFR 201.25(c)(2).
Carton labeling			

1.	As currently presented, the NDC is denoted by a placeholder (XXXXX-XXXX-XX) on all carton labeling.	The similarity of NDC's on carton labeling has led to selecting and dispensing of the wrong strength and wrong drug. The product code (middle 3-4 digits) is traditionally used by healthcare providers to check the correct product, strength, and formulation and the package code portion (last 1-2 digits) is used to identify container size[c].	Once assigned, please submit NDC's for all the carton labeling. Please ensure that the product code portion is different and non-sequential (e.g. -6666-, -6670- vs, -6666-, 6667) between the 7.5 mg strength and the 15 mg strength. Furthermore, the package code portion should be different and non-sequential between the cartons containing 10 tablets, 30 tablets and 90 tablets.
2.	The net quantity statement is bolded and more prominently displayed than the strength statement on all carton labeling.	The strength statement should be prominently displayed on the principal display panel for ease of readability.	To improve readability, consider revising the strength statement so that it is more prominent than the net quantity statement on all carton labeling.
3.	There is not a statement pertaining to the Medication guide on the carton labeling.	Per 21 CFR 208.24(d), products with medication guides should contain a statement that instructs the authorized dispenser to provide a medication guide to the patient.	Include the statement, "Dispense the enclosed Medication Guide to each patient" or similar statement that is prominently displayed on the principal display panel of each carton.
4.	As currently presented the location for the lot number is not provided.	The lot number statement is required on the carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Include the intended location for the lot number on the carton labeling and submit for our review.
5.	As currently presented the location for the expiration date is not provided.	The expiration date is required on the carton labeling per 21 CFR 201.17.	Add the expiration to carton labeling to comply with 21 CFR 201.17. To minimize confusion and reduce the risk

[c] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

			for deteriorating drug medication errors, identify the format you intend to use. We recommend using a format like either DDMMMYYYY (e.g., 31JAN2013) MMMYYYY (e.g., JAN2013) YYYY-MM-DD (e.g., 2013-JAN-31) YYYY-MM-DD (e.g., 2013-01-31)
6.	The package type is not included on the carton labeling.	The package type statement helps to identify how the medication should be safely handled and used.	Include the package type on carton labeling to identify that each carton contains blister packs. For example, for the 30 count carton labeling include a statement such as "Contains: 30 tablets (3 x 10-count blister packs)".

4 CONCLUSION

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 2 above for the Division. We also have provided recommendations in Table 3 above and ask that the Division conveys Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for meloxicam that TerSera Therapeutics LLC submitted on 5/18/2018, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and meloxicam

Product Name	**Meloxicam**	**Mobic**
Initial Approval Date	N/A	4/13/2000
Active Ingredient	meloxicam	meloxicam
Indication	Osteoarthritis (OA), Rheumatoid Arthritis (RA), Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course, in patients who weigh ≥ 60 kg	Osteoarthritis (OA), Rheumatoid Arthritis (RA), Juvenile Rheumatoid Arthritis (JRA) in patients who weigh ≥ 60 kg
Route of Administration	oral	oral
Dosage Form	Orally disintegrating tablet	tablet
Strength	7.5 mg, 15 mg	7.5 mg, 15 mg
Dose and Frequency	OA and RA: • starting dose: 7.5 mg once daily • Dose may be increased to 15 mg once daily JRA: 7.5 mg once daily in children ≥ 60 kg	OA and RA: • starting dose: 7.5 mg once daily • Dose may be increased to 15 mg once daily JRA: 7.5 mg once daily in children ≥ 60 kg
How Supplied	Each blister pack contains 10 tablets each; 1 blister pack contained in 10 count sample cardboard carton; 3 blister packs contained in 30 count cardboard carton; 9 blister packs contained in 90 count cardboard carton	7.5 mg tablets in bottles of 100 tablets; 15 mg tablets in bottles of 100 tablets
Storage	Room temperature	Room temperature
Container Closure	Aluminum blister packs composed of multi-layered (5 layers) laminated blister film and a lidding foil	Bottles

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 11, 2018, we searched the L:drive and AIMS using the terms, (b) (4) to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews relevant to this label and labeling review.

