

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204803Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 204803

APPEAL DENIED

Durect Corporation
10260 Bubba Road
Cupertino, CA 95014

Attention: Todd D. McIntyre, PhD
Vice President, Regulatory Affairs

Dear Dr. McIntyre:

Please refer to your New Drug Application (NDA) submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Posimir (bupivacaine extended-release solution for instillation) 660 mg/ 5mL (132mg/mL), 13.2%.

We also refer to your November 21, 2014, request for formal dispute resolution (FDRR) received on November 21, 2014. The appeal concerned the February 12, 2014 Complete Response letter from the Division of Anesthesia, Analgesia, and Addiction Products.

We also refer to the meeting held between FDA and Durect Corporation on December 16, 2014, hereafter referred to as the FDRR meeting, where the issues raised in your request for formal dispute resolution were discussed.

Dr. Curtis J. Rosebraugh, MD, MPH, has delegated your Office of Drug Evaluation II (ODE II) level appeal to me, the Deputy Director of ODE II.

I have carefully reviewed the materials you submitted in support of your appeal, FDA reviews, including but not limited to the clinical and statistical reviews for NDA 204803, End-of-Phase 2 and pre-NDA meeting minutes, issued on October 12, 2007 and July 27, 2012, respectively, and a Special Protocol Assessment No-Agreement letter issued on September 18, 2008. I have also consulted with Staff in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), hereafter referred to as the Division, and Dr. Rosebraugh from ODE II.

Your FDRR requested resolution regarding the decision rendered by the Division in the Complete Response (CR) letter, the End-of-Review (EOR)-Cycle meeting held on September 23, 2014, and corresponding minutes to that meeting from the Division and Durect.¹ At the FDRR meeting I informed you that I had reviewed the EOR meeting package and the minutes to this meeting. I was aware that there were differences between Durect's and the Division's minutes captured for this meeting. I informed you that I would not adjudicate the EOR meeting minutes as I was not in attendance at the EOR meeting and would not be able to verify the discussions

¹ Formal Dispute Resolution Request: Type A Meeting Request dated November 21, 2014

that actually took place between the Division and Durect on September 23, 2014. I informed you that I advised the Division to review your meeting minutes and determine if any amendment to FDA's version was appropriate. I reminded you that this is in line with the Agency's policy on resolution of disputes about minutes.² The FDRR meeting therefore focused on the Division's Discipline Review (DR) letter issued on January 14, 2014, Durect's response to the DR letter dated February 3, 2014, and the Complete Response letter.

I have completed my review of your request for formal dispute resolution and also considered the discussions at the FDRR meeting and deny your appeal. I describe below the basis for my decision and provide recommendations for two possible paths forward: 1) work with the Division to design a prospective trial(s) to better characterize the benefit-risk profile of Posimir or 2) respond to the CR action through a resubmission addressing the deficiencies based on additional information presented in your EOR background materials and a justification to conclude that this additional information supports a favorable benefit-risk profile of Posimir.

On page 3 of your FDRR, you requested the following:

"The Agency's agreement that the efficacy and safety of POSIMIR™ (SABER®-Bupivacaine) have been established in the original NDA (204803), and the clarifications offered in the pre-meeting package submitted August 15, 2014 in support of the End-of-Review-Cycle meeting (September 23, 2014)."

You acknowledged that upon "re-reading the NDA in light of receiving the DR letter and subsequent CR letter" you had not unambiguously presented the safety data and that unclear descriptions may have contributed to the Division's CR action. Your proposed corrective action, as described in your EOR meeting package and your FDRR, included more detailed explanations for the safety concerns identified as deficiencies in your NDA, longer-term follow-up information of patients in your arthroscopic shoulder surgery trials, and re-analyses of adverse events related to potential neurotoxicity. While there was some debate at the FDRR meeting as to what constituted new information, I would point to page 7 in your FDRR where you stated the following (with emphasis in bold):

"Importantly, at the September 23 meeting we did share some **new** information, i.e., that DURECT had conducted a survey of all shoulder investigators after receiving the DRL/CRL.....We recognize that this survey data **was not in the original NDA**, but we do believe that it has value in attenuating concerns."

Please note that throughout this letter I have emphasized what information provided in your FDRR was not in the original NDA, as this is relevant to my final decision on your appeal.

In reviewing the CR letter, I am aware that the deficiencies summarized by the Division dealt only with safety concerns. However, by virtue of your above-stated request, my consideration of your FDRR includes a review of *both* efficacy and safety for your product. This decisional letter

² See Section XI. Resolution of Dispute About Minutes in *Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants*. <http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf>

will first discuss efficacy of Posimir followed by safety concerns related to shoulder surgeries, surgical incision site, and potential neurotoxicity.

Efficacy

To evaluate Posimir, “*an extended-release bupivacaine, an amide-type local anesthetic indicated for administration into the surgical incision to produce post-surgical analgesia,*” the primary efficacy endpoints in your pivotal and supportive trials were based on pain-intensity after surgery. In addition, supportive efficacy endpoints included opioid-sparing and reduction in opioid-related side effects.

In the DR letter you were informed that efficacy of Posimir was demonstrated for arthroscopic acromial decompression surgery but not for other surgical procedures. In your response to the DR letter, you presented your arguments for concluding efficacy of Posimir in “soft tissue” surgeries. As noted earlier, the CR letter did not mention efficacy as a deficiency so one might assume that the Division accepted your arguments and agreed that efficacy has been established with Posimir. However, submission of your FDRR requesting my determination of *both* efficacy and safety of your product required me to review all evidence in your NDA. Upon doing so, it was apparent that there was not concurrence on efficacy within the review team.

You submitted the results of 7 active- and placebo-controlled studies in support of efficacy. The following table summarizes these 7 studies. Studies CLIN 803-006-0006 and BU-002-IM were considered pivotal by you.

Table 1. Clinical Studies Reviewed for Efficacy*

Study	Surgery	Treatment Groups		
		Posimir N	SABER-placebo N	Bupivacaine HCL N
CLIN 803-006-0006 CLIN 005-0010	Inguinal hernia	47 21	32 21	
BU-002-IM C803-017 CLIN005-0006	Arthroscopic shoulder	53 40 21	25 20 28	
803-025	Laparotomy (Cohort 1) Lap Cholecystectomy (Cohort 2) Lap-assisted Colectomy (Cohort 3)	26 30 125	 77	17 20
BU-001-IM	Hysterectomy	60	27	27

*Some studies included Posimir 2.5 and 7.5 mL doses which were not included in this table

At the FDRR meeting, I asked the Division to explain the reason why it did not believe efficacy had been established for surgeries other than the arthroscopic shoulder surgeries. Dr. Simone summarized the primary efficacy results for each of the “soft tissue” surgical procedures in Table 1 and noted that while the designated pivotal trial CLIN803-006-0006 met the primary efficacy endpoint analysis for reduced pain in inguinal hernia repairs, another similarly designed trial, CLIN005-0010, failed to demonstrate efficacy. I would add that the FDA statistical review for both these trials also concluded efficacy was demonstrated for CLIN803-006-0006 but not for CLIN005-0010. Furthermore, the statistical reviewer evaluated a supportive measure of

efficacy, proportion of subjects using *all* opioids, not just those coded as rescue medication, and for CLIN803-006-0006, there were fewer patients requiring opioids with Posimir whereas for CLIN005-0010, placebo-treated patients had less post-surgical pain and used less rescue medication.

The inconsistency between these two studies which evaluated efficacy in the same surgical procedure (inguinal hernia repair) could not be attributed to any notable difference in conduct, design or demographics. Even though the failed trial may not have enrolled a sufficient number of patients to demonstrate superiority of Posimir to placebo, one would have at least anticipated a point estimate favoring Posimir.

In your response to the DR letter you stated that the lack of efficacy in CLIN005-0010 was traced to a large imbalance in patient age between the active and placebo groups and reanalyzed the data using an analysis of covariance including treatment as main effect, age as the covariate and the interaction of age and treatment. By pooling the results of the two hernia trials, you were then able to show a statistically significant treatment effect of Posimir over SABER-placebo for hernia repairs. While I am aware of your objection to the Division's previous characterization of your analyses as post-hoc, I would, without reservation, consider this re-analysis as post-hoc as you were clearly aware of the results under the pre-specified analysis plan but determined what differences existed between the two trials and then selected a different analysis based on that information. I also refer you to FDA advice given in your End-of-Phase 2 meeting minutes under Question 11.

The mean pain intensity will be analyzed using an analysis of covariance model with site and treatment as factors. You state, "Additional covariates such as baseline characteristics may be included to evaluate their impact on the main ANCOVA findings." Any covariates that are to be included in the primary efficacy analysis should be pre-specified. Additional covariates may be evaluated as exploratory analyses.

At best, the effect of age on treatment from your analysis should be considered exploratory and not explanatory.

There were four other studies in Table 1 that evaluated the efficacy of Posimir in "soft tissue" surgeries. Trial C803-025 evaluated Posimir in different types of major abdominal surgeries and BU-001-IM was conducted in patients undergoing hysterectomies. The three different surgical procedures in C803-025 were laparotomy (Cohort 1), laparoscopic cholecystectomy (Cohort 2), and laparoscopic assisted colectomy (Cohort 3). Cohorts 1 and 2 employed an active control, bupivacaine HCl, whereas Cohort 3 compared Posimir to SABER-placebo. BU-001-IM compared Posimir to SABER-placebo or bupivacaine HCl.

