UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PACIRA PHARMACEUTICALS, INC., DR. LOREN J. HARRIS, and DR. JOSEPH W. BELL, Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION; UNITED STATES OF AMERICA; DR. STEPHEN OSTROFF, in his official capacity as Acting Commissioner of Food and Drugs; UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES; and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services, Defendants.	Civil Action No. 1:15-cv-07055-RA

Declaration of Lawrence Goldkind, M.D.

I, Lawrence Goldkind, M.D., hereby declare as follows:

1. I currently serve as an Assistant Professor of Medicine in the Department of Gastroenterology at Walter Reed National Military Medical Center and the Uniformed Services University of the Health Sciences School of Medicine in Bethesda, Maryland. I hold a bachelor's degree, *summa cum laude*, from the University of Pennsylvania and received my medical degree from the University of Maryland.

2. From 2001-2003, I was the Deputy Director and Acting Director of the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products ("DAAODP") in the Center for

Drug Evaluation and Research ("CDER") at the Food and Drug Administration ("FDA" or the "Agency").[1] My responsibilities while serving in this position included supervisory review and regulatory decision-making for all anti-inflammatory and non-narcotic analgesic drug products. From 1998-2000, I was a Medical Officer in the Division of Gastrointestinal and Coagulation Drug Products at CDER. In this role, I provided extensive consultative support to the DAAODP regarding the drug development and clinical trial analysis of analgesic drug products.

3. During my tenure at the Agency, I was involved in the clinical development and approval of dozens of drugs used to treat pain. I accordingly have considerable experience in analgesic drug development, particularly with respect to issues related to defining clinical indications and clinical trial design. I also provided guidance to drug companies regarding the studies needed to demonstrate the safety and efficacy of new analgesic drug products, which the companies relied upon to gain approval for the indications being sought. Additionally, in my role as Deputy Division Director of DAAODP, I was principally responsible for negotiating with pharmaceutical manufacturers the wording to be included in the Prescribing Information ("PI" or "label") for a variety of different drugs, including many drugs indicated for the treatment of pain. I was also one of the organizers of an FDA advisory committee meeting in 2002 that addressed the development and labeling of analgesic drug products, and I presented at that meeting. While I was at the Agency, I received two awards for my service: the Special Recognition Award in 1999 and the Award of Excellence in 2003.

4. Prior to joining FDA, I had a private gastroenterology practice in Tampa, Florida, from 1987-1998. I also served as the Chairman of the Division of Gastroenterology at

[1] DAAODP was one of the precursors to FDA's Division of Anesthesia, Analgesia, and Addiction Products ("DAAAP"), the division responsible for the approval of EXPAREL, a drug manufactured by Pacira Pharmaceuticals, Inc. ("Pacira") that is indicated for "administration into the surgical site to produce postsurgical analgesia." *See* Prescribing Information for EXPAREL.

University Hospital in Tampa from 1994-1998 and was a member of the Institutional Review Board at Tampa's Jaeb Center for Health Research from 1993-1998. I am Board Certified in Gastroenterology and Internal Medicine. My publication and presentation record spans more than 30 years and covers a wide range of topics, including analgesic drug development and the clinical benefits and risks of non-steroidal anti-inflammatory drugs, known as "NSAIDs." I have served on the review boards for five medical journals. My *curriculum vitae* is attached hereto as Exhibit A.

5. I have been retained by attorneys for Pacira Pharmaceuticals, Inc. ("Pacira") and various individual doctors to provide this declaration concerning the medical aspects of pain, the scientific and regulatory considerations associated with the study and FDA approval of analgesic drugs, and the scope of the approved indication for Pacira's product, EXPAREL. I am being compensated at my normal rate of $600 per hour for my time in this matter. To prepare this declaration, I consulted the EXPAREL PI, various materials from EXPAREL's regulatory history, materials regarding the clinical development and FDA approval of various analgesic drugs, and various FDA regulations and guidance documents. In preparing this declaration, I rely on my knowledge of FDA's regulations and practices, and of scientific understanding and medical practice surrounding pain medications.

I. THE MEDICAL ASPECTS OF PAIN

A. *Characteristics of Pain*

6. Pain is characterized by a number of features, including its duration and pattern of occurrence, its intensity, its cause, and its location. Knowledge and understanding of these features is critical to determining how pain medications may be appropriately studied, as well as

which methods of pain relief may be appropriate for a particular patient. I will discuss each of these characteristics in turn.

7. *First*, pain is characterized by its temporal features. Acute pain is tied to a particular injury or ailment (*e.g.*, a broken arm, a kidney stone, or a surgical procedure) and lasts for a short period of time (*e.g.*, a few hours, a few weeks). Once the underlying injury has resolved, the pain no longer persists. Chronic pain, on the other hand, may last for months or longer. It may be episodic or continuous, may be associated with an initial injury or with an underlying disease or condition, and may originate from damage to tissue or from direct nerve damage. Examples include arthritis, chronic low back pain, and diabetic peripheral neuropathy.