APPENDIX C. N/A

APPENDIX D. N/A

APPENDIX E. N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following meloxicam labels and labeling submitted by TerSera on 5/18/2018.

- Blister pack labels
- Carton labeling
- Medication Guide (image not shown)
- Prescribing Information (Image not shown)

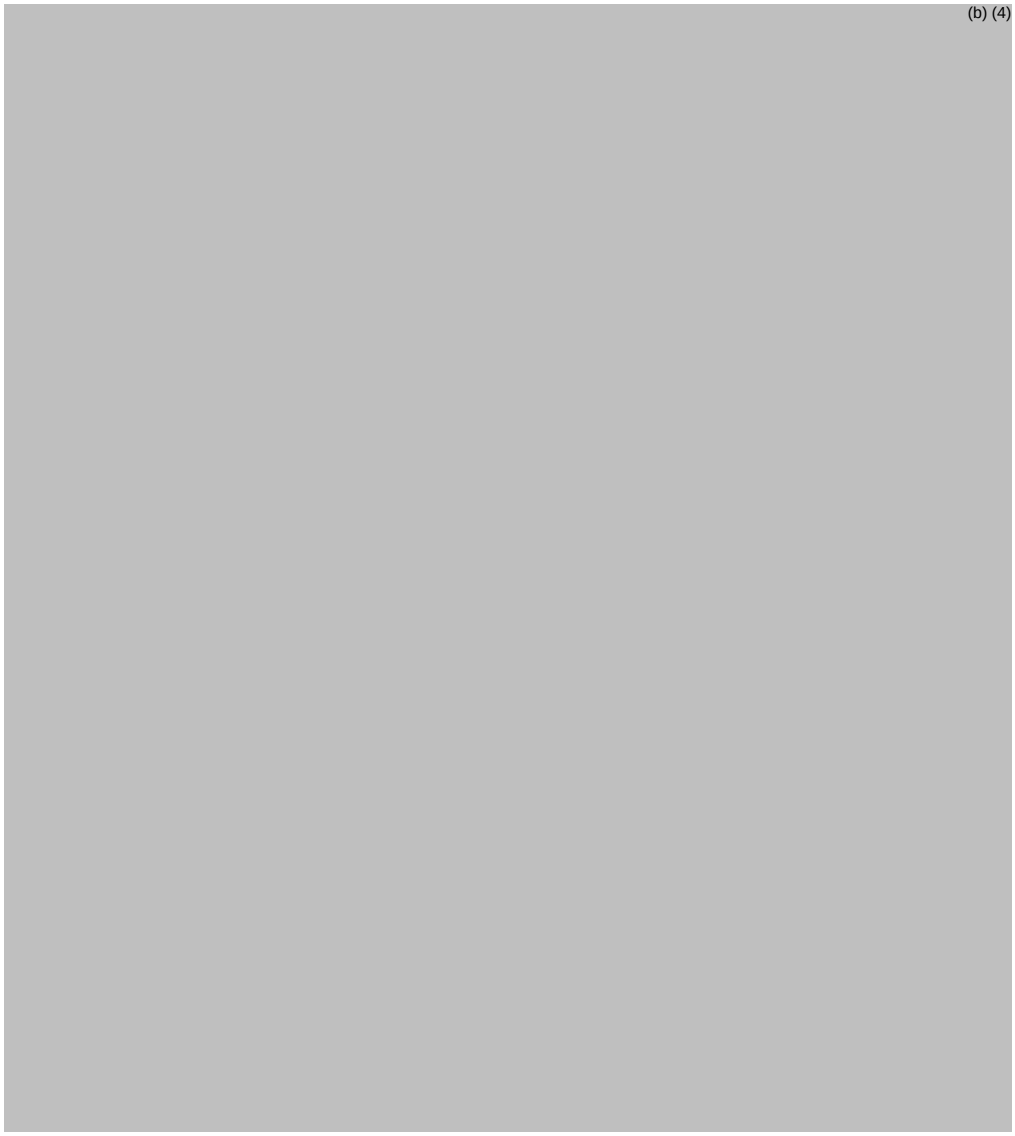
F.2 Label and Labeling Images

7.5 mg Blister pack label