The following table, adapted from your NDA clinical study report, summarized the primary efficacy results for the three different cohorts in C803-025.

Table 2. Efficacy Results in Study C803-025

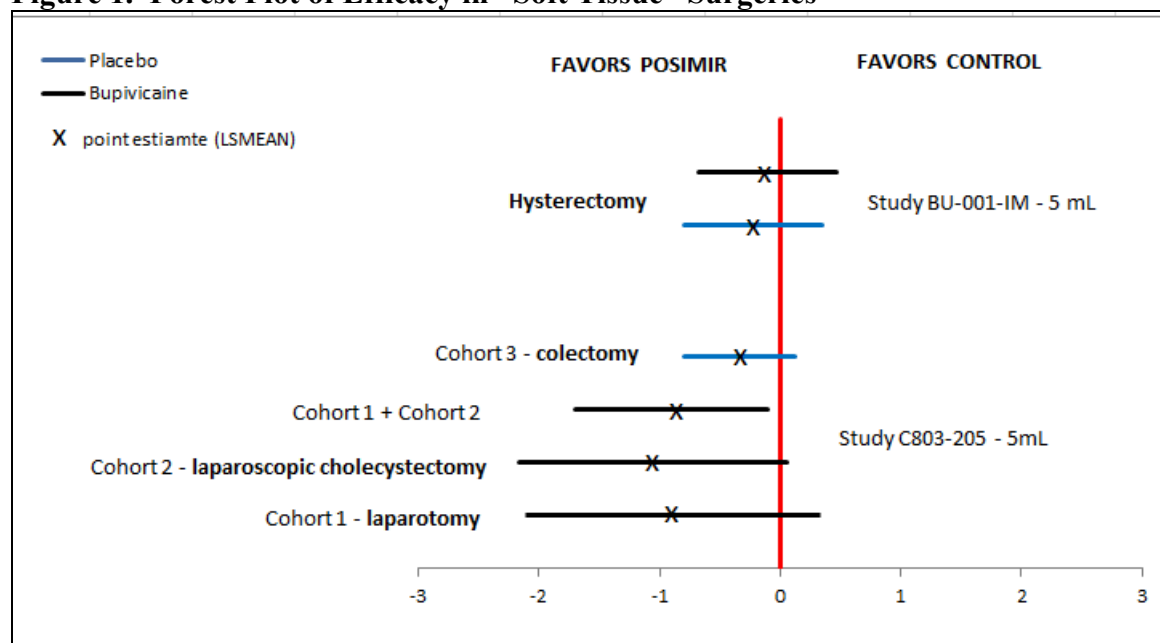
Cohort	Normalized AUC ₇₂			p-value
	Control	Posimir 5 mL	Difference (95% CI)	
1	5.8	4.9	-0.9 (-2.1, 0.3)	0.15
2	3.9	2.8	-1.1 (-2.2, 0.05)	0.06
3	5.1	4.8	-0.34 (-0.8, 0.12)*	0.15

*Table 15 in your CSR should have had a negative sign before 0.34. This error has been verified with FDA statistician.

While the treatment difference favored Posimir in all three cohorts, none reached statistical significance. You concluded efficacy based on the pooled analysis of Cohorts 1 and 2; however, the FDA statistical and clinical reviewer deemed such an analysis inappropriate as the two study populations and surgical procedures were different.

In BU-001-IM, the comparison of Posimir to SABER-placebo or bupivacaine favored Posimir but failed to show superiority. Similar to the forest plot submitted in your response to the DR letter (Figure 1 on page 8 of 14), the following plot was created by FDA to summarize only the results from the 4 “soft tissue” surgeries.

Figure 1. Forest Plot of Efficacy in “Soft Tissue” Surgeries



Dr. Simone summarized the above findings at the FDRR meeting, and you commented that other efficacy assessments should be taken into consideration including use of opioid medications. You also presented figures from your EOR meeting package for repeated measures analyses performed to evaluate pain control over the 72-hr post-surgical period. These graphs (page 14 and 15 of your EOR meeting package) were for Studies BU-002-IM (shoulder) and Clin 803-006-0006 (hernia), not the above “soft tissue” surgeries. Furthermore, your briefing material specifically referred to these as “exploratory analyses.”

You raised the importance of opioid sparing with Posimir and that this endpoint should be factored in FDA's final benefit-risk assessment. The effect of rescue opioid medications and use of non-opioid analgesics was evaluated by FDA reviewers. In general, if the trial was able to show a statistically significant reduction in pain intensity score (primary endpoint), reduced use of opioids also supported the primary endpoint. Similarly, trials which failed to show superiority of Posimir over comparator also failed to show a statistically significant difference in opioid usage. In other words, the secondary assessment of opioid sparing tracked with the primary efficacy findings, so that in trials in which you were not able to establish efficacy on the pre-defined primary endpoint, looking to opioid sparing did not yield a different conclusion.

As an example, your NDA evaluated total morphine equivalent opioid medication use from 0-72 hours in the subgroup of "soft tissue" surgery trials. As has already been described in Figure 1, these trials did not produce a statistically significant treatment effect of Posimir over comparators. In line with that finding, the treatment difference between Posimir and SABER-placebo on total morphine equivalent opioid medication use was not significant.³ Hence, while we agree that adequate pain management that also leads to reduced opioid use is an important public health finding, this was not consistently evident for the "soft tissue" surgical procedures.

As explained to you at the FDRR meeting, FDA's conclusion regarding efficacy is not based solely on achieving statistical significance on an agreed-upon primary endpoint. The robustness of the finding and consistency of results across multiple subgroups or trials are also factored into our final determination. Secondary endpoints are often considered supportive of an observed benefit based on the primary endpoint. Reliance on secondary endpoints to counter a negative or non-significant finding on the primary endpoint is nearly always deemed inappropriate. Finally, the overall benefits of a therapy cannot be judged with efficacy results alone. The efficacy must be weighed against the risks. Robust and unequivocal efficacy supporting a clinically meaningful treatment effect may justify tolerating certain risks. Marginal or modest efficacy requires more judicious consideration of those same risks.

In conclusion, I acknowledge that you were able to demonstrate efficacy with Posimir in one of your "soft tissue" surgical studies for hernia repair. However, the observation that a similarly designed trial for the same surgical procedure favored placebo and four other "soft tissue" surgical trials failed to show superiority of Posimir over SABER-placebo leads me to conclude that your product's efficacy is modest and inconsistent thereby requiring a more careful consideration of risks.

I would highlight that the DR letter stated that you have adequately demonstrated efficacy of Posimir for arthroscopic acromial decompression surgery. While the benefits of Posimir for this type of surgical procedure still need to be judged against the risks, I would note that, unlike the "soft tissue" surgeries, I did not uncover differing conclusions on efficacy by FDA review staff for this type of shoulder surgery.

³ Table 18, page 15 of Section 5.3.5.3 of NDA 204803

Safety

The DR letter identified the following safety concerns:

1. For arthroscopic acromial decompression surgery (Trials CLIN005-0006, C-803-017, and BU-002-IM) you have adequately demonstrated the efficacy of SABER-bupivacaine. However, the risk of chondrolysis, based on the incident observed with SABER-bupivacaine treatment, outweighs the benefit of SABER-bupivacaine for this surgical procedure.
2. For the other surgical procedures studied, you have not adequately demonstrated the efficacy of SABER-bupivacaine. In addition, the incidence of somnolence, dizziness, dysgeusia, hematoma, bruising, dehiscence, and pruritus were greater with SABER-bupivacaine, and SABER-placebo treatments than with bupivacaine HCl. Therefore, the risks of SABER-bupivacaine have outweighed the benefits for the non-arthroscopic procedures studied to date.

The CR letter reiterated some of the safety concerns from the DR letter. As I read the chronology of communications between the Division and Durect leading up to this FDRR, including the disputed minutes to the EOR meeting, I have identified instances where FDA communication was not clear. I have brought this to the attention of the Division. As a result, I sought clarification from the Division at the FDRR meeting. Specifically, I asked Dr. Simone if the second deficiency identified in the DR letter pertained only to the other surgical procedures or did some of these concerns involve the arthroscopic shoulder surgeries. He stated that AEs representing potential neurotoxicity concerns (somnolence, dizziness, and dysgeusia) were applicable to all surgeries but the surgical incision site AEs were specific to the “soft tissue” surgeries.

After meeting internally with the Division and considering the discussions at the FDRR meeting I will focus my assessment of safety for Posimir on the following:

1. Chondrolysis and other adverse events related to the shoulder joint and surrounding soft tissues
2. Surgical incision site complications, specifically hematoma and dehiscence
3. Potential neurotoxicity due to the high concentration of benzyl alcohol released acutely

Chondrolysis and Other AEs Related to the Shoulder Joint and Surrounding Soft Tissues

It is my understanding that for arthroscopic shoulder procedures, the concerns regarding chondrolysis were based on the cases identified in the NDA review and you have adequately addressed the specifics of those cases. However, the Division remains concerned about other adverse events related to the shoulder joint and surrounding soft tissue because of the nonclinical findings of chronic granulomatous inflammation in rats and rabbits and because the number of follow-up assessments at 18 months was too limited to address the long-term safety of Posimir.