8. *Second*, pain is characterized by its intensity. As a general matter, pain is understood to occur on a continuum and may be classified as mild, moderate, or severe. Due to the inherent subjectivity and variability of pain, the intensity of pain experienced by an individual is frequently assessed by self-reported pain scores. The Numeric Rating Scale, for example, in which patients rate their pain intensity from 0 ("no pain") to 10 ("worst possible pain"), is a widely used instrument for pain assessment.

9. *Third*, pain is characterized by its cause. An individual may experience a superficial burn to the skin, for example, or may have a muscle ache due to straining one's back. Pain also may result from a particular trauma, such as with postsurgical pain, where the patient feels pain at or around the surgical incision site due to the cutting of the skin and underlying tissue. Additionally, pain may be caused by an underlying disease or condition such as fibromyalgia, arthritis, chronic low back pain, or diabetes.

10. *Fourth*, pain is characterized by whether its origin is nociceptive or neuropathic. Nociceptive pain arises from the stimulation of specialized sensory nerves called nociceptors.

These nerves are located throughout the soft tissues, such as muscles and skin, as well as the internal organs. Nociceptive pain is further categorized into visceral and non-visceral (or somatic) pain. Visceral pain results from the activation of nociceptors of the thoracic, pelvic, or abdominal organs. Non-visceral pain, on the other hand, results from the activation of nociceptors in the skin, muscles, bones, joints, or connective tissue. Neuropathic pain is caused by damage, dysfunction, or injury in the central or peripheral nervous system.

B. ***The Study of Medications to Treat Pain***

11. The study of analgesic therapy is challenging for multiple reasons. How patients experience and express pain is subjective. The assessment of pain is typically dependent on self-reported pain intensity scores, as described above. But even among patients experiencing the same type of pain from the same type of stimuli (*e.g.*, postsurgical pain from an appendectomy), the reported pain scores may be highly variable. In addition, pain resulting from a self-resolving source such as post-operative pain resolves at different rates in different patients that undergo the same procedure. Recall of pain over time is highly variable as well. As a result, demonstrating the pain-relieving effect of an analgesic drug in a clinical study is a daunting task.[2]

12. The difficulty of studying analgesic medications is compounded by ethical concerns. While placebo-controlled clinical studies are considered to be the "gold standard" in study design, it is simply unethical to allow patients to suffer in pain without offering any form of relief. Accordingly, clinical studies in analgesic drug development are often conducted as "active-controlled" studies, in which the study drug is compared against a standard pain treatment, or as placebo-controlled studies, in which patients have the opportunity to take "rescue medication," typically in the form of an opioid. Both study designs present challenges

[2] FDA itself recognizes that "[a]ll analgesics have characteristics that create a challenge for clinical trial design." FDA, *Guidance for Industry: Analgesic Indications: Developing Drugs and Biological Products* 15 (Draft Guidance Feb. 2014) (hereinafter the "*Analgesic Draft Guidance*").

for the interpretation of data and the demonstration of clinical benefit. For example, an active-controlled study may suggest that a new drug is similar in efficacy to an approved drug but may not prove with statistical significance that the new drug is superior to the comparator; this "failure," however, does not indicate that the new drug is ineffective for pain control. In a placebo-controlled study, moreover, the use of rescue medication sooner or more often by subjects in the placebo arm may well obscure the benefit of the study drug. This may be the case even with statistical manipulations to minimize bias against the study drug. Indeed, "failed" placebo-controlled studies are common in the clinical development programs of analgesic medications that are ultimately approved by FDA.

II. FDA'S APPROACH TO ANALGESIC DRUGS IS TO GRANT THE BROADEST APPROPRIATE INDICATION

13. Extrapolation of analgesic efficacy is the application of clinical trial results from a study in one setting or model (such as post-appendectomy pain) to another setting or model (such as post-bunionectomy pain). For analgesic drugs, in particular, there are numerous scientific considerations that support extrapolation. More specifically, administering an anesthetic agent into the site of one surgical location can reasonably be extrapolated to other incision sites unless there is a specific rationale for why this extrapolation is not reasonable. These scientific considerations support FDA's long-held approach of granting the broadest appropriate indication for an analgesic drug.

A. *Scientific Considerations*

14. There are two principal scientific considerations relevant to extrapolation. The first is the pain itself, as characterized by the temporal features, intensity, causes, and origin as described above. If the pain to be treated is caused by a superficial burn to the skin, for example, the method of treating that pain would be the same regardless of where on the body the burn

occurred. The same is true for treating the pain from a broken arm, broken leg, or broken wrist, all of which would be expected to respond to the same analgesic drug. Postsurgical pain, too, which is caused by trauma to the skin and underlying tissue from the surgical incision and treated with infiltration of the site with a local anesthetic agent, should respond to the same treatment regardless of the location in which the surgery is performed.