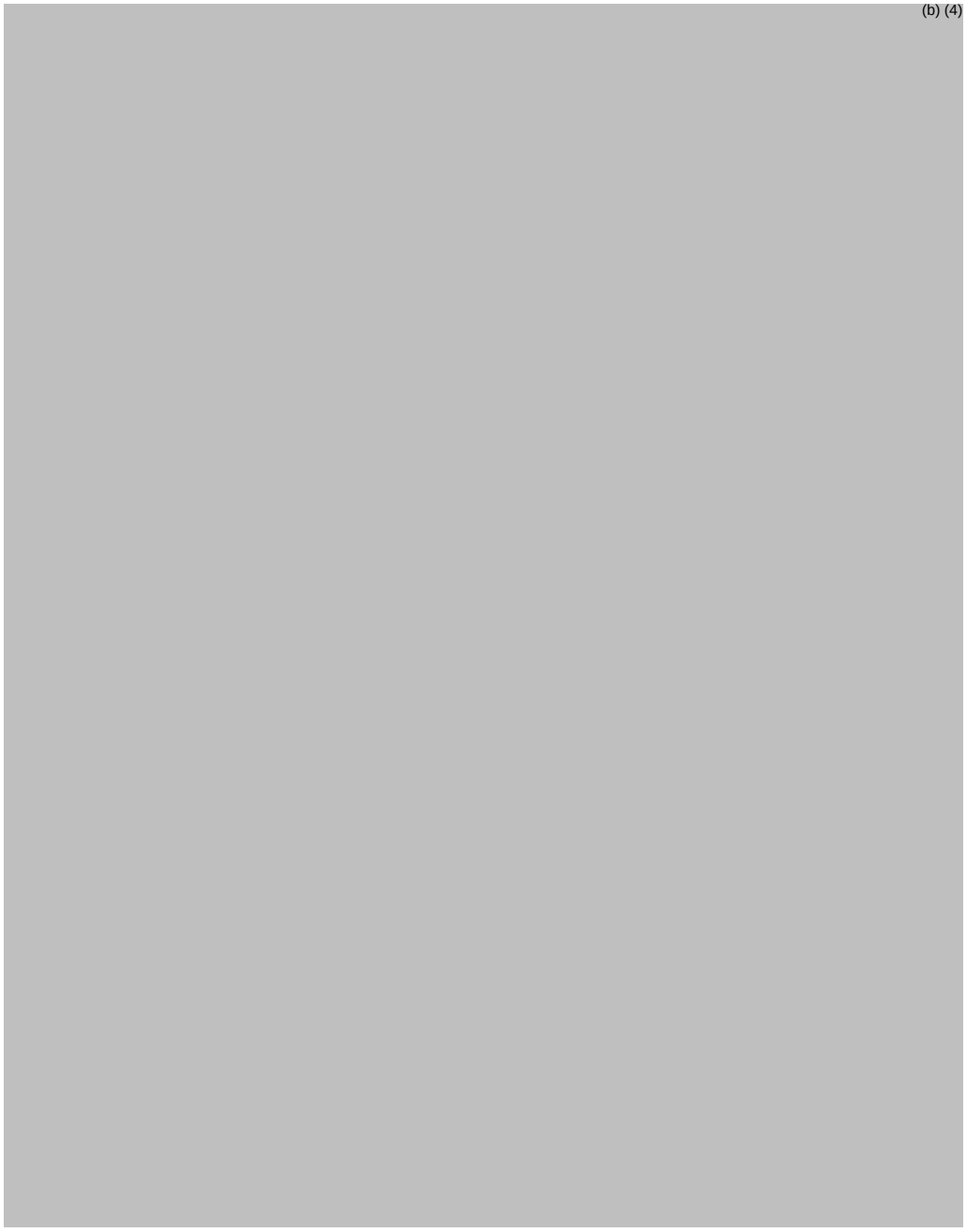
15 mg Blister pack label

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

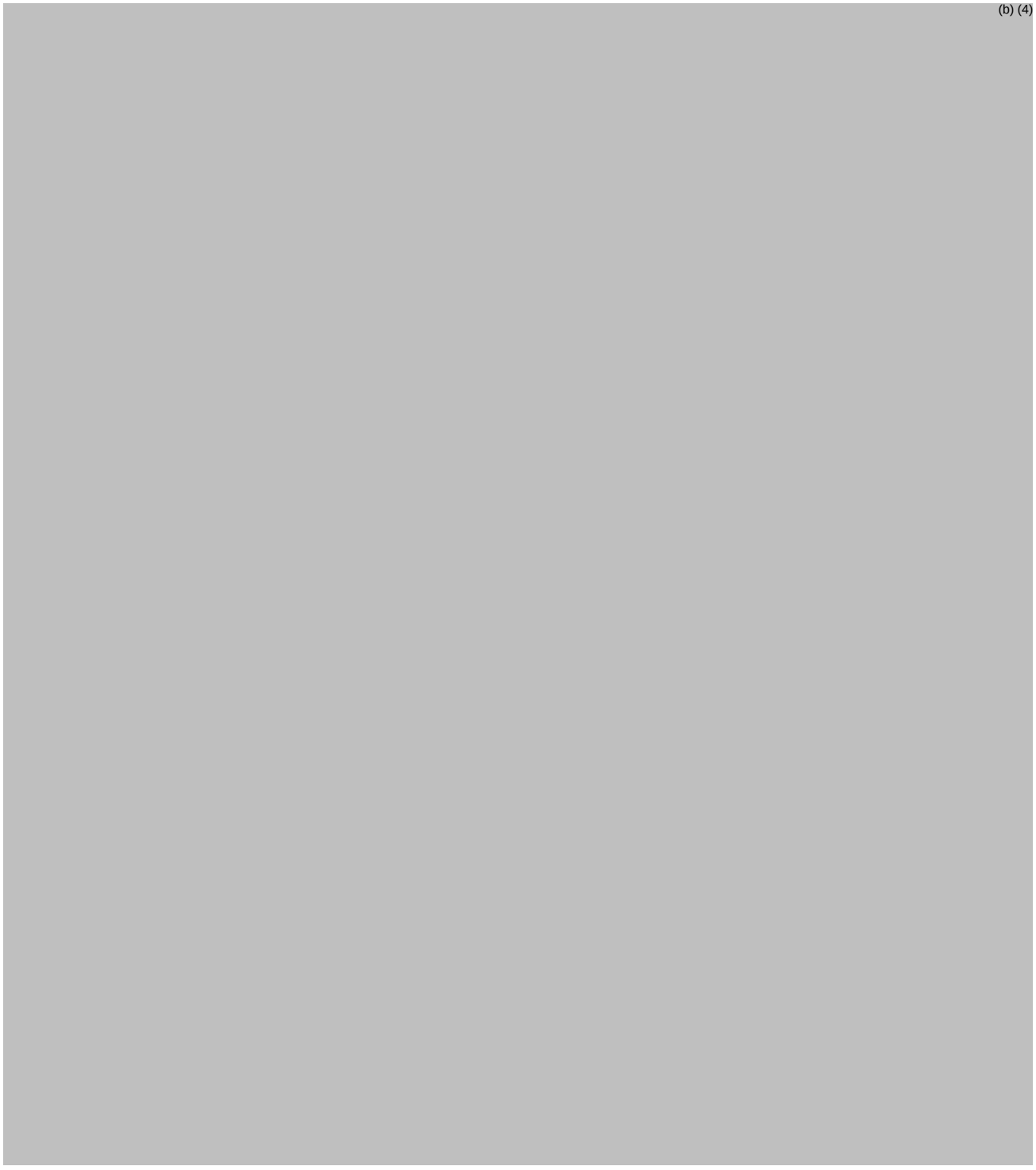
7.5 mg professional sample carton label 10-count