At the FDRR meeting you referenced consultative reviews by outside pathologists who deemed the nonclinical findings to be a typical reaction to foreign body and subsequent wound healing observed with other approved products. You also referenced long-term follow-up data on patients in your arthroscopic surgical studies, including inquiries of patients out to 3 years post-surgery. You also referenced two published articles, not submitted to the original NDA. One publication, which was submitted in your EOR background package, described no risk of chondrolysis when local anesthetics were instilled only into the subacromial space.⁴ The second publication, submitted in response to the DR letter, described that infusion of local anesthetics via a pain pump directly into the joint increased the risk of chondrolysis.⁵

I appreciate the concern raised by the Division on possible permanent damage to the joint based on the prolonged residence time of sucrose acetate isobutyrate (SAIB) in the tissues. This should not be viewed as a minor risk especially if one cannot conclude superiority of Posimir over the referenced approved product, bupivacaine HCl. However, I consider the follow-up data from two extension studies (6 months in BU-002-IM and 18 months in C803-017e) and new information on patients from a survey of investigators that suggest little evidence of chondrolysis or deterioration of shoulder function with follow up out to 3 years relevant for assessment of this potential risk. Although data from the extension studies and the survey are not controlled data, I believe that verifiable evidence of long-term recovery post-exposure to Posimir for a substantial number of patients may address this safety concern. However, as this is new information these data need to be reviewed by the Division first to determine if they adequately address this deficiency.

Surgical Incision Site Complications

For any surgical procedure, the Division identified adverse events related to bruising, hematoma, pruritus, and dehiscence as possible signs of surgical incision site complications. Of these, hematoma and dehiscence were of the most concern because they might result in poor wound healing, increase the risk of post-operative infection, and require additional invasive corrective measures (e.g., incision and drainage or surgical repair).

For hematoma, you explained that the identification of this adverse event through review of verbatim terms identified only a few cases as true hematomas. You further directed me to Table 14 in your EOR background package, which showed similar rates of hematoma across the treatment groups, bupivacaine HCl, SABER-placebo, and Posimir. These hematoma cases required aspiration and drainage, but these patients did not develop poor wound healing nor did they require antibiotics due to a super-infection.

For dehiscence, you acknowledged a greater incidence in the SABER treatment groups but stated that the majority of these cases were superficial breaks of a few subcuticular stitches. However, you did identify two patients who experienced fascial dehiscence (Patients (b) (6) and (b) (6)) and one patient who had a full length superficial dehiscence (Patient (b) (6)). At the FDRR

⁴ Busfield BT et al. Sub-acromial pain pump use is safe after arthroscopic rotator cuff repair. *J Orthopaedics*. 2014;11:64-67.

⁵ Matsen FA and Papadonikolakis A. Published evidence demonstrating the causation of glenohumoral chondrolysis by postoperative infusion of local anesthetic via a pain pump. *J Bone Joint Surg Am*. 2013; 95-A (12):1126-1134.

meeting you confirmed that all three patients were in the SABER treatment groups and that the patients required surgical repair of the dehiscence, including repeat laparotomy in at least one patient. While three patients represent a small number, all three were in the SABER treatment group and repeat surgery for failed surgical site closure introduces additional risks to the patient.

I did not find your explanation in Table 4 of your response to the DR letter sufficient grounds to ignore the potential seriousness of dehiscence, if due to Posimir. Table 4 summarized three methods for collecting incidence rates of dehiscence in the C803-025 trial, which reported 16 of the 18 adverse events of dehiscence. You directed me to the number of cases reported on Day 30 via a structured wound healing questionnaire conducted by telephone. The question posed to the patient was, “Are there any areas of your wound that are opening or not healing together properly?” This questionnaire captured more events in the control arm (bupivacaine HCl) minimizing the imbalance between bupivacaine and SABER-treatment groups. As per your response to the DR letter, “the apparent imbalance in dehiscence is no longer present” based on the cases captured on Day 30 via telephone. However, at the FDRR, I commented that the question posed via telephone is non-specific and it is conceivable that a patient dissatisfied with the cosmetic appearance of his/her incision site could respond ‘yes’ and such a response would be counted as a report of dehiscence. You confirmed that affirmative responses were not followed up by a physical exam to determine the seriousness of the AE. Finally, the three cases noted above, which we can all agree to as serious because they resulted in additional surgical corrective time, were captured via spontaneous adverse event reporting – the same methodology in which an imbalance in rates of dehiscence between SABER treatment groups and bupivacaine HCl was observed. Reliance on the less specific questionnaire at Day 30 can obfuscate a true risk associated with Posimir.

At the FDRR meeting you attributed the dehiscence of the three concerning cases to other causes (e.g., large surgical incision site in obese patient and return to manual labor post-surgery). While these other circumstances could be causative, similar circumstances could have also been at play in the control group and yet no serious cases of dehiscence were reported in the bupivacaine HCl group. Regardless, I recognize this was a small database with few events and the imbalance in dehiscence could still be a chance finding. Of course, the limited size of the study also contributed to the difficult risk assessment by the Division.

In conclusion, I cannot dismiss the possibility of increased risk for surgical incision site complications. Of these adverse events, dehiscence is the most concerning. However, you have also presented explanations for some of these cases that may be causative or contributory to the dehiscence and the Division should review the validity of your arguments.

Potential Neurotoxicity Related to Benzyl Alcohol

Concern for potential neurotoxicity stems from the high amount of benzyl alcohol (BA) formulated in Posimir to enable the drug product to remain in solution for instillation. The 5 mL dose of Posimir contains 1210 mg of BA which apparently diffuses and is cleared systemically within 12-24 hrs, with the maximum level at approximately 1 hour post-dose. The Division noted imbalances in somnolence, dizziness, and dysgeusia occurring more frequently in the SABER treatment groups than in the bupivacaine group, and deemed these as possibly related to

benzyl alcohol. In your EOR background document you related the imbalance due to different methods for collecting these AEs (spontaneously reported versus queried) and that when trials utilizing similar methods for assessing potential neurologic AEs were evaluated, the only imbalance noted not favoring Posimir was headaches. At the FDRR meeting I asked if any of the neurologic AEs were deemed serious and both Durect and FDA concurred that these events resolved without serious sequelae. I also noted your analysis of time to discharge from the post-anesthesia care unit (PACU) and saw no difference between treatment groups, even among those patients who reported neurologic AEs.

Overall, I found your responses relevant for reconsideration by the Division; however, as re-analyses of previously submitted data are considered new information, I can not make a determination on your appeal based on this new information prior to the Division's assessment.

Conclusion

Your FDRR requested that I conclude Posimir to be safe and effective based on the data submitted in the original NDA and information provided in your EOR background materials. I have reviewed your FDRR and also held discussions with the Division and met with you at the FDRR meeting. After considering all the facts of your submission, I am denying your request for a determination that efficacy and safety of Posimir have been established in the original NDA.

In reviewing your FDRR and additional materials cited earlier, I believe efficacy is present with Posimir but it is modest and inconsistent across different surgical procedures. My conclusion on efficacy precludes complete dismissal of the safety concerns raised by the Division.

By your own admission, you did not present data in an 'unambiguous' manner and 'unclear descriptions' may have contributed to the CR action. While I would concur with you that your NDA submission and some of your data presentations in the FDRR lacked clarity, I do believe you have made a reasonable attempt to address the deficiencies in the CR letter through re-analysis of current trial data and by providing more extensive explanations of specific cases and new long-term safety data. However, I am unable to consider your re-analyses and new long-term safety data in the determination of efficacy and safety of Posimir, as requested in your FDRR. The *FDA Guidance for Industry and Review Staff on Formal Dispute Resolution: Appeals Above the Division Level*, clearly states that no new information should be submitted as part of a request for reconsideration of appeal. The Guidance also specifically states "new analyses of data previously reviewed should be considered new information".⁶ Consequently, the new long-term safety data and re-analyses must first be reviewed by the Division to determine if they adequately address the deficiencies in your program. I would caution that such re-analyses and follow-up data may not fully address the deficiencies because they were not prospectively planned and can, therefore, generate a degree of skepticism on their validity. For this reason I recommend two potential pathways for you to address the deficiencies identified in the CR letter:

⁶<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm343101.pdf>

1. Plan and discuss with the Division a prospective trial that will specifically assess the safety concerns related to surrounding tissues of the joint, surgical incision sites, and potential complications of acute exposure to high doses of benzyl alcohol, *or*
2. Prepare for resubmission the materials, re-analyses, and data presentation proposed in your End-of-Review briefing materials. This resubmission will be classified as a Class 2 resubmission as it will, at a minimum, include additional long-term data on patients not previously reviewed in the NDA. You are encouraged to discuss with the Division your proposed resubmission, which will be subject to a 6-month review cycle and may also be presented before a public advisory committee meeting should the Division deem it necessary to seek outside expert opinion on your application.

Questions regarding next steps as described in this letter should be directed to Ayanna Augustus, Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products, at (301) 796-3980.

This constitutes the final decision at the ODE II level. If you wish to appeal this decision to the next level, your appeal should be directed to John Jenkins, MD, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the IND administrative file as an amendment, and a copy should be sent to the Center's Formal Dispute Resolution Project Manager, Ms. Khushboo Sharma. Any questions concerning your appeal should be addressed to Ms. Khushboo Sharma at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
01/15/2015



IND 066086

MEETING PRELIMINARY COMMENTS

Durect Corporation
10260 Bubba Rd
Cupertino, CA 95014

Attention: Jill K. Burns
Director, Regulatory Affairs

Dear Ms. Burns:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SABER-Bupivacaine.