15. The second scientific consideration in determining the appropriateness of extrapolation is the drug itself—specifically, its mechanism of action and pharmacology. FDA has recognized "whether the finding of analgesia should be replicated in specific patient populations (i.e., subjects with particular types of pain) versus across patient populations depends on how much is known about the pharmacology of the drug under development."[3] Local anesthetics that have a well-understood pharmacological profile and decades of proven effectiveness have been approved for and are used clinically to treat post-operative pain in a broad range of surgical incision sites. EXPAREL is a good example of a drug for which studies in a limited number of surgical settings are sufficient to support a broad indication of locally infiltrative delivery of analgesic treatment of post-operative pain.

16. Based on the scientific considerations described above, if the characteristics of the pain are the same, and the pharmacology of the drug indicates that it will work in the same way, it is appropriate to extrapolate from data in one surgical setting to broader use in the other surgical settings. Indeed, in light of the ethical considerations associated with studying pain, extrapolation is desirable unless there is information to suggest that using an analgesic drug in a new pain model would present safety concerns.[4] Put another way, the proper inquiry is not *why* extrapolation is appropriate, but rather why *not*?

[3] *Id.* at 7.
[4] *Id.* at 4 (indicating that narrow indications, *i.e.*, without extrapolation, are appropriate, for example, "when

B. *FDA Policy and Practice Supports Extrapolation*

17. For decades, and including during my tenure at FDA, the Agency has favored extrapolation and broad indications for analgesic medications wherever appropriate. As far back as 1992, FDA made its position clear in a guidance document about the development and evaluation of analgesic drugs, stating that "[e]vidence that an agent has analgesic activity in pain of several different etiologies will justify 'general purpose' analgesic labeling unless special considerations indicate that this is not appropriate."[5] That guidance was in effect while I was at FDA, and I understood it to mean that, so long as an analgesic was demonstrated safe and effective for a specific type of pain and there were no safety concerns weighing against extrapolation, the drug should be approved with as broad an indication as possible.

18. That approach was prevalent while I was at the Agency and has continued. Dr. Bob Rappaport, the former director of DAAAP and the final signatory authority responsible for approving the label and specifically the indication for EXPAREL, has outlined the concept of extrapolation of evidence in the field of pain management on more than one occasion. In his July 2010 Division Director's memorandum regarding approval of CYMBALTA (duloxetine) for the broad indication of chronic pain, Dr. Rappaport discussed the history of analgesic indications for chronic and acute pain.[6] His comments were in the context of a drug for chronic pain, but the rationale is relevant, and indeed even more persuasive, for drugs to treat acute pain such as EXPAREL. Specifically, he stated that

> [t]he Agency is working to balance the need for adequate scientific rigor for demonstration of efficacy for the treatment of chronic pain with the feasibility of

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substantial safety concerns result in an acceptable risk-benefit analysis only in limited, defined situations of use"); *see also id.* (stating that the labeling for drugs with safety concerns based on formulation or toxicity profile should reflect the narrow patient population appropriate for treatment).

[5] FDA, *Guidance for Industry: Guideline for the Clinical Evaluation of Analgesic Drugs* 22 (Dec. 1992).

[6] Bob A. Rappaport, M.D., "Overview of the August 19, 2010 ALSDAC Meeting to Discuss NDA-22-516 for Cymbalta for the Treatment of Chronic Pain" (July 26, 2010), *available at* http://tinyurl.com/n99zm5r.

> studying every patient population in which chronic pain occurs . . . . At present, if a Sponsor can submit a collection of studies that meets a 'weight-of-evidence' argument[,] we would consider granting a general chronic pain indication, although we intend to include negative studies in the labeling and the relevant types of pain that were not studied.[7]

Dr. Rappaport went on to state that "where the mechanisms of action are well defined and there is extensive use of these drugs for a multitude of painful conditions," the weight of evidence would be less than for New Molecular Entities ("NMEs") (*i.e.*, new drugs that are not related to other drugs on the market from which experience may be drawn) that are not traditional analgesics.[8]

19. Dr. Rappaport reiterated this approach to broad indications in the field of pain in a presentation in 2012.[9] When discussing the rationale for and benefits of extrapolation, Dr. Rappaport emphasized the dual aims to "get new analgesics to the market" and "to have analgesics with broader indications."[10] He highlighted examples of analgesics broadly indicated "for the treatment of pain"[11] and explained that a broad indication could be extrapolated from a trial in a narrower clinical setting.[12] In particular, he stressed that while FDA considers the rationale for extrapolation on a case-by-case basis, "[i]n some cases, extrapolation of safety and/or efficacy data may be allowed, resulting in approval based on [a] single trial or smaller number of subjects."[13]

