ANESTHESIOLOGY

Anesthetic and Analgesic Drug Products Advisory Committee Activity and Decisions in the Opioid-crisis Era

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ANESTHESIOLOGY 2020; 133:740–9

ABSTRACT

The United States Food and Drug Administration is tasked with ensuring the efficacy and safety of medications marketed in the United States. One of their primary responsibilities is to approve the entry of new drugs into the marketplace, based on the drug's perceived benefit–risk relationship. The Anesthetic and Analgesic Drug Product Advisory Committee is composed of experts in anesthesiology, pain management, and biostatistics, as well as consumer and industry representatives, who meet several times annually to review new anesthetic-related drugs, those seeking new indications, and nearly every opioid-related application for approval. The following report describes noteworthy activities of this committee since 2017, as it has grappled, along with the Food and Drug Administration, to balance the benefit–risk relationships for individual patients along with the overarching public health implications of bringing additional opioids to market. All anesthesia advisory committee meetings since 2017 will be described, and six will be highlighted, each with representative considerations for potential new opioid formulations or local anesthetics.

(ANESTHESIOLOGY 2020; 133:740–9)

The United States Food and Drug Administration is tasked with ensuring the efficacy and safety of medications marketed in the United States. One of their primary responsibilities is to approve the entry of new drugs into the marketplace, based on the drug's perceived benefit–risk relationship. The Food and Drug Administration's approval of pain treatment medications has influenced the trajectory of the nation's opioid crisis. The most salient and criticized decision was the 1995 approval of OxyContin (Purdue Pharmaceuticals, Stamford, Connecticut), a long-acting oral oxycodone preparation, on the false premise of its lower risk for opioid use disorder when used to treat chronic pain.[1,2] Critics of this approval cite the lack of evidence that opioids are effective or safe in the treatment of chronic pain.[3–5] At the same time, Purdue's aggressive marketing of OxyContin contributed to one of the worst public health crises in modern history.[6] In 2010, the approval of the abuse-deterrent formulation of OxyContin is widely considered an important cause of the increase in overdose deaths from heroin and other lethal street drugs.[7,8] As a result, the Food and Drug Administration has endeavored to consider the effects of opioid approvals on public health in addition to the benefit–risk relationship for pain treatment.[9]

The drug development process that leads to eventual approval is complicated and lengthy. The relationship between a pharmaceutical manufacturer ("sponsor") and the Food and Drug Administration begins with the sponsor's submission of an Investigational New Drug application. The Investigational New Drug applicaton informs the Food and Drug Administration of the results of preclinical (*i.e.*, animal) studies of the sponsor's drug and may also contain human data from its use in other countries. After Investigational New Drug submission, the Food and Drug Administration gives "permission" (in the form of a nonresponse in the first 30 days after filing the Investigational New Drug) for the sponsor to proceed with human studies.

The human studies proposed within the Investigational New Drug proceed along a long-accepted phased continuum of clinical human trials (table 1).[10] The results of these trials are submitted to the Food and Drug Administration as a New Drug Application to determine its final approval. In the interest of brevity, this is a gross oversimplification of a multi-years-long process, which typically involves many back-and-forth communications between the sponsor and the Food and Drug Administration.

As a precondition for approval, the Food and Drug Administration prefers the submission of two prospective phase 3 trials in different populations that demonstrate the drug's efficacy and safety. This requirement, however, is not absolute, and there are many examples of approvals with only one phase 3 study in select circumstances. The Food and Drug Administration may require a sponsor to perform postmarketing (*i.e.*, after approval) studies to elucidate rare or unique risks that were not evident in the phase 3 trials[11] or to supplement knowledge in certain subpopulations, such as pediatric patients.

For many New Drug Applications, the Food and Drug Administration staff, which includes clinicians, scientists, and pharmacoepidemiologists, independently decides on approval. However, when the science underpinning a

Submitted for publication April 30, 2020. Accepted for publication July 1, 2020. Corrected on October 14, 2020. Published online first on August 3, 2020. From the Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; Institute for Safe Medication Practices, Horsham, Pennsylvania.