We also refer to your September 7, 2011, correspondence, received September 8, 2011, requesting a meeting to discuss finalization of the key elements of your Phase 3 studies.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 31, 2012, at 12:00 PM between Durect and the Division. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE



MEETING ATTENDEES

Meeting Date and Time: July 31, 2012 at 12:00 PM

Meeting Location: White Oak, Bldg 22, Rm 1311

Application Number: IND 066086

Product Name: SABER-Bupivacaine

Regulatory Status: Active IND

Proposed Indication: extended relief of post-surgical pain

Sponsor/Applicant Name: Durect Corporation

Meeting Type/Category: Type B, Pre-NDA

Meeting Chair: Christopher Breder, M.D., Ph.D., Clinical Team Leader, Anesthetics
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

Industry Representatives	Title
Christina Blevins	Scribe
James Brown, DVM	President and Chief Executive Officer
Jill Burns	Senior Director, Regulatory Affairs
Linval DePass, Ph.D.	Executive Director, Nonclinical Safety
David Ellis, M.D., Ph.D.	Vice President, Clinical and Regulatory Affairs
Ramachandra Hegde, Ph.D.	Executive Director, Program Management & Project Manager
Judy Joice	Vice President, Operations and Corporate Quality Assurance
(b) (4)	Consultant, Biostatistics
Andrew Miksztal, Ph.D.	Vice President, Pharmaceutical Systems R&D
Jaymin Shah, Ph.D.	Executive Director, Pharmacokinetics
(b) (4)	Consultant, Biostatistics
Neil Verity, Ph.D.	Executive Director, Pharmacology & Program Leader
FDA	Title
Bob A. Rappaport, M.D.	Director, DAAAP
Rigoberto Roca, M.D.	Deputy Director, DAAAP
Arthur Simone, M.D., Ph.D.	Medical Officer, DAAAP
Christopher Breder, M.D., Ph.D.	Clinical Team Leader, DAAAP
Danae Christodoulou, Ph.D.	Chemistry Team Lead, Office of New Drug Quality Assessment (ONDQA)
Gary Bond, Ph.D.	Pharmacology/Toxicology Reviewer, DAAAP
Adam Wasserman, Ph.D.	Supervisory Pharmacologist, DAAAP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader
Dionne Price, Ph.D.	Biostatistics Team Leader, Division of Biometrics II (DBII)
David Petullo, Ph.D.	Biostatistics Reviewer, DBII
Kim Compton	Sr. Regulatory Project Manager, DAAAP

1.0 BACKGROUND

The Sponsor has stated that their purpose for this meeting is to seek the Division's guidance, recommendation, and concurrence on the items included in the meeting package, with the ultimate goal being to allow them to submit an evaluable and approvable application.

The Sponsor is planning to submit an application under 505(b)(2) for a sustained-release, injectable formulation of a sterile solution of the local anesthetic bupivacaine. The product consists of bupivacaine base in a controlled-release matrix of an esterified sugar derivative and is intended for direct instillation into the wound. The Sponsor intends for their application to rely, in part, on prior findings of safety and efficacy for approved bupivacaine product(s) to be specified at the time of NDA submission. In addition, they intend to rely on the findings of the two pivotal studies conducted with their product: Study CLIN-803-006-0006, for inguinal hernia repair, and Study BU-002-IM, for subacromial decompression as evidence of efficacy in the relief of post-operative pain.

2.0 DISCUSSION

2.1 Chemistry

Chemistry Question 1 (Product Color)

SABER-Bupivacaine changes color from light yellow to brown (amber) over its proposed 36 month shelf life. Extensive research has been conducted to determine the reasons for the color change and identify the key factors responsible for the formulation color change. Although a definitive impurity responsible for the observed color has not been identified, the most significant factors implicated in the formation of color have been determined. Data indicates that there is no association between the formulation color change and quality attributes of the drug product. All of the supportive data (color methodology, stability data, specification, degradant identification and proposed mechanisms, nonclinical toxicology) will be provided in the NDA.

DURECT believes that the color change observed for the product has been adequately studied because: (1) a deeply colored SABER-Bupivacaine lot was tested and a NOAEL was established in a GLP toxicology study, and (2) a specification was established to control the degree of coloration in the product which will be included in the NDA. Does the Division concur that DURECT has sufficiently characterized and established adequate controls to address and limit the product color?

FDA Response

We concur with your approach to establish a quantitative color test and specification to limit the color of the drug product. Even though the proposed test is based on the pharmacopeial EP 2.2.2 method, submit a description of your in-house method and standards with appropriate validation, consistent with ICHQ2 principles, in the NDA. The adequacy of your attempts to characterize and limit the colored degradants observed on stability will be assessed upon review of the NDA. Therefore, submit to the NDA the following:

- a. A detailed explanation in the Pharmaceutical Development Report, supported by literature references, of your attempts to characterize the colored degradants and assess degradation of the excipients sucrose acetate isobutyrate (SAIB) and benzyl alcohol in the presence of bupivacaine
- b. A specification and acceptable range for the assay of the excipient SAIB, in the drug product specifications
- c. A characterization, specifications, and limits for degradants resulting from degradation of SAIB in the specifications of the drug product
- d. A Letter of Authorization (LoA) to the Drug Master File (DMF) supporting the novel excipient SAIB to permit our review of the DMF
- e. Stability data for the GLP toxicology lot used for the establishment of the NOAEL

Additional Chemistry Comments

Provide a leachables/extractables evaluation of your container/closure system with the drug product in the NDA, with characterization and assay of any new impurities and degradants. With regard to extractables and leachables testing, refer to Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf> and the PQRI leachables/extractables recommendations to the FDA found at: http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

Refer to the non-clinical comments regarding the safety evaluation of your leachables/extractables.

2.2 Non Clinical

Nonclinical Question 1 (Submission of Nonclinical Pharmacology Summary (2.6.2))

DURECT proposes that Section 2.6.2 (nonclinical pharmacology summary) is unnecessary for inclusion in the SABER-Bupivacaine NDA as the pharmacology of bupivacaine is well understood. Does the Division concur?

FDA Response

No. While we agree that the pharmacology of bupivacaine is well understood you must nevertheless provide adequate summary information in the NDA submission.

Nonclinical Question 2 (Nonclinical Studies)

Nonclinical studies conducted by DURECT in rodent and non-rodent species were designed to provide an assessment of the toxicological safety profile of SABER-Bupivacaine appropriate for

the proposed single-dose, post-surgical application of the product. The formulation composition that was tested in the pivotal toxicology studies was identical to the formulation composition used in controlled Phase 2 and Phase 3 clinical trials and to the product proposed for marketing. Does the Division agree that the nonclinical studies with SABER-Bupivacaine and SABER vehicle conducted by DURECT, supported by the existing toxicology information on bupivacaine (Marcaine®), and published data on the excipients (sucrose acetate isobutyrate and benzyl alcohol) are sufficient to support the 505(b)(2) NDA for the proposed indication?

FDA Response

The Division agrees, pending our determination that the aged and degraded drug product used in the repeat-dose (4 weekly injections) nonclinical study is sufficiently comparable to the released drug product, to extrapolate local safety. Comparability would also make the repeat dose nonclinical study valid for assessing repeat dose systemic toxicity of the drug product. Refer to Agency recommendations found in Guidance for Industry and Review Staff: *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079245.pdf>.

Additionally, while the nonclinical studies, combined with literature references submitted, appear to support human safety based on your summaries, final determination will depend on Agency review of the data.

Nonclinical Question 3 ((b) (4))

Given toxicological evaluations and literature information, the excipient related degradants, (b) (4), have been qualified at levels above the proposed drug product specification limit ((b) (4), respectively).

Does the Division agree that the excipient related degradants, (b) (4) have been qualified and no further toxicology studies are required for the NDA?

FDA Response

Yes. The degradants are qualified at the proposed drug product specification limits.

Nonclinical Question 4 (Genotoxic Impurity)

DURECT was advised at the SABER-Bupivacaine End of Phase 2 Meeting (14 September 2007) to control exposure to potentially genotoxic impurities to not exceed (b) (4) µg/person/day. DURECT proposes to include a specification limit of (b) (4) ppm for (b) (4) based on optimized control of manufacturing and stability data. Although this limit would result in a higher exposure than that recommended in the current Draft Guidance on Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008), DURECT considers that this specification is justified and has provided a detailed rationale below for this proposed limit. Does the Division concur with the proposed limit of (b) (4) ppm for (b) (4)?

FDA Response

At projected impurity release rates for (b) (4) over 4 days, values still exceed (b) (4) mcg/day TDI at the proposed specification limit of (b) (4) ppm for (b) (4). While we agree that (b) (4) ppm could be acceptable for this single-dose drug product, since you note that actual values of (b) (4) are (b) (4) ppm, we would prefer a limit of (b) (4) ppm, which would result in all projected daily exposures being (b) (4) mcg/day TDI.