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[7] *Id.*
[8] *Id.*
[9] Bob A. Rappaport, M.D., "Regulatory Issues Related to the Development of Drugs to Treat Painful Peripheral Neuropathy," Presentation at the 2012 Foundation for Peripheral Neuropathy National Research Symposium (Mar. 15, 2012).
[10] *Id.* at 10.
[11] *Id.* at 3.
[12] *Id.* at 5.
[13] *Id.*

20. These concepts were reaffirmed in a guidance document FDA issued in 2014.[14] The guidance states that sponsors of a New Drug Application ("NDA") seeking an indication for "the treatment of general acute pain" need only conduct two successful clinical trials. Despite the breadth of that indication, and the many types of acute pain that a patient may experience, the guidance states that one study in visceral pain and one study in non-visceral pain "likely will capture the majority of acute pain situations . . . ."[15]

21. Because FDA has stated in its *Analgesic Draft Guidance* that two clinical studies are sufficient to obtain an indication for the treatment of acute pain—broadly encompassing acute pain of all types—it is reasonable to infer that two clinical studies in postsurgical models would be sufficient to support an acute pain indication encompassing only postsurgical pain. EXPAREL was approved to provide postsurgical analgesia and is specifically delivered by infiltration into a surgical site, so the approval already represents a clearly defined population within the setting of acute pain. That conclusion is consistent with how I, along with other scientists and physicians, understand pain, and it tracks FDA's approach to the development and approval of analgesic drugs over the years.

22. FDA's preference for broad indications in the analgesic context is borne out in practice, as FDA has routinely approved pain medications on the basis of limited clinical models. In 2001, for example, FDA determined that CELEBREX (celecoxib) had demonstrated efficacy "for acute pain" even though there were multiple failed studies in postsurgical models and the successful clinical studies were in dental surgery and dysmenorrhea only.[16] Additionally, FDA approved OFIRMEV (intravenous acetaminophen) for mild to moderate pain on the basis of one

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[14] *See Analgesic Draft Guidance*, *supra* note 2.
[15] *Id.* at 5.
[16] FDA, CDER, Medical Officer Review of Celebrex 7-10 (sNDA # 20,998 received Dec. 19, 2000), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/20-998S010_Celiebrex_Medr_P1.pdf.

study in abdominal laparoscopic surgery and one in total hip or knee replacement. Even more instructive, the Agency approved NUCYNTA (tapentadol)—a controlled substance with significant abuse potential and serious safety issues—for the relief of "moderate to severe acute pain" on the basis of one clinical study in bunionectomy and one in end-stage osteoarthritis of the hip or knee.[17] Minutes from the sponsor's pre-NDA meeting indicate that FDA was comfortable with this approach even though this was an NME and even though FDA had not yet reviewed the relevant dataset.[18]

23. In sum, there are numerous scientific considerations that support extrapolation from limited pain models to pain relief more broadly. Unless there are safety or other concerns specific to the drug, extrapolation is appropriate. I held this view when I was at FDA, where it was consistent with the Agency's policy and practice to grant broad acute pain indications on the basis of data in two pain models. Where the indication is not for acute pain generally, but for the subcategory of local infiltration of anesthetic therapy for the treatment of postsurgical pain, extrapolation from two surgical models to general postsurgical use is particularly appropriate.

III. CLINICAL DATA IN THE EXPAREL NDA WAS SUFFICIENT FOR FDA TO GRANT A POSTSURGICAL PAIN INDICATION GENERALLY THAT WAS NOT LIMITED TO POSTSURGICAL PAIN ARISING FROM BUNIONECTOMY OR HEMORRHOIDECTOMY

24. Pacira's NDA for EXPAREL contained data from pivotal studies of bunionectomy and hemorrhoidectomy. The data from those pivotal studies provided robust evidence for the efficacy of EXPAREL when delivered by the surgeon or anesthesiologist into the surgical site according to accepted and longstanding technique.

25. EXPAREL's safety has been broadly demonstrated. Indeed, the safety of doses more than twice those used in the bunionectomy and hemorrhoidectomy pivotal studies was well

[17] *See* Prescribing Information for NUCYNTA.
[18] FDA, CDER, Minutes of Sponsor Meeting of June 5, 2007, at 7, *available at* http://tinyurl.com/n9fy6wr.

evidenced in the NDA. The FDA medical officer's safety review of the EXPAREL NDA described three potential safety concerns related to local wound complications, neurotoxicity, and cardiac toxicity, but he ultimately concluded that the safety of EXPAREL with respect to these three issues, as well as the drug's overall safety profile, was similar to a placebo and standard bupivacaine, a local anesthetic and analgesic – and the active ingredient in EXPAREL. FDA's safety determination was informed by a large database that included data from over 1,000 subjects treated with EXPAREL doses ranging from 120 mg to 750 mg. In addition, two studies that specifically studied the cardiac safety of EXPAREL doses up to 750 mg were performed and did not suggest any safety issues.