 Anesthesiology 2020; 133:740–9. DOI: 10.1097/ALN.0000000000003485

Table 1. Phases of Clinical Studies during the Drug Approval Process (modified from reference 10)

Phase 1	• Typically performed in healthy subjects or individuals with the condition to be treated • Designed to confirm human pharmacokinetics, dose range, and lack of toxicity or unexpected side effects • Enrolls 20 to 100 participants • Typical timeframe to complete: several months • Approximately 70% of drugs continue to Phase 2
Phase 2	• Efficacy, dose-responsiveness, and safety, in patients with the targeted condition • May be an observational, open label, longitudinal design, but may also include prospective, blinded trials in certain situations • Enrolls several hundred patients • Typical timeframe to complete: 1–2 years • Approximately 33% of drugs continue to Phase 3
Phase 3	• Efficacy and safety tested in patients with the targeted condition • Ideally prospective, randomized, controlled, blinded design • Several hundred to >1,000 participants • Typical timeframe to complete: phase 3 trials may take anywhere from 12 weeks to 2 years to complete. • Approximately 25% to 30% of drugs in this phase become Food and Drug Administration approved
Phase 4	• Usually performed after Food and Drug Administration approval and in use by public (also called "postmarketing study") • Prospective or retrospective design • Useful for detecting real-world efficacy and safety, in different types of populations (*e.g.*, pediatrics), especially when compared with existing therapies, and previously undetected rare side effects or unanticipated benefits

drug approval is relatively specialized or involves extenuating circumstances, the Food and Drug Administration asks an ad hoc standing advisory committee to provide their judgments regarding approval based on their future predictions of the benefit–risk relationships. The Food and Drug Administration is not required to adhere to the recommendation of these committees, but it usually does. There are currently 31 advisory committees; the Anesthetic and Analgesic Drug Product Advisory Committee (henceforth referred to as the "Anesthesia Advisory Committee") reviews and provides advice on new anesthetic-related drugs, those seeking new indications, and nearly every opioid-related New Drug Application. There are 12 members of the Anesthesia Advisory Committee with expertise in either anesthesiology, pain management, or biostatistics. One member is a voting consumer representative, and another is a nonvoting industry representative.[12]

This report describes six noteworthy and representative meetings of the Anesthesia Advisory Committee since 2017, as it has struggled, along with Food and Drug Administration, to balance the benefit–risk relationships for individual patients along with the overarching public health implications of bringing additional opioids to market. In each of the following discussions, the minutes of the meetings were used to form a synopsis of the committee's interpretations. All of the committee's activities since 2017 are listed in table 2.

Extended-release Oxymorphone (Opana ER)

In March 2017, the Anesthesia Advisory Committee convened with the Drug Safety and Risk Management Advisory Committee (this committee consists of specialists in pharmacoepidemiology and drug safety; the two committees often meet in combination) to discuss Opana ER (Endo Pharmaceuticals, Malvern, Pennsylvania), an oral oxymorphone formulation indicated for "the treatment of chronic moderate-to-severe pain and for which alternative treatment options are inadequate."[13]

Opana was originally approved in 2006, but in 2011, Endo introduced a redesigned formulation with a high-molecular-weight polyethylene oxide matrix covering to resist physical and chemical manipulation. Although the submitted clinical studies did not meet criteria for abuse deterrence, the Food and Drug Administration approved the new Opana formulation without abuse deterrent indications and Endo discontinued the older product that did not contain the tamper-resistant covering.[14]

After introduction of the redesigned Opana, reports surfaced of unique harms when the tablets were crushed for IV injection.[13] Therefore, the Food and Drug Administration asked the two advisory committees to revisit the original New Drug Application, in light of the concerning postmarketing data, and determine whether the benefits of Opana still outweighed its harms. Two lines of new evidence of harm were addressed: the 2015 outbreak of human immunodeficiency virus and hepatitis C infections in Indiana,[15] and reports of thrombocytopenic thrombotic purpura in recreational drug abusers in Tennessee,[16] both of which were associated with IV injection of crushed Opana.