2.3 Clinical Pharmacology*Clinical Pharmacology Question 1*

As SABER-Bupivacaine is a local anesthetic, plasma levels of bupivacaine have been measured in clinical trials as an indicator of safety. Therefore, the clinical pharmacology section will consist of descriptive pharmacokinetic data of SABER-Bupivacaine after a single dose in the evaluated surgical settings and additionally compared to commercial bupivacaine, where appropriate. Pursuant to DURECT's 505(b)(2) application, additional clinical pharmacology information will refer to the reference listed drugs (RLD) for bupivacaine, Marcaine® and Exparel®. CNS and CVS safety assessments will be evaluated in relation to the pharmacokinetic data. Does the Division agree that the proposed approach is sufficient to support NDA approval?

FDA Response

You did not provide details on the clinical pharmacology program for your product in the meeting package. We have the following comments on your NDA submission based on the information you submitted.

- a. The pharmacokinetic (PK) profiles of bupivacaine products for local anesthesia indication will depend on the total dose of drug administered, the route of administration, and the vascularity of the administration site. Therefore, the PK profiles of your product will be different in different surgical procedures. You should provide PK information for each surgical procedure that you are seeking for approval.
- b. You indicated that you will use Marcaine and Exparel as the listed drugs in this package. We remind you that you must establish a scientific bridge (e.g., via comparative bioavailability data) between your proposed drug product and each of the listed drugs which you propose to rely upon to demonstrate that such reliance is scientifically justified; also, see our general comments on the 505(b)(2) pathway. The final to-be-marketed formulation should be used in the PK studies and clinical safety and efficacy studies. Otherwise, you will need to provide adequate bridging information or justify why the study results can be extrapolated to your final to-be-marketed product.

2.4 Clinical

Clinical Question 1 (Adequate and Well-Controlled Trials)

At the End-of-Phase 2 (EOP2) meeting the Division determined that only one adequate and well-controlled trial would be needed for this 505(b)(2) NDA (see EOP2 meeting minutes dated 12 October 2007). DURECT has completed two clinical trials (CLIN-803-006-0006 and BU-002-IM) to fulfill this requirement.

Can the Division confirm the acceptability of these studies, for providing the basis of establishing SABER-Bupivacaine's effectiveness for this 505(b)(2) NDA?

FDA Response

While the Division indicated that only one adequate and well-controlled trial would be required, it was also stated that the results of the trial should be robust and able to withstand sensitivity analyses. The purpose of the single trial was to provide evidence of efficacy and safety for multiple surgical procedures and to allow a determination of the adequacy of the dosing paradigm to be used with SABER-Bupivacaine – all of which would be needed for a broad indication.

Your pivotal studies included inguinal hernia repair and subacromial decompression, with supporting data provided from the laparotomy, laparoscopy and hysterectomy studies. The extent to which these studies, taken together, will support a finding of efficacy and safety for a broad indication will be a matter for review. In the NDA submission, you need to provide a rationale for how the results of these studies, as well as the dosing and methods of administration, may be extrapolated to other surgical procedures. In particular, the technique of instillation (e.g., using a catheter, spinal needle, syringe without a needle) will need to be clearly described as well as the amount of drug product that is to be instilled in the various tissue layers.

Note that the proposed indication, “extended relief of post-surgical pain,” will need to be modified. Specifically, the term “extended” is vague, and the indication is more properly labeled as post-operative analgesia. The duration of the analgesic effects can be described in the clinical studies (and, potentially, the clinical pharmacology) section(s) of the product labeling.

Note also that replicated, significant reductions in opioid use can be described in the clinical studies section of the label but will require the following caveat be included with the description: “...the clinical benefit of which was not demonstrated.”

Clinical Question 2 (Integrated Summary of Efficacy)

DURECT proposes that the results of the two adequate and well-controlled trials (CLIN-803-006-0006 and BU-002-IM) and the totality of efficacy data from the other Soft Tissue and Orthopedic trials presented in the proposed ISE demonstrate substantial evidence of efficacy for the claimed indication and adequately characterizes the use and benefit of SABER-Bupivacaine. This evidence is supported by the efficacy data from other controlled studies that further explore and define the nature of the drug's effectiveness and provides information on how

the drug should be used. Does the Division concur that the proposed ISE format and ISE statistical analysis plan (SAP) are adequate and sufficient to support the proposed indication of “extended relief of postsurgical pain” for SABER-Bupivacaine?

FDA Response

Your statistical analysis plan appears acceptable at this point; however, we may request more analyses during the review cycle depending on the findings from your data. Note that the final decision will be based on the totality of the data from all your studies. See response to Clinical Question 1 regarding your proposed indication.

Clinical Question 3 (Overall Safety)

DURECT asserts that results of the Phase 2 and 3 controlled trials demonstrate substantial evidence of safety for the claimed indication and adequately characterizes the use and risks of SABER-Bupivacaine. Does the Division concur that the proposed ISS format and ISS statistical analysis plan (SAP) are adequate and sufficient to support the proposed indication of “extended relief of postsurgical pain” for SABER-Bupivacaine?

FDA Response

Your plan to combine the Phase 2 and 3 trials involving the to-be-marketed formulation in the integrated summary of safety is appropriate. However, the safety data from the Phase 1 and histopathology studies, which also use this formulation, need to be included in the analyses where appropriate.

You will also need to provide evidence that SABER-Bupivacaine does not interact with materials it may come into contact with in the surgical wound, i.e., various types of suture, surgical mesh, prostheses. Such evidence may be derived from in vitro studies, e.g., tensile strength testing of suture and mesh products following exposures to SABER-Bupivacaine for durations that are consistent with those expected in the clinical setting.

Clinical Question 4 (Cardiac Safety)

Does the ECG data collection and analyses from the C803-025 trial and pooled ECG data across trials adequately address the Division’s requirements for assessment of Cardiac safety and QT effects?

FDA Response

In Study C803-025, 12-lead Holter monitoring was used to collect ECG data on patients free of baseline ECG abnormalities (e.g., atrial fibrillation or flutter, RBBB or LBBB) that would preclude reliable assessment of ECG intervals. This study lacks several of the components necessary to characterize the QT effect of SABER-Bupivacaine, which include:

- adequate sample size**
- placebo and positive control**
- triplicate ECGs**
- adequate sampling**

- supra-therapeutic dose (which would capture the near worst case scenario in a patient population)

As indicated in our March 24, 2009, advice letter, you could rely on the Agency's findings for Sensorcaine and, therefore, not need to conduct a Thorough QTc study, provided you demonstrate that systemic exposure (C_{max}) to bupivacaine from SABER-Bupivacaine does not exceed that of Sensorcaine for any of the proposed sites of administration.

An alternative method would be to compare the C_{max} values for Sensorcaine and SABER-Bupivacaine following an injection at the site where maximal systemic exposure is expected to occur. If serum levels of bupivacaine are the same or less for SABER-Bupivacaine, the argument can be made that the findings for cardiac safety and, indeed, neurological safety, for Sensorcaine should apply to SABER-Bupivacaine as well. A rationale for how the surgical site, dose and administration technique result in maximal exposures to bupivacaine needs to be provided as well.

Clinical Question 5 (Submission of Safety Information for Ongoing Clinical Trial)

DURECT plans to provide safety information from an ongoing trial, C803-027, entitled, "Open-Label, Histological Evaluation of Surgical Wounds in Subjects Treated with POSIDUR™ (SABER-Bupivacaine)" in the NDA and additional information at the time of the 120-day safety update. Is this plan acceptable?

FDA Response

The finding of wound discoloration following the administration of SABER-Bupivacaine raises safety concerns that need to be addressed before a benefit risk analysis can be performed to determine whether the product should be approved. Specifically, the following questions need to be resolved:

- a. What is the etiology of the discoloration, i.e., infectious, mechanical, chemical, immunological?
- b. Can anything be done to prevent the discoloration, e.g., change in formulation, dose, or method of administration?
- c. To what extent does the discoloration limit a surgeon's ability to assess the wound for infection, adequate hemostasis and potential dehiscence?
- d. Is it possible to identify particular patient populations that are at greater risks for this event?

Study C803-027 needs to be submitted with the initial filing of the NDA and not as part of the 120-day Safety Update. Whether this study is adequate to address the concerns

raised by the skin discoloration will depend to a large extent on the results of the trial and your ability to answer the questions listed above with the data from the trial.

Clinical Question 6 (Case Report Forms (CRFs))

In the NDA, DURECT plans to provide only CRFs for all patient deaths, discontinuations due to adverse events, and serious adverse events. NDA inclusion of additional CRFs based on targeted safety events of interest is not planned. Does the Division agree with this approach?

FDA Response

This approach is acceptable.

Clinical Question 7 (Risk Management Plan (RMP))

DURECT purports that there are no safety concerns that warrant risk management strategies, beyond describing the risks and benefits of the SABER-Bupivacaine drug product in the proposed labeling and performing required safety reporting, to ensure that the benefits of the proposed drug product outweigh its risks. As there have been no safety concerns identified in the development and clinical program for SABER-Bupivacaine, labeling and routine reporting requirements are sufficient to mitigate any probable risks and preserve its benefits.

In accordance with FD&C Act Section 505-1 [21 USC § 355-1], DURECT certifies to comply should the Agency become aware of new safety information, as defined in 505-1(b)(3), and determines that such a strategy is necessary to ensure that the benefits of the SABER-Bupivacaine drug product outweigh its risks. Thus, if notified by the Agency that a REMS is necessary, DURECT will submit a proposed REMS within 120 days, or within such other reasonable time as FDA requires to protect the public health [section 505-1(a)(2)(B)]. Does the Division concur?