26. With respect to efficacy, there is no reason to expect that EXPAREL's analgesic effect would differ when administered in surgical sites other than the surgical sites created by bunionectomies and hemorrhoidectomies. Indeed, non-pivotal studies submitted to the FDA suggested efficacy in other settings similar to the active control, bupivacaine (*i.e.*, a drug approved and in use for decades for the broad indication of post-operative pain).

27. Furthermore, bunionectomies and hemorrhoidectomies represent opposite ends of the surgical spectrum when it comes to the human anatomy. Bunionectomies are performed in the foot, where there is a high concentration of bone, ligaments, joints, and tendons, but very little soft tissue (*e.g.*, fat, muscle, nerves, internal organs, and blood vessels). Hemorrhoidectomies, on the other hand, are performed in the anal area. That area consists entirely of soft tissue – it is muscular, highly vascular, densely packed with nerve endings, and in close proximity to the colon – and there is no bony anatomy whatsoever. Hence, even the successful placebo-controlled pivotal studies represented a broad range of settings upon which to extrapolate to the setting of local infiltration delivery of the drug in other surgical sites.

28. That EXPAREL demonstrated safety and effectiveness in these two highly differentiated anatomical areas indicates that EXPAREL is safe and effective in producing postsurgical analgesia in surgical procedures conducted in other anatomical areas. This understanding is bolstered by the fact that there is nothing unique or exceptional about bunionectomies or hemorrhoidectomies to suggest that EXPAREL should be limited to use in those procedures.

29. As noted, the mechanism of action of the active ingredient in EXPAREL, bupivacaine, is well understood because it has been used widely and extensively by surgeons and anesthesiologists since FDA approved it in 1972 for use as a local anesthetic and analgesic. As with other local analgesics, bupivacaine blocks the generation and conduction of nerve impulses, which reduces the sensation of pain. This mechanism of action applies regardless of the anatomical location into which bupivacaine is administered.

30. Thus, EXPAREL's safety and effectiveness in two very different anatomical locations, coupled with bupivacaine's mechanism of action, demonstrates that FDA's approval of EXPAREL for a general postsurgical analgesic indication, not limited to bunionectomy and hemorrhoidectomy, was scientifically valid and appropriate.

IV. FDA GRANTED EXPAREL AN ALL-PURPOSE INDICATION FOR THE PRODUCTION OF POSTSURGICAL ANALGESIA, NOT A SPECIFIC ONE RESTRICTED TO ANALGESIA FOLLOWING BUNIONECTOMY OR HEMORRHOIDECTOMY ONLY

A. *A Bunionectomy and Hemorrhoidectomy Indication Would Have Required Two Bunionectomy and Two Hemorrhoidectomy Studies*

31. If FDA had intended to approve EXPAREL for use in managing postsurgical pain arising only from bunionectomies and hemorrhoidectomies, it should have required Pacira to conduct two studies of EXPAREL in bunionectomies and two studies of EXPAREL in

hemorrhoidectomies, for a total of four pivotal studies. This is because for each indication "it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."[19] FDA reiterated this position in its *Analgesic Draft Guidance* when it stated that an "analgesic that is to be used to treat a specific pain condition should be supported by at least two adequate and well-controlled studies."[20]

32. Because of FDA's position on the studies needed to support approval of drugs generally and to support approval of pain medications specifically, I believe that the single pivotal study in bunionectomies and the single pivotal study in hemorrhoidectomies supporting FDA's finding of effectiveness of EXPAREL would be, from FDA's perspective, insufficient to support specific pain indications of "post-surgical analgesia following bunionectomy" and "post-surgical analgesia following hemorrhoidectomy" unless these two studies represented models of pain that cross-support efficacy for a more general indication. The fact that the drug was approved under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act also suggests that the Agency took into account the efficacy of the active drug, bupivacaine, when it determined the extent of the efficacy studies needed to support the general indication of postsurgical analgesia.

B. *The Indications and Usage Section of the EXPAREL PI Does Not Limit EXPAREL's Use to Bunionectomy or Hemorrhoidectomy*

33. The FDA-approved PI for EXPAREL states in the "Indications and Usage" section that the drug is "indicated for administration into the surgical site to produce postsurgical analgesia." I have reviewed correspondence between FDA and Pacira concerning the

[19] FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* 3 (May 1998).
[20] *Analgesic Draft Guidance*, *supra* note 2, at 4.

negotiation of the EXPAREL PI, and the language in the "Indications and Usage" section in the FDA-approved PI is nearly identical to the language that Pacira originally proposed in its NDA for EXPAREL. Only two terms changed during the course of the negotiations: "amide" was modified to "amide-type" and "wound" was modified to "site." Neither of these changes affected the meaning of the indication for "postsurgical analgesia."