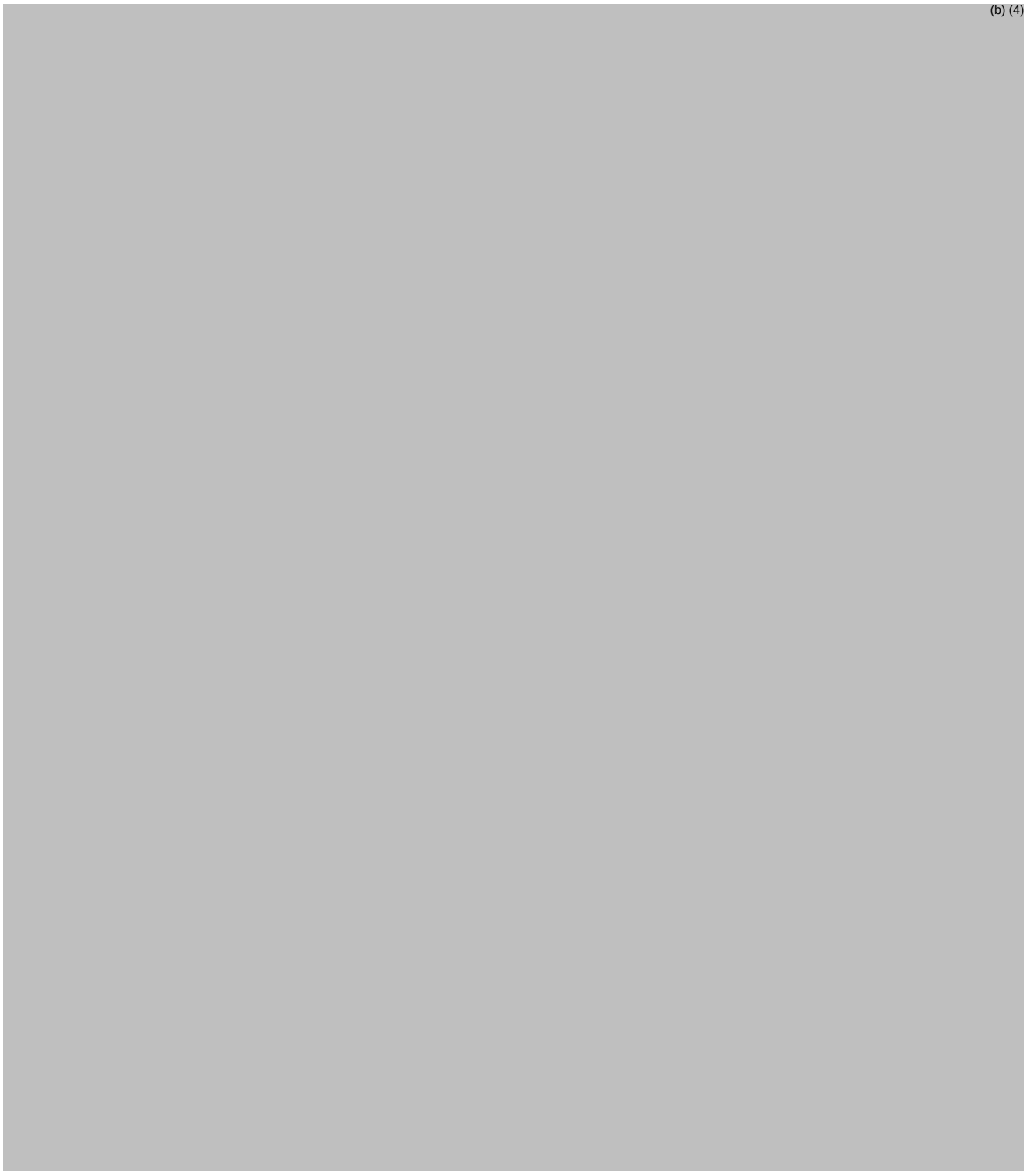
15 mg professional sample carton label 10-count



7.5 mg carton labeling 30-count



15 mg carton labeling 30-count



7.5 mg carton labeling 90-count

15 mg carton labeling 90-count

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAMERON D JOHNSON
08/08/2018

OTTO L TOWNSEND
08/08/2018