The meeting was notable for the presentation by anesthesiologist Jerome Adams, M.D., M.P.H., then Indiana State Health Commissioner, and presently U.S. Surgeon General. Dr. Adams described how the high potency and street cost of Opana led recreational users to share the drug and the equipment used to prepare and inject it, which contributed to the human immunodeficiency virus and hepatitis outbreaks.[13] Other experts discussed the mechanisms of thrombocytopenic thrombotic purpura–related harm as a result of the intrarenal accumulation of the high-molecular-weight polyethylene oxide covering that was unique to

Table 2. Activities of the Anesthetic and Analgesic Drug Product Advisory Committee from 2017 to the Present

Date	Sponsor	Drug	Topic	Committee Vote	Food and Drug Administration Decision
March 2017	Endo	Oxymorphone (Opana)	Evaluation of postmarketing complications: Do the benefits of reformulated Opana ER continue to outweigh its risks?	Yes: 8 No: 19	Yes. The Food and Drug Administration asked Endo to remove Opana from market
April 2017	Inspirion	Oxycodone IR (RoxyBond)	Consideration of new drug application for immediate-release oxycodone with abuse deterrent indication	Approve: 19 Do Not Approve: 0	Approved for abuse deterrent indication by nasal and IV routes
July 2017	Intellipharmaceutics	Oxycodone ER (IPC Oxy)	Consideration of new drug application for extended-release oxycodone with abuse deterrent indication	Approve: 1 Do Not Approve: 22	Not approved
September 2017	Purdue	Transdermal buprenorphine (Butrans)	Consideration of supplemental new drug application for pediatric indication: ages 7 through 16 years	No vote	Pediatric indication not approved but language added to label: "BUTRANS has been evaluated in an open-label clinical trial in pediatric patients. However, definitive conclusions are not possible because of the small sample size."
February 2018	Charleston Laboratories	Hydrocodone, acetaminophen, and promethazine (Hydexor)	Consideration of new drug application approval for combination formulation intended to reduce opioid-related nausea and vomiting	Approve: 2 Do Not Approve: 19	Not approved
February 2018	Pacira	Bupivacaine liposomal (Exparel) for nerve block	Consideration of supplemental new drug application to add nerve block indication.	Approve:4 Do Not Approve: 6	Approved for interscalene block for shoulder surgery
May 2018	Insys	Buprenorphine sublingual spray (Buvaya)	Consideration of new drug application for treatment of moderate-to-severe acute pain where the use of an opioid analgesic is appropriate	Approve: 1 Do Not Approve: 18	Not approved
June 2018	Pain Therapeutics	Oxycodone ER ADF (Remoxy ER)	Consideration of new drug application for extended-release oxycodone with abuse deterrent indication	Approve: 3 Do Not Approve: 14	Not approved
August 2018	Insys	Discussion of results from assessments of the transmucosal immediate release fentanyl medicines' risk evaluation and mitigation strategy.			
October 2018	Trevena	Oliceridine	Consideration of new drug application for management of moderate-to-severe acute pain in adult patients for whom an intravenous opioid is warranted	Approve: 7 Do Not Approve: 8	Approved after resubmission
October 2018	AcelRx	Sufentanil sublingual (Dsuvia)	Consideration of new drug application for management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting	Approve: 10 Do Not Approve: 3	Approved
November 2018	SpecGx (Mallinckrodt)	Oxycodone IR (MNK-812)	Consideration of new drug application for management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate with abuse deterrent indications	Approve: 10 Do Not Approve: 7	Not approved
November 2018	Discussion of opioid analgesic sparing outcomes in clinical trials of acute pain		Q1: Is any reduction in opioid use sufficient to warrant labeling as opioid sparing?	Q1: Yes: 1 No: 11 Abs: 1	Not applicable
			Q2: Is it sufficient to claim opioid-level analgesia for a novel analgesic based on the clinical trial population and without an opioid active comparator?	Q2: Yes: 1 No: 12	