34. Based on my experience revising and approving PIs for many different drugs, including pain medications, I have always understood that the "Indications and Usage" section of the PI must set out all of the approved indications for the drug, as well as all of the limitations on the approved indications. This understanding is borne out in FDA's regulations, which state that the "Indications and Usage" section controls the breadth of the approved indications. 21 C.F.R. § 201.57(c)(2). The regulation specifically states that the "Indications and Usage" section must indicate "[m]ajor limitations of use (*e.g.*, lack of effect in particular subsets of the population or second line therapy status)." Hence, FDA's regulations provide the Agency with a specific mechanism for limiting the approval of a drug if the applicant can demonstrate safety and effectiveness only in selected subgroups of the proposed indication. 21 C.F.R. § 201.57(c)(2)(i)(B).

35. The only limitation on the indication for EXPAREL relates to use in patients younger than 18 years of age. There is nothing in the "Indications and Usage" section to suggest that EXPAREL is approved only for postsurgical analgesia following bunionectomy or hemorrhoidectomy. If FDA had considered such limitations necessary, this would have been the section of the label to make that clear.

C. *The Indications and Usage Section Is Not Limited by the Dosage and Administration Section*

36. Although the "Dosage and Administration" section of the EXPAREL PI includes specific doses for bunionectomies and hemorrhoidectomies, the inclusion of such information does not limit the scope of the "Indications and Usage" section to use in bunionectomies or hemorrhoidectomies. There are several reasons why this is so.

37. *First*, the "Dosage and Administration" section includes more than just dosing information for bunionectomies and hemorrhoidectomies. The specific dosing information is prefaced by a statement that "[t]he recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area." Because the indication is not limited to specific surgical procedures, this statement is most logically interpreted as a guide to the dose range informed by the clinical trials but not limited to those specific surgical settings. Based on my experience as a practicing physician and as an FDA official approving and negotiating PIs, I understand this introductory sentence to provide general guidance on the dosing of EXPAREL and to explain that the physician should use his or her discretion in dosing EXPAREL such that enough drug is used to cover the surgical site for the indication of post-operative analgesia. Furthermore, my review of approved labels of other drugs in the same class as EXPAREL supports this understanding of the EXPAREL label.

38. FDA itself has recognized that such discretion is necessary and appropriate in the context of administering local anesthetics during surgery. For example, the "Dosage and Administration" section in the FDA-approved PI for CHIROCAINE (levobupivacaine) states that "[t]he dose of any local anesthetic differs with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the intensity of the block, the degree of muscle relaxation required, the duration of the anesthesia

desired, individual tolerance, and the physical condition of the patient." Similar language can be found in the "Dosage and Administration" section in the FDA-approved PI for MARCAINE (bupivacaine), which additionally states that "[f]or specific techniques and procedures, refer to standard textbooks." The "Dosage and Administration" section for NAROPIN (ropivacaine HCl), furthermore, contains substantively similar language. Medical practice has not changed over the years to warrant a change in the use of this class of drugs. Furthermore, the concept of a dose range is not unique to locally delivered analgesia. Systemic oral analgesics generally include a range of approved doses. The clinician is expected to use judgment and experience in choosing the optimal dose for each patient. The concept is no different for EXPAREL. The dosing information for bunionectomy and hemorrhoidectomy thus provides two examples of how to interpret the general guidance in the introductory sentence.

39. *Second*, if the EXPAREL indication were actually limited to use in producing postsurgical analgesia in bunionectomies and hemorrhoidectomies, there would be no need to include the introductory statement at all – providing the specific dosing information for the two procedures would be sufficient. The presence of the introductory statement leads to the conclusion that dosing guidance for EXPAREL is *not* limited to use in bunionectomies and hemorrhoidectomies.

40. *Third*, inclusion of specific doses in the "Dosage and Administration" section does not control or otherwise limit the indication provided in the "Indications and Usage" section. 21 C.F.R. § 201.57(c)(2). This is because the breadth of a drug's indication is controlled, not surprisingly, by the "*Indications* and Usage" section.

41. For these reasons, I do not interpret the inclusion of dosing information that is specific to bunionectomy and hemorrhoidectomy as limiting the indication of EXPAREL to use

in producing postsurgical analgesia in those two types of procedures. Again, if FDA had intended the indication to be limited to analgesia for post-operative pain of bunionectomy and/or hemorrhoidectomy, it had the opportunity to do so in the appropriate section of the label.

D. ***The Indications and Usage Section Is Not Limited by the Clinical Studies Section***

42. The statement in the "Clinical Studies" section of the PI that EXPAREL has not been demonstrated to be safe and effective in procedures other than bunionectomy and hemorrhoidectomy does not limit the indications of EXPAREL either. That type of statement educates the prescriber about the extent of the evidentiary basis relied upon to establish the efficacy of the drug for the approved indication. As a physician myself, I understand that such specific information is rarely available for all of the possible surgical procedures that may be performed with a drug broadly indicated for postsurgical analgesia. The EXPAREL PI is not substantially different than labels of other analgesic drugs, all of which describe the pivotal studies supporting approval of the drug. For example, it is clear when reading the PI of a drug such as CELEBREX or NUCYNTA that the settings or models establishing efficacy were limited to those noted in the Clinical Studies section. And, as mentioned previously, the "Indications and Usage" section controls the indication for a drug, not the "Clinical Studies" section or any other section.