FDA Response

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application. However, given what we know of the product at this time, we do not believe that a REMS would be necessary.

2.5 Statistical

Statistical Question 1 (Data Format and Documentation)

The plan for the presentation of clinical data, both individual trials as well as pooled trials, in CDISC format is provided in the Information Package. Is the proposed content, format, and structure acceptable for NDA submission?

FDA Response

In general the format, content, and structure of the data submitted appear acceptable. However, we could not locate a define definition file for the ADaM datasets submitted. This should be included in the NDA submission.

Additional Statistical Comments

- a. For both studies, it is not clear that your analysis of the primary endpoint, AUC of pain intensity scores out to 72 hours, accounted for the use of rescue medication. Since the use of rescue medication may influence pain scores, you should propose an analysis method that does not attribute a treatment benefit to assessments potentially affected by the use of rescue medication. Additionally, the associated ADaM datasets should indicate when rescue medication was used and if the analysis accounted for its use.
- b. We request that you submit all programming code utilized for the primary endpoints in the pivotal studies and ISE.

2.6 Label and Labeling Comments (from DMEPA)

- a. We note that you submitted two potential names for your product Proprietary Name Review, but that they were denied via our letter dated December 23, 2011. Clarify if you intend to submit another name for Proprietary Name Review for this product in the future.
- b. We note that in three cohorts of your clinical trial C803-025, your product was administered using a needle-free instillation method (b) (4). Clarify if your intent is for this device to be the primary mode of instillation for your product. If so, clarify if you plan to co-package this device with your product.
- c. Although your product is still in the investigational stage, we suggest differentiation of your product from the currently marketed Bupivacaine products via the following methods:
 - 1) Warnings on the carton and container label such as “For instillation only” and “Not for intravenous, caudal, or spinal use” when the final labels and labeling for your product are submitted in the New Drug Application. Administering your product by routes other than instillation may cause serious clinical consequences, such as thromboses at the site of administration.
 - 2) Visibly enhancing the strength statement for your product on the carton and container labels and labeling, since currently marketed Bupivacaine products with the same fill volume may contribute to selection errors. Also indicate the presence of benzyl alcohol in your product on your carton, container labels, and labeling so that caution is taken in the event that the product is used by a nursing mother.

- d. Since your product experiences caramelization, which does not affect the stability or efficacy of your product throughout its shelf life, be sure to address this color change in your product labels and labeling to alert clinicians of this occurrence.**

3.0 OTHER IMPORTANT INFORMATION

3.1 Prescribing Information

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

3.2 Manufacturing Facilities

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Attachment 1: Additional Comments for Pre-NDA Stage of Drug Development

Nonclinical Comments

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.
2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 draft Guidance for Industry: *Applications Covered by Section 505(b)(2)*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack

adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.

4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following Guidance for Industry: *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

As noted in the document cited above, “the phrase ***new excipients*** means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure, duration of exposure, or route of administration.**” (emphasis added).

5. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled “Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.” Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds

the qualification threshold should be adequately justified for safety from a toxicological perspective.

8. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics*. The evaluation of extractables and leachables from the drug container closure system or from a transdermal patch product must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents “Container Closure Systems for Packaging Human Drugs and Biologics” and “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation.” Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.
9. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

Chemistry, Manufacturing and Control (CMC) Comments

1. Include a well-documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
2. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.
3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk

approvability of the NDA

4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (nonclinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries

2.4 Nonclinical Overview

This section should include a brief statement outlining the nonclinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

General Clinical Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the NDA that has the following columns for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites)
7. Number of protocol violations (Major, minor, definition)

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

Common PLR Labeling Errors

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement “See full prescribing information for complete boxed warning.” Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI.

[See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
20. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
24. Do not refer to adverse reactions as “adverse events.” Refer to the Guidance for Industry: *Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological*

Products – Content and Format, available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.
30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. See Guidance for Industry: *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*. The same applies to PPI and MG.
33. For fictitious examples of labeling in the new format, refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices' website, <http://www.ismp.org/Tools/abbreviationslist.pdf>

SPL Submission

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Integrated Summary of Effectiveness

Please refer to the Guidance for Industry: *Integrated Summary of Effectiveness*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to **Guidance for Industry: *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document***, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

CDER Data Standards Reference Guide/Checklist

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
 - b. Study/protocol number
 - c. Patient's treatment assignment
 - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
 - e. Dosing at time of adverse event
 - f. Dosing prior to event (if different)
 - g. Duration of event (or start and stop dates)
 - h. Days on study drug at time of event
 - i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
 - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - k. Marker for serious adverse events
 - l. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the *ICH MedDRA Term Selection: Points to Consider* document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
13. All datasets must contain the following variables/fields (in the same format and coding):
 - a. Each subject must have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment
 - d. Demographic characteristics (age, race, gender, etc.)
14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.

15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
17. With reference to the table on the following page, note that the HLGt and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGt terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

LIST OF GUIDANCE DOCUMENTS WHICH MAY BE USEFUL IN PREPARING NDA SUBMISSIONS

Center for Drug Evaluation and Research List of Guidance Documents

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

Biopharmaceutics

Guidance for Industry: *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>

Guidance for Industry: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070237.pdf>

Guidance for Industry: *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/ In Vivo Correlations*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070239.pdf>

Guidance for Industry: *Food-Effect Bioavailability and Fed Bioequivalence Studies*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf>

Guidance for Industry: *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf>

Biopharmaceutics Draft

Guidance for Industry: *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070111.pdf>

Chemistry, Manufacturing, and Controls (CMC)

Guidance for Industry: *Botanical Drug Products*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070491.pdf>

Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf>

Guidance for Industry: *INDs for Phase 2 and Phase 3 Studies; Chemistry, Manufacturing, and Controls Information*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf>

Guidance for Industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf>

Guidance for Industry: *NDA: Impurities in Drug Substances*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070577.pdf>

Guidance for Industry: *Orally Disintegrating Tablets*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070578.pdf>

Guidance for Industry: *Residual Drug in Transdermal and Related Drug Delivery Systems*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220796.pdf>

Guidance for Industry: *Residual Solvents in Drug Products Marketed in the United States*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070621.pdf>

Chemistry, Manufacturing, and Controls (CMC) Draft

Guidance for Industry: *Comparability Protocols – Chemistry, Manufacturing, and Controls Information*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070545.pdf>

Clinical Medical

Guidance for Industry: *Acceptance of Foreign Clinical Studies*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071290.pdf>

Guidance for Industry: *Adaptive Design Clinical Trials for Drugs and Biologics*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>

Guidance for Industry: *Collection of Race and Ethnicity Data in Clinical Trials*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071596.pdf>

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors:
Exception from Informed Consent Requirements for Emergency Research
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf>

Guidance for Industry: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: *Waiver of IRB Requirements for Drug and Biological Product Studies*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072069.pdf>

Clinical Medical Draft

Guidance for Industry: *Assessment of Abuse Potential of Drugs*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

Guidance for Industry: *Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA)*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071577.pdf>

Guidance for Industry: *Non-Inferiority Clinical Trials*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf>

Guidance for Industry: *Qualification Process for Drug Development Tools*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

Guidance for Industry: *Suicidality: Prospective Assessment of Occurrence in Clinical Trials*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf>

Clinical Pharmacology

Guidance for Industry: *Pharmacokinetics in Patients with Impaired Hepatic Function - Study Design, Data Analysis, and Impact on Dosing and Labeling*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf>

Guidance for Industry: *Population Pharmacokinetics*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf>

Clinical Pharmacology Draft

Guidance for Industry: *Clinical Lactation Studies – Study Design, Data Analysis and recommendations for Labeling*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072097.pdf>

Guidance for Industry: *Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Trials*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243702.pdf>

Guidance for Industry: *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

Guidance for Industry: *General Considerations for Pediatric Pharmacokinetics Studies for Drugs and Biological Products*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072114.pdf>

Guidance for Industry: *Pharmacokinetics in Patients with Impaired Renal Function; Study Design, Data Analysis, and Impact on Dosing and Labeling*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf>

Guidance for Industry: *Pharmacokinetics in Pregnancy - Study Design, Data Analysis, and Impact on Dosing and Labeling*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072133.pdf>

Current Good Manufacturing Practices/Compliance

Guidance for Industry: *CGMP for Phase 1 Investigational Drugs*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.pdf>

Guidance for FDA Staff and Industry: *Marketed Unapproved Drugs - Compliance Policy Guidance*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf>

Drug Safety

Guidance Medication Guides – Distribution Requirements and Inclusion of Medication Guides in Risk Evaluation and Mitigation Strategies (REMS)

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf>

Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>

Drug Safety Draft

Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf>

Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>

Guidance for Industry: Safety Labeling Changes - Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf>

Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf>

Electronic Submissions

Guidance for Industry: Indexing Structured Product Labeling

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072317.pdf>

Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Content of Labeling

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072331.pdf>

Electronic Submissions Draft

Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – General Considerations*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072362.pdf>

ICH - Efficacy

Guidance for Industry: *E2F Development Safety Update Reports*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073109.pdf>

Guidance for Industry: *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf>

ICH –Joint Safety/Efficacy (Multidisciplinary)