(*Continued*)

Table 2. (*Continued*)

Date	Sponsor	Drug	Topic	Committee Vote	Food and Drug Administration Decision
December 2018	Committees asked to provide input and advice on strategies to increase the availability of naloxone products intended for use in the community		Would labeling language that recommends co-prescription of naloxone for all or some patients prescribed opioids, or more targeted prescribing for patients otherwise at high risk for death from opioid overdose be an effective method for expanding access to naloxone and improving public health?	Yes: 12 No: 11	Not applicable
June 2019	The Anesthesia Advisory Committee was asked to discuss the clinical utility and safety concerns associated with the higher range of opioid analgesic dosing (both in terms of higher strength products and higher daily doses) in the outpatient setting, particularly with regard to patient populations, clinical risks, and public health consequences, when compared with lower doses and strength formulations.				
January 2020	Nektar	Oxycodegol (NKT-181)	Consideration of new drug application for the management of chronic low back pain in adults with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, or as a general extended-release/long-acting opioid analgesic chronic pain indication	Approve: 0 Do Not Approve: 27	New Drug Application withdrawn by Nektar
January 2020	Esteve	Tramadol-celecoxib (CTC)	Consideration of new drug application for management of acute pain in adults that require an opioid analgesic and for which alternative treatments are inadequate	Approve: 13 Do Not Approve: 13	Not approved at this time.
January 2020	Intellipharmaceutics	Oxycodone ER ADF (Aximris XR)	Consideration of new drug application for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate	Approve: 2 Do Not Approve: 24	Not approved at this time.
January 2020	Durect	SABER-bupivacaine (Posimir)	Consideration of new drug application for single-dose instillation into the surgical site to produce post-surgical analgesia	Approve: 6 Do Not Approve: 6	Not approved at this time.

this product (all other abuse deterrent formulations have a lower molecular weight matrix covering).[17]

After extensive discussion and debate, the committees voted 18 to 8 that the benefits of Opana no longer outweighed its risks. These discussions featured disparate and strongly held beliefs between committee members. Advocates of Opana's continued use considered its role in "opioid rotations" in chronic pain patients, whereas those favoring withdrawal believed that there was no role for any oxymorphone formulation for the treatment of chronic pain. Several months later, the Food and Drug Administration asked Endo to remove Opana from the marketplace,[18] and Endo complied. Generic oral oxymorphone formulations without the higher-molecular-weight matrix covering, however, remain approved and available for sale.

Liposomal Bupivacaine (Exparel)

The use of regional anesthesia is one strategic solution to decrease opioid use after surgery. Liposomal bupivacaine (Exparel, Pacira Pharmaceuticals, Parsippany, New Jersey) was originally approved in 2011 for infiltration into a surgical incision, and in February 2018, the Anesthesia Advisory Committee evaluated a supplemental New Drug Application requesting an additional indication for "nerve block to produce regional analgesia."

To support the supplemental New Drug Application, Pacira submitted results of two clinical trials.[19] The first was a multicenter, randomized, double-blind, placebo-controlled study that evaluated Exparel for femoral nerve block in 230 patients undergoing total knee arthroplasty. Subjects received either 133 mg Exparel (10 ml Exparel + 10 ml saline), or 266 mg Exparel (20 ml), or placebo (20 ml saline). All three treatment groups also received 16 ml 0.25% bupivacaine as a periarticular infiltration before placement of the prosthesis.

The second study was a multicenter, randomized, double-blind, placebo-controlled study that evaluated Exparel for brachial plexus nerve block in 140 subjects undergoing total shoulder arthroplasty or rotator cuff repair. The blocks were performed by either supraclavicular or interscalene approach, both under ultrasound guidance. There were three arms with the same amounts of Exparel as in the first study, but without additional bupivacaine infiltration.Data from two previously submitted studies that used Exparel for femoral nerve block in total knee arthroplasty and intercostal nerve block in posterior-lateral thoracotomy were also reviewed.