E. ***The Approved PI Is an Outright Rejection of the FDA Medical Reviewer's Suggestion to Limit the Indication to Bunionectomy and Hemorrhoidectomy***

43. The basis of approval for EXPAREL that is publicly available on FDA's website further reveals the general postsurgical indication. The reviews of the NDA submission include the Clinical Review drafted by Dr. Arthur Simone, the FDA medical reviewer of the EXPAREL NDA. In the Clinical Review, Dr. Simone made a specific labeling recommendation that the

"[i]ndications [for EXPAREL] should be modified to postoperative analgesia following hemorrhoidectomy and bunionectomy."[21]

44. The "Indications and Usage" section of the EXPAREL PI was never modified as Dr. Simone suggested. In fact, the "Indications and Usage" statement remained essentially the same throughout labeling negotiations between FDA and Pacira; FDA never attempted to modify the statement pursuant to Dr. Simone's recommendation. The final authority in the approval of EXPAREL was not Dr. Simone, but Dr. Rappaport, who had been the Division Director for many years and was highly experienced in regulatory science and labeling. Dr. Rappaport affirmatively decided to approve the EXPAREL label, without implementing Dr. Simone's recommendation, after multiple interactions and reviews of pre-approval draft labeling submissions.

45. Based on my extensive experience negotiating and approving PIs on behalf of FDA for various drugs, including many pain drugs, this outcome reveals FDA's outright rejection of Dr. Simone's proposal. I believe that by not acting upon Dr. Simone's recommendation to modify the language in the "Indications and Usage" section, FDA agreed with Pacira that the indication as approved not be limited to bunionectomies and hemorrhoidectomies.

46. Had FDA intended to limit the indications for EXPAREL to postsurgical analgesia in the context of bunionectomies and hemorrhoidectomies only, it could have easily adopted Dr. Simone's recommendation and referred specifically to bunionectomy and hemorrhoidectomy in the "Indications and Usage" section.

[21] *See* FDA, CDER, Arthur Simone, M.D., Ph.D., Amended Clinical Review for EXPAREL (NDA 022-496), at 76 (Am. Rev. Completed Oct. 7, 2011).

47. FDA has limited the indications of other pain drugs in the past to very specific settings. For example, the analgesic indication for SUFENTA is limited to use "as an analgesic adjunct in the maintenance of balanced general anesthesia *in patients who are intubated and ventilated*" (emphasis added); the indication for methadone hydrochloride injection is limited to "treatment of moderate to severe pain *not responsive to non-narcotic analgesics*" (emphasis added); DEPODUR is indicated for "treatment of pain *following major surgery*" (emphasis added); and VICOPROFEN is indicated for "short-term . . . management of acute pain" and "*is not indicated for* the treatment of such conditions as osteoarthritis or rheumatoid arthritis" (emphasis added). Each of these examples includes limiting language in the "Indications and Usage" section. The EXPAREL PI "Indications and Usage" section contains no such limiting language.

F. *FDA's Application of PREA to EXPAREL Makes Clear That FDA Interpreted the Indication as Not Limited to Bunionectomy and Hemorrhoidectomy*

48. Furthermore, the way in which FDA has applied the Pediatric Research Equity Act ("PREA") to EXPAREL demonstrates that FDA itself interpreted the EXPAREL indications to encompass analgesia in *all* postsurgical settings, not just in the context of bunionectomies and hemorrhoidectomies. PREA is a statute that requires drug companies, in certain circumstances, to study their products in children. PREA is limited in its authority because it only grants FDA the authority to require pediatric studies of drugs in the approved, or on-label, indications of those drugs.

49. This understanding is confirmed in multiple FDA sources. FDA's official blog, for instance, states that "[w]hen pediatric studies are required, they must be conducted with the same drug and for the same use for which they were approved in adults."[22] FDA's guidance on

[22] FDAVoice (FDA's official blog "brought to you from FDA's senior leadership and staff"), *available at*

PREA states that "[u]nder PREA . . . a pediatric assessment is required only on those indications included in the pending [drug] application."[23] FDA has also stated that "PREA requires studies only in the specific indications for which the triggering application is approved . . . . For example, under PREA, a product approved for the treatment of chronic myeloid leukemia in adults might have the potential for activity against neuroblastoma in younger children, but studies *could not be required* as it is not the same indication as that in the application that triggered PREA" (emphasis added).[24]

50. Under PREA, FDA can waive studies in children if they are not necessary. According to FDA's blog, pediatric studies would not be necessary, "for example, if the disease or condition for which the drug is being used in adults does not exist in children, such as prostate cancer," in which case "FDA would waive studies for children."[25]

51. The approval letter for EXPAREL requires Pacira to conduct, under PREA, studies of EXPAREL in pediatric patients aged 0 to 17 years "undergoing multiple surgical procedures."[26] This description does not limit the required studies to studies of pediatric patients undergoing bunionectomies or hemorrhoidectomies, a fact that echoes the broad indication approved for EXPAREL.