Guidance for Industry: *M2 eCTD: Electronic Common Technical Document Specification*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073240.pdf>

Guidance for Industry: *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf>

ICH – Quality

Guidance for Industry: *Q1A(R2) – Stability Testing of New Drug Substances and Products*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073369.pdf>

Guidance for Industry: *Q1C – Stability Testing for New Dosage Forms*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073374.pdf>

Guidance for Industry: *Q2A – Text on Validation of Analytical Procedures*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073381.pdf>

Guidance for Industry: *Q2B Validation of Analytical Procedures: Methodology*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073384.pdf>

Guidance for Industry: *Q3A Impurities in New Drug Substances*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>

Guidance for Industry: *Q3B (R2) Impurities in New Drug Products*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

Guidance for Industry: *Q3C Impurities: Residual Solvents*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073394.pdf>

Guidance for Industry: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm>

Guidance for Industry: *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf>

Labeling

Guidance for Industry: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>

Guidance for Industry: *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf>

Guidance for Industry: *Contents of a Complete Submission for the Evaluation of Proprietary Names*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

Guidance for Industry: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075066.pdf>

Guidance for Industry and Review Staff : *Labeling for Human Prescription Drug and Biological Products – Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM186607.pdf>

Guidance for Industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>

Labeling Draft

Guidance for Industry: *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf>

Guidance for Industry: *Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf>

Pharmacology/Toxicology

Guidance for Industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>

Pharmacology/Toxicology Draft

Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf>

Procedural

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm>

Guidance for Industry: *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf>

Guidance for Industry: *End-of-Phase 2A Meetings*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079690.pdf>

Guidance for Industry: *Fast Track Drug Development Programs - Designation, Development, and Application Review*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf>

Guidance for Industry: *Formal Dispute Resolution: Appeals Above the Division Level*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079743.pdf>

Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

Guidance for Industry: *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080569.pdf>

Guidance for Industry: *Special Protocol Assessment*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf>

Procedural Draft

Guidance for Industry: *Applications Covered by Section 505(b)(2)*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>

Add CFR reference/ 21 CFR314.50(i)(1)(i)(A) (1) – (4), 21 CFR314.50(i)(1)(ii), 21 CFR314.50(i)(1)(iii)

Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators*

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM256525.pdf>

Guidance for Industry: *How to Comply with the Pediatric Research Equity Act*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>

User Fees

Guidance for Industry: *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf>

Guidance for Industry: *User Fee Waivers, Reductions, and Refunds for Drug and Biological Products*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079298.pdf>

Other references

Product Quality Research Institute leachables/extractables recommendations to the FDA: http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

Agency's interpretation of this statutory provision (see Dockets 2001P- 0323, 2002P- 0447, and 2003P-0408

<http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/01p-0323-pdn0001-vol1.pdf>

Manual of Policies and Procedures –Review Classification Policy: Priority(P) and Standard (S)

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082000.pdf>

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/s/

KIMBERLY A COMPTON
07/27/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 66,086
Durect Corporation
2 Results Way
Cupertino, CA 95014-5924

Attention: Jill K. Burns
Director, Regulatory Affairs

Dear Ms. Burns:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for your SABER-Bupivacaine product.

We also refer to the Type B, End-of-Phase 2 meeting between representatives of your firm and FDA on September 14, 2007. The purpose of the meeting was to provide you with feedback on the questions in your August 4, 2007 meeting package, which were specifically related to your preparations for your Phase 3 studies with this product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

**Meeting Date:** September 14, 2007**Time:** 12:00 noon EST**Location:** White Oak, Building 22, Conference Room 1313**Application:** IND 66, 086**Regulatory Status:** Active IND**Product:** SABER bupivacaine**Proposed Indication:** (b) (4)**Sponsor:** Durect Corporation**Type of Meeting:** Type B- End-of-Phase 2 (EOP2)**Meeting Chair:** Rigoberto Roca, M.D., Deputy Director

Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Minutes Recorder: Kimberly Compton, Project Manager, DAARP

Durect, Corporation Representatives	Title
Nacer Abrouk, PhD	Vice President, Biostatistics
Jill Burns	Director, Regulatory Affairs
Linval DePass, PhD	Executive Director, Nonclinical Safety
Ramachandre Hegde, PhD	Executive Director, Program Management & Project Manager
Peter Langecker, MD, PhD	Chief Medical Officer
Linda Lintao	Senior Regulatory Associate & Scribe
Dmitri Lissin, MD	Director, Clinical Research
Paula Mendenhall, PharmD	Executive Vice President, Operations
Andrew Mikszta, PhD	Vice President, Pharmaceutical Systems R&D
Suzanne Salasky	Director, Clinical Operations
Jaymin Shah, PhD	Executive Director, Pharmacokinetics
Neil Verity, PhD	Executive Director, Pharmacology & Program Leader
(b) (4)	
Charles Grudzinskas, Ph.D.	Regulatory Consultant
FDA	Title
Bob Rappaport, M.D.	Director, DAARP
Rigoberto Roca, M.D.	Deputy Director, DAARP
Yasmin Choudhry, M.D.	Medical Officer, DAARP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAARP
Dionne Price, Ph.D.	Statistical Team leader, Division of Biometrics II (DBII)
Kate Meaker, M.S.	Statistical Reviewer, DBII
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Kim Compton	Regulatory Project Manager, DAARP
Ali Al Hakim, Ph.D.	Chief, Branch 2, Division of PreMarketing Assessment 1, Office of New Drug Quality Assessment (ONDQA)
Prasad Peri Ph.D.	Pharmaceutical Assessment Lead (PAL), ONDQA
Stephen Langille, Ph.D.	Senior Microbiology Reviewer, Office of Pharmaceutical Science
Lester Schultheis, M.D., Ph.D.	Medical Officer, DAARP
Arthur Simone, M.D., Ph.D.	Medical Officer, DAARP
Neville Gibbs, M.D.	Medical Officer DAARP

Meeting Objective:

The purpose of the meeting was to provide the sponsor with feedback on questions from their August 4, 2007, meeting package, which were specifically related to their preparations for Phase 3 studies with this product.

Background:

On September 11, 2007 (prior to the September 14, 2007 meeting) the Agency forwarded to the firm comments and responses to the questions posed by the sponsor in their August 4, 2007, meeting package. Chemistry Questions 1 (8.1.1), and 4 (8.1.4), Nonclinical Question 6 (8.2.1) and Clinical Questions 8 (8.3.1), 9 (8.3.2.1), 10 (8.3.2.2), 13 (8.3.4), and 14 (8.3.5), and Clinical Comment 1, were discussed at the meeting.

Presented below are the Agency comments related to the sponsor's background material and responses to questions in the background meeting package. The sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. The sponsor's comments, responses and requests for clarification dated September 13, 2007 can be found in normal text indented below the Agency response. Discussion that took place at the meeting is in normal text following the question and/or comment to which it pertains.

Meeting:

The sponsor opened the discussion by reading a prepared statement that is appended to these minutes (see Attachment A) which referred to an Agency Guidance where one clinical trial would be acceptable for approval. The statement also referred to the Division comments of December 27, 2006, which stated that a minimum 400 patients would need to be studied on this drug for considerations of approval of the product and requested feedback on these two points. Dr. Roca stated that the Division would discuss the matter internally and provide feedback to the firm at a later time.

Chemistry Questions

Question 1 (8.1.1)

Are the test attributes listed in the specification as outlined in this Information Package for SABER™-Bupivacaine acceptable for commercial product?

FDA Response

1. The following are comments on your specifications for the bupivacaine base

- a. You may choose to have different specifications for different vendors.
- b. Include a specification for melting point.
- c. Qualify all impurities per ICH Q3A(R) limits. Give special consideration for impurities considered as structural alerts (b) (4)
- d. Provide justifications for the levels of (b) (4) etc. proposed based on toxicological considerations.

- e. **Justify the necessity for specifications for bacterial endotoxins.**
 - f. **Include a specification for microbial count.**
2. **The following are comments on your specifications for the drug product**
- a. **Qualify all impurities per ICH Q3B(R) limits. Give special consideration for impurities considered as structural alerts** (b) (4)
[REDACTED]
 - b. **Justify the acceptance criteria for bacterial endotoxins with data.**
 - c. **Justify any overages of overfill proposed for the drug product.**
 - d. **Include specifications for leachables in the drug product on stability. This should be based on stability data typically at the end of shelf-life and based on toxicological evaluation.**

DURECT Response (9-13-07)-

In accordance with standard practice for parenteral products, we have implemented and are already conducting a leachables study as part of the stability program on one ICH batch to determine levels of leachables and evaluate any potential toxicological concerns. Assuming no safety concerns arise throughout the stability study (targeted 3 years), we propose that a specification for leachables for our commercial product is not necessary.

Discussion

Dr. Peri stated that the firm's proposal seemed reasonable but the Agency's final assessment will ultimately depend on the data provided in the NDA. If the sponsor identifies any leachables, they will need to conduct a toxicological assessment. The firm indicated that they have revised their plan to test for leachables and are now planning to test three batches of drug product for leachables.

- e. **The acceptability of the proposed drug release specification will be evaluated in the NDA review.**

Question 2 (8.1.2)

Is the specification as outlined in this Information Package for Sucrose Acetate Isobutyrate (SAIB), a novel excipient included in this parenteral product, acceptable?