The primary efficacy endpoints for all four studies were based on area-under-the-curve estimates of pain relief for the first 48 to 72 h after surgery. The secondary endpoint was opioid rescues. Of the four studies, only the brachial plexus nerve block met both primary and secondary endpoints.

During discussion,[20] the majority of committee members agreed that efficacy was demonstrated to support the use of Exparel as a nerve block for the brachial plexus but were concerned by the lack of an active comparator group. Most members were uncomfortable assigning a label indication for "long-acting" when Exparel was not directly compared with standard bupivacaine. Furthermore, some members were concerned about the absence of an animal model proving the usefulness of IV fat emulsion (Intralipid) rescue for Exparel cardiotoxicity because the use of a local anesthetic for a nerve block has an inherently higher chance of accidental intravascular injection. The majority of the committee agreed that the submitted data did not support an indication to include nerve block and that larger studies were needed to adequately determine safety. The final vote was 6 to 4 against approval.

On April 6, 2018, the Food and Drug Administration announced their approval of Exparel for "use as an interscalene brachial plexus nerve block to produce post-surgical regional analgesia following shoulder surgery in adults."[21] This was the first time the Food and Drug Administration approved a local anesthetic agent for a specific and directed purpose and may prove to be a paradigm for local anesthetics evaluated in the future in the ongoing effort to decrease postoperative opioid use.

Oliceridine

On October 11, 2018, the Anesthesia Advisory Committee considered an New Drug Application for oliceridine (Trevena, Inc., Chesterbrook, Pennsylvania), a novel μ-receptor agonist, for "the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted." During activation of the G protein–coupled receptor complex of the μ-receptor, oliceridine is thought to preferentially stimulate the G protein–biased ligand, which is primarily responsible for analgesia, in comparison with its stimulation of the β-arrestin pathway, which is primarily responsible for opioid side effects (fig. 1).[22–24]

Trevena submitted data from two phase 3 placebo-controlled, randomized, blinded clinical studies.[25] In the first, three doses of oliceridine (0.1, 0.35, and 0.5 mg) each provided greater analgesia in the first 48 h after bunionectomy compared with placebo but were less effective than morphine. In the second study, two of the three doses of oliceridine (0.35 mg and 0.5 mg) were more effective than placebo in the first 24 h after abdominoplasty, but only the 0.5-mg dose was as effective as morphine. The studies were complicated by a variety of different rescue dosing choices, resulting in a wide range of patient exposures, which made the overall comparisons of efficacy, safety, and potency comparisons with morphine difficult to discern. Safety signals were also seen in the oliceridine group, and because of the complexity of the protocols, it was difficult to determine their incidence compared with placebo and morphine. Side effects in all groups included respiratory depression, hepatic enzyme elevation, and QT prolongation.

During discussion, committee members were largely in agreement that oliceridine was not as effective as active control.[26] Most members agreed with its relative safety but were concerned about the limited dose-related data on QT prolongation. Importantly, some members opined that its perceived safety with regard to respiratory depression may lead abusers to prefer oliceridine over other recreational drugs.