52. It would have been impossible for FDA to require studies of EXPAREL in pediatric patients undergoing bunionectomies and hemorrhoidectomies. This is because bunions and hemorrhoids are conditions that do not occur with any frequency in the pediatric population.

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http://blogs.fda.gov/fdavoice/index.php/tag/pediatric-research-equity-act-prea/.

[23] FDA, *Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act* 14 (Sept. 2005).

[24] FDA, *Retrospective Review of Information Submitted and Actions Taken in Response to PREA* 11 (2003), *available at* http://tinyurl.com/qjaunmf.

[25] FDAVoice, *supra* note 23.

[26] Letter from B. Rappaport to Pacira Pharmaceuticals, Inc. (Oct. 28, 2011).

53. I have reviewed correspondence between Pacira and FDA concerning the design of the studies that would satisfy the PREA requirement. In that correspondence, FDA itself acknowledges that "neither of [hemorrhoidectomy or bunionectomy] is commonly performed in any segment of the pediatric patient population."[27] If the indication for EXPAREL were limited to producing postsurgical analgesia after bunionectomies and hemorrhoidectomies, then FDA would have waived the requirement for PREA studies because those conditions do not exist in children.

54. The correspondence also reveals that Pacira proposed many different types of clinical trials to FDA as it attempted to design studies to satisfy the PREA requirement. Those proposals included exploratory laparoscopy, genito-urinary surgery, lower extremity orthopedic surgery, tonsillectomy, and "various surgical procedures."

55. Requiring a company to conduct a pediatric study of a drug for a use that has not even been approved in adults would raise serious ethical issues, as pediatric patients should not be used as guinea pigs for unproven treatments. FDA would not have acted in an unethical manner by requiring Pacira to conduct off-label studies of EXPAREL. The fact that FDA required PREA studies of EXPAREL at all, combined with the fact that bunionectomies and hemorrhoidectomies do not occur in children, means that FDA understood EXPAREL to be approved (and therefore safe and effective) for use in all postsurgical settings, not just in bunionectomies and hemorrhoidectomies.

V. CONCLUSIONS ABOUT THE APPROVED INDICATION FOR EXPAREL

56. Based on (i) my expertise concerning FDA's approach to approving pain medications and its desire to grant broad analgesic indications whenever possible; (ii) FDA's application of PREA to EXPAREL; (iii) the language in the "Indications and Usage" section of

[27] FDA General Advice Letter from B. Rappaport to G. Knott (Nov. 20, 2012).

the PI that the drug is indicated for "postsurgical analgesia"; and (iv) the lack of any recommendation in PI against use in surgeries other than bunionectomies and hemorrhoidectomies, the only reasonable conclusion that can be drawn is that FDA approved EXPAREL generally to produce postsurgical analgesia and did not limit such approval to use only in bunionectomies and hemorrhoidectomies. In light of the scientific rationale supporting extrapolation of analgesic efficacy, extensive precedents in FDA approvals of analgesic drugs to treat acute pain, and the prominent deliberations related to the construction of pain indications, if FDA, and specifically Dr. Rappaport, had intended a narrower indication for EXPAREL, then this should have been expressed specifically in the Indications and Usage section of the PI.

57. It is therefore entirely reasonable, and consistent with FDA's regulations, for Pacira to promote EXPAREL for use in producing postsurgical analgesia in surgical procedures other than bunionectomies and hemorrhoidectomies.

58. The warning letter issued by FDA's Office of Prescription Drug Promotion ("OPDP") to Pacira misinterpreted the EXPAREL PI when it stated that surgeries other than bunionectomy or hemorrhoidectomy represent "new intended uses" of EXPAREL. OPDP's interpretation of the PI is too narrow and does not reflect the language of the approved indication agreed upon by DAAAP, the scientific division within FDA responsible for approving EXPAREL; it also is inconsistent with Division Director Dr. Rappaport's stated approach to the construction of labeled indications and FDA's long-standing approach to analgesic drugs as evidenced by the *Analgesic Draft Guidance* and past practice.

59. The OPDP warning letter appears to me to be an attempt by FDA to rewrite the EXPAREL PI. There are limited circumstances under which FDA may revise the label of an approved drug and even if those circumstances applied here, FDA would be required to follow

certain processes before doing so. Those processes would not encompass issuance of a warning letter to the drug's manufacturer.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge, information, and belief.

This Declaration was executed on September 02, 2015.

Lawrence Goldkind MD

Lawrence Goldkind, M.D.