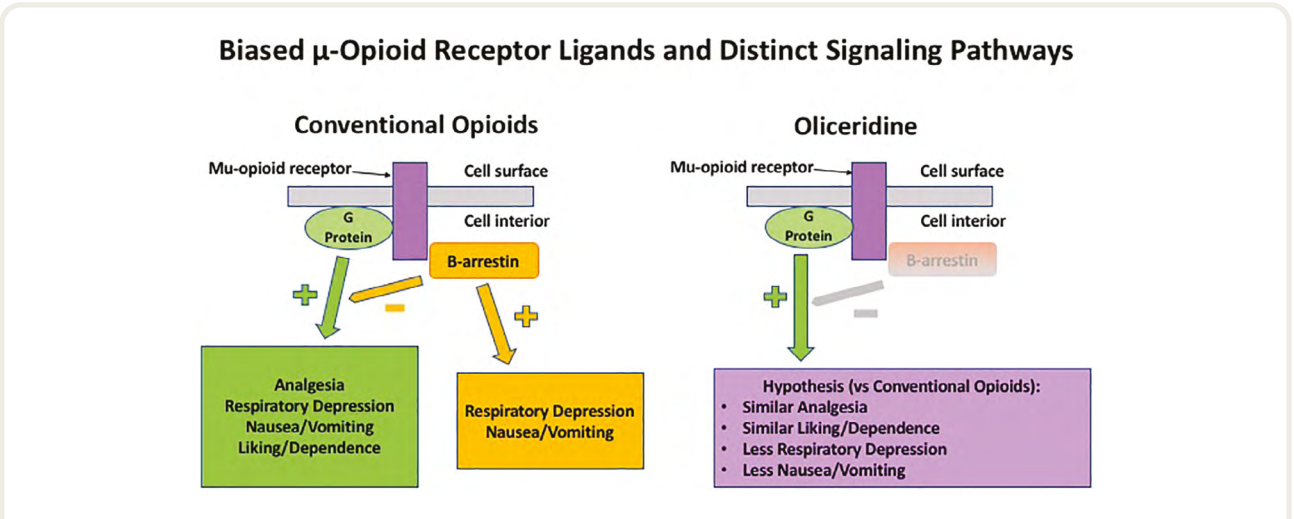

Fig. 1. Oliceridine pathway. Publicly available from the United States Food and Drug Administration at https://www.fda.gov/media/121235/download (accessed July 22, 2020).

Overall, there was no consensus and the committee split the vote, seven for approval and eight against. The Food and Drug Administration subsequently issued Trevena a "complete response letter" indicating nonapproval and the reasons for such. Trevena addressed the concerns of the committee and resubmitted the New Drug Application in February 2020.[27] Oliceridine has now been approved by the Food and Drug administration in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Recent studies, however, have demonstrated that β-arrestin knockout mice develop dose-dependent respiratory depression that is indistinguishable from wild-type mice,[28] inferring that the purported pharmacologic pathways and their response to μ-receptor stimulation may not be as clear-cut as once hoped.

Sublingual Sufentanil (Dsuvia)

On October 12, 2018, in what would prove to be a meeting mired in controversy, the Anesthesia Advisory Committee debated the merits of sublingual sufentanil (Dsuvia, AcelRx Pharmaceuticals, Redwood City, California). Dsuvia was formulated in collaboration with the U.S. Department of Defense, as an analgesic option for wounded soldiers on the battlefield who may incur delays in gaining IV access. Each tablet contains 30 mcg sufentanil and is supplied in a single-dose, prefilled applicator that dispenses the small tablet under the patient's tongue (fig. 2). It was estimated that this sufentanil preparation is equivalent to 5 mg morphine, but formal comparisons have not been performed. AcelRx sought labeling for the "management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting."

Fig. 2. Dsuvia (sublingual sufentanil) is applied under the patient's tongue with a prefilled applicator device (photo used by permission of AcelRx).

AcelRx submitted data from one phase 3 placebo-controlled study, two phase 3 open-label studies, and safety data accumulated for Zalviso, an identical product that had been previously approved and used in Europe. Although concerns were raised about slow times to meaningful pain relief (median about 50 min), inability to titrate, and the small size of the tablet that might increase the chance of diversion, the majority of committee members felt that the overall benefits outweighed the risks. The vote to approve was 10 to 3.

Six days later, in an unexpected and unprecedented move, the Food and Drug Administration leadership received a letter that was critical of the committee's vote and was signed by Dr. Raeford Brown, who was then the sitting Chair of the Anesthesia Advisory Committee (Dr. Brown was not present at the meeting because of a previous commitment) and Dr. Sidney Wolfe of the Public Citizen's Health Research Group.[29] Dr. Brown's and Public Citizen's criticisms focused on the risk of diversion and harm to medical personnel and the high potential to contribute to the national opioid crisis. The letter also accused the Food and Drug Administration of deliberately excluding the Drug Safety and Risk Management committee from the meeting to "tilt the outcome…in favor of approval." Two weeks later, the Food and Drug Administration announced its approval of Dsuvia "in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments."[30] Food and Drug Administration commissioner Scott Gottlieb published an explanation of the decision in the face of gathering criticism. Gottlieb stated: "We should consider whether we could do more in weighing approvals to ensure that new opioids are sufficiently better than existing drugs to justify their addition to the market in the context of the current crisis of abuse."[31]

As of March 31, 2020, approximately 16 months after its approval, the Food and Drug Administration's Adverse Drug Events Reporting System reported three events for Dsuvia: one gastrointestinal, one psychiatric, and one respiratory/thoracic. All were considered "nonserious." In April 2020, AcelRx announced that Dsuvia cleared an initial hurdle for military use.[32]

Oxycodegol (NKTR-181)

On January 14, 2020, the Anesthesia Advisory Committee and the Drug Safety and Risk Management Committee discussed oxycodegol (NKTR-181, Nektar Therapeutics, San Francisco, California), a pure μ-agonist formulated with a polyethylene glycol side chain for the "management of chronic low back pain in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." The polyethylene glycol side chain slows the drug's transport across the blood–brain barrier, thus

delaying and mitigating the euphoria that accompanies opioid-related pain relief. In theory, this delay would result in a suboptimal "high" and therefore would not appeal to recreational users.

Nektar presented data demonstrating that oxycodegol resulted in a lower rate of centrally mediated adverse effects and addictive behaviors when compared with ingestion of equianalgesic doses of oxycodone in animals.[33] In human volunteers, it had a slower onset of action and lower "drug liking," both of which could lead to less propensity for addiction.[34,35]

On the basis of these studies, oxycodegol appeared to be an ideal opioid: effective analgesia with less euphoria, abuse, and addiction. Yet, criticism of oxycodegol was widespread by members of both committees. Nektar presented data from one 12-week double-blind, placebo-controlled phase 3 trial,[36] along with a 52-week unblinded cohort study that demonstrated longer-term safety.[37] But, some members of the committees expressed the view that approval based on just one prospective efficacy trial that lasted only 12 weeks was insufficient evidence to approve a drug for chronic pain, even though it was accompanied by a longer-term open label cohort. More important, committee members were skeptical of the phase 3 study's "enriched enrollment" design, which initially tests the drug on all eligible patients and then uses only the positive responders for the subsequent placebo-controlled efficacy trial, a strategy called "predictive enrichment."[36] This type of study was encouraged by the Food and Drug Administration in an industry guidance document,[38] but the Food and Drug Administration did not envision this type of methodology the way that Nektar did (see section V of reference 35). Predictive enrichment with an open trial before randomization is useful for proof-of-concept studies or for detecting subpopulations that are less likely to benefit from the drug owing to unique physiologic or genetic considerations, or when the investigators want to understand longer term risks in responders who will maintain therapy after an initial trial period. It should not have been used to predict clinical efficacy in patients with chronic back pain because it falsely increased the drug's overall efficacy. Furthermore, committee members expressed their concern that opioid use in patients with chronic back pain was an outdated and ultimately harmful practice. As a result, the advisory committees recommended against approval by a vote of 27 to 0. Several hours after the vote, Nektar issued a press release stating that it was withdrawing the New Drug Application and discontinuing all further investment in oxycodegol.[39]

SABER-Bupivacaine (Posimir)

On January 16, 2020, the Anesthesia Advisory Committee met to discuss the approval of SABER-bupivacaine, a long-acting local anesthetic preparation (Posimir, DURECT Corporation, Cupertino, California) indicated for postsurgical analgesia. SABER-bupivacaine is formulated as a 12% solution (132 mg bupivacaine/ml) and contains two main excipients: benzyl alcohol, which reduces viscosity, and sucrose acetate isobutyrate, which forms the depot matrix. Because of its high potency, a maximum of only 5 ml (660 mg) can be administered at any one time. The Investigational New Drug application was first filed in 2002, with subsequent reformulations since then. The most recent New Drug Application submitted in 2013 was not approved, primarily because of "modest and inconsistent efficacy" and concern about risks that included tissue damage, bruising, dehiscence, and neurologic symptoms such as dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence, which were possibly related to benzyl alcohol toxicity.[40]

In a resubmission of the New Drug Application in 2019, DURECT addressed the previous safety and efficacy concerns by performing a new phase 3 pivotal study called "Placebo-controlled or Active-controlled Trial of SABER-Bupivacaine for the Management of Postoperative Pain Following Laparoscopic Cholecystectomy)," as well as reanalyzing a large body of data from all previous studies to conclusively determine its overall efficacy and safety.[40]

These materials were reviewed by the Anesthesia Advisory Committee members before the meeting; however, during the meeting, DURECT asked the committee members to now disregard the Management of Postoperative Pain Following Laparoscopic Cholecystectomy study because it was not "adequate and well controlled." Instead, the committee was asked to consider data from a completely different pivotal study that used SABER-bupivacaine for postoperative analgesia after open mesh inguinal hernia repair, along with a combination of data from five other studies, each with a different methodology. These studies included use of SABER-bupivacaine for pain control after subacromial decompression, abdominal hysterectomy, laparoscopic-assisted colectomy, and laparoscopic cholecystectomy (using some patients included in Management of Postoperative Pain Following Laparoscopic Cholecystectomy study). In total there were 699 study subjects.

From the committee perspective, evaluating the aggregate efficacy and safety from six different pivotal studies without prior review and analysis was confusing and difficult. Thus, many committee members agreed that the sponsor did not provide sufficient information to support the proposed indication.[41] Deficiencies included mixed research methodologies, difficulty understanding the method of administration of only 5 ml of local anesthetic into an open incision, and inconsistencies in data presentation, among others. In the end, the votes for approval were split 6–6. Members who favored approval were influenced by the hernia study that demonstrated less opioid use in the first few postoperative days, whereas those who did not favor approval felt that the efficacy did not outweigh the potential risks related to the high concentration of bupivacaine and the excipients.[42] At the time of this writing, the

Food and Drug Administration has not publicly announced a decision on SABER-Bupivacaine.

Conclusions

Since 2017, with notable exceptions (*e.g.*, Dsuvia), the Anesthesia Advisory Committee and the Food and Drug Administration have demonstrated a critical eye toward approval of novel opioid formulations that do not show a convincing benefit–risk relationship in comparison with similar formulations currently on the market and with regard to overall public health. The unique approval of Exparel for a targeted type of anatomic nerve block demonstrates the Food and Drug Administration's capacity to think differently with regard to local anesthetic approvals, the goal being the reduction of postoperative opioid use. All materials related to these Advisory committee meetings are freely available on the Food and Drug Administration website (https://www.fda.gov/advisory-committees/anesthetic-and-analgesic-drug-products-advisory-committee/anesthetic-and-analgesic-drug-products-advisory-committee-roster; accessed July 22, 2020).

Acknowledgments

The author is grateful to Christopher L. Wu, M.D., Assistant Attending Anesthesiologist, Hospital for Special Surgery, Clinical Professor of Anesthesiology, Weill Cornell Medical College, New York, New York, for his critical review of the manuscript and many helpful suggestions.

Research Support

Support for this study was provided solely from institutional and/or departmental sources.

Competing Interests

The author has been a member of the Anesthetic and Analgesic Drug Products Advisory Committee from 2017 to the present. The author declares no competing interests.

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