FDA Response

- 1. **Provide a letter of authorization to a Drug Master File (DMF) for SAIB or provide details of its manufacture and quality control information.**

2. **Revise the acceptance criterion for Assay** (b) (4)
3. **Use a quantitative method for Color** (b) (4).
4. **Include a specification for** (b) (4)
5. **Consider including a specification for optical rotation.**
6. **Justify the limits for bacterial endotoxins.**

Question 3 (8.1.3)

Does the Agency concur that the proposed ICH stability program is adequate to support marketing licensure?

FDA Response

Your proposal is reasonable for filing an NDA. Include specifications for leachables in the drug product based on stability data from long-term and accelerated stability conditions.

Question 4 (8.1.4)

Based on the justification included in the Information Package, is (b) (4) acceptable to the Agency as a method of sterilization for SABER™-Bupivacaine?

FDA Response

(b) (4)

DURECT Response (9-13-07)-

Additional justification and supporting data (including lower sterilization doses of (b) (4) regarding (b) (4) of commercial batches will be provided after the meeting. We would like to obtain further guidance from the Agency soon after review of this data.

Discussion

Dr. Peri stated that a microbiologist will be consulted to review the data in this regard once it has been submitted. The sponsor clarified that their product will be sterilized using (b) (4). Dr. Langille reminded the firm that ICH Q8 states that they will need to provide justification for their choice of

sterilization method and container/closure system. He noted that (b) (4) is generally considered to be the more reliable method of sterilization as evidenced by the number of sterility assurance recalls (b) (4) sterilized drug products. In addition, the Agency would prefer that the container closure system not dictate the method of drug product sterilization.

Question 5 (8.1.5)

Does the Agency concur with DURECT's strategy in qualifying their two API vendors?

FDA Response

- 1. Your proposal is reasonable for filing.**
- 2. As earlier indicated, provide letters of authorization for DMFs for the two API suppliers. The DMFs will be evaluated during the review of the NDA.**
- 3. Specifications for the two vendors need not be the same and may reflect their routes of synthesis.**
- 4. Periodically verify the results obtained from the vendors in their certificates of analyses.**

Additional Chemistry Comments

- 1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.**
- 2. At the beginning of the CMC section, include a table of all facilities, include specifically what the function is of each facility, the contact name and address, the CFN number, and the complete name and address of the facility.**
- 3. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in the NDA cover letter.**
- 4. Provide tabular summaries of your stability data, organized by test parameter, and separated by manufacturing site, batch, storage condition, and container closure system. Provide graphical summaries of any trending stability data, organized by test parameter, including mean and individual data.**

Nonclinical Questions

Question 6 (8.2.1)

Does the Agency concur that the nonclinical package is complete to support Phase 3 and market licensure?

FDA Response

- 1. In general, your proposed animal toxicology program, including reference to published literature and the Agency's previous findings of safety for your identified referenced drug product (Sensorcaine, appear acceptable to support your proposed Phase 3 clinical trials (intra-wound and subacromial administration) and may be acceptable for filing an NDA submission, with the following caveats:**
 - a. Your NDA application should address the safety of the novel use of both benzyl alcohol and SAIB. Specifically, although benzyl alcohol has been used as an excipient in FDA approved injectable products at a maximum potency of (b) (4) %, you are proposing to use higher concentrations in this drug product. In addition, although considered GRAS via the oral route of administration, SAIB is technically considered a novel excipient due to the route(s) of administration proposed. Your NDA should provide your rationale, including data/information to support the safety of the proposed exposure to these excipients.**

DURECT Response (9-13-07)-

We acknowledge that SAIB and BA (at the concentration in SABER™-Bupivacaine) are novel excipients. We believe that their safety has been adequately evaluated in nonclinical studies.

Discussion

Dr. Mellon stated that the sponsor will need to address all of these items when they submit their NDA.

- b. Refer to the following guidance document: *Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients* (May 2005) which is available on the CDER web page at the following <http://www.fda.gov/cder/guidance/guidance.htm>.**
- c. Adequate safety qualification may include reference to information in the public domain, in lieu of animal studies; however, you should clearly justify how and why any referenced information supports the safety of your drug product.**
- d. Your NDA application should contain justification for the safety of the proposed specifications for (b) (4) in your drug product formulation (b) (4) taking into consideration the maximum daily exposure to all components of the drug**

product. Such justification may be based on adequate information contained in the published literature, if available. The approach for toxicological evaluation of the safety of (b) (4) should be based on good scientific principles and take into account the specific route of administration and dose regimen (chronic vs. short-term dosing).

- 2. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds should be adequately qualified for the NDA submission (ICHQ3A, ICHQ3B(R)). Adequate qualification should include:**

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

DURECT Response (9-13-07)-

We propose that it is acceptable to test the drug substance and/or drug product containing the impurity in genetic toxicology studies as opposed to testing the isolated impurity.

Discussion

Dr. Mellon stated that typically the assay should be conducted using the isolated impurity, noting that sometimes, however, that is not possible to do. Therefore, the Division will consider the firm's proposed approach if the sponsor provides a rationale for why it was not feasible to perform the assay with the isolated impurity.

- b. Repeat dose toxicology of appropriate duration to support the proposed indication.**

DURECT Response (9-13-07)-

Since SABER™-Bupivacaine is a single use (per surgery) product, we believe that "repeated dose toxicology" studies are not applicable.

Discussion

Dr. Mellon stated that the sponsor should consider the proposed clinical use of the product and determine if there is any potential situation in which the patient might be administered the product again (a surgery repeated, etc.). He stated that the firm should provide a rationale to support that this could not/would not occur, and how it could be properly addressed in the labeling, and the Division will consider it. He emphasized though that the determination depends on the potential clinical use and that is the standpoint from which the sponsor should address this issue.

- c. Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT (b) (4) mcg/day should be set for genotoxic or potentially genotoxic residual intermediates in the synthetic scheme unless otherwise justified.**

DURECT Response (9-13-07)-

The only published guidance we are aware of that indicates a threshold of NMT (b) (4) mcg/day for genotoxic impurities makes allowances for more limited treatment regimens.

Discussion

Dr. Mellon stated that the Agency is developing a Guidance Document on this issue, and noted that the current policy is to require sponsors to reduce potentially genotoxic impurities to NMT (b) (4) mcg/day. There are opportunities to have higher levels of these impurities during development, but at the time of NDA submission, the policy is NMT (b) (4) mcg/day regardless of if the product is one-time use or not. If the firm can demonstrate that the impurities were in the preclinical batches tested and have data to address the potential general toxicity of impurities, this may be helpful in addressing this issue.

Dr. Mellon stated that if the sponsor wants to consider the impurity as genotoxic based on available information in the literature, they should limit the exposure to (b) (4) mcg/day. However, the Division recognizes that this product is designed to release drug over a three day period. Therefore, if the sponsor can provide a scientifically valid rationale for what the daily exposure to a specific impurity would be, the Division may be able to work with the sponsor to adjust permissible limits of the impurity. In the absence of an acceptable justification, the Division will have to assume the worst-case exposure scenario that all of the product is available immediately on Day 1 of administration, etc. The sponsor referred to currently approved products without this limit or with a different impurity limit within USP limits and inquired if they could rely on them, noting that ropivacaine had a USP limit 50 times higher for this impurity. Dr. Mellon stated that the Agency follows ICH specifications, not USP, and that if the sponsor has safety data or an appropriate justification for their proposed impurity specifications for their product, the Division would consider it.

d. Adequate safety qualification for any potential genotoxic impurities should be provided with the NDA submission and should include:

- 1.) Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
- 2.) Repeat dose toxicology of appropriate duration to support the proposed indication.**

DURECT Response (9-13-07)-

See above.

- e. Should this qualification produce positive or equivocal results, the impurity specification should be set at NMT (b) (4) mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

DURECT Response (9-13-07)-

See above.

- f. The Division recommends that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and, if needed, decrease the limit of these impurities.
3. The NDA submission should contain information on potential leachables and extractables from the drug container closure system. Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic vs. short-term dosing).

DURECT Response (9-13-07)-

See discussion in Question 1.

4. Final determination of the adequacy of your nonclinical program to support a recommendation of approval of the drug product can only be provided upon review of the NDA.
5. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/guidance.htm> for further information.

Question 7 (8.2.2)

Does the Agency agree that DURECT does not need to perform reproductive toxicology studies for inclusion in the NDA on the basis of submitting a 505(b)(2) application?

FDA Response

1. Further reproduction and developmental toxicology studies for bupivacaine drug substance will not be required for your proposed 505(b)(2) NDA submission referencing the Agency's previous findings of safety of Sensorcaine.

2. **As previously noted, your drug product also contains benzyl alcohol at levels greater than those found in FDA approved injectable products and SAIB is technically considered a novel excipient due to the route of administration. Your NDA application should contain justification for the safety of the entire drug product formulation taking into consideration the maximum daily exposure to all components of the drug product. Such justification may be based on adequate information contained in the published literature, if available.**

Discussion

Dr. Mellon clarified that the responses were in regard to the excipients specification.

Clinical Questions

Question 8 (8.3.1)

Does the Clinical Program as outlined include sufficient data to move forward with the proposed Phase 3 program (patients and surgical situations studied, dose ranges explored, adverse event profile, PK profile, and clinical activity)?

FDA Response

To date, your Clinical Program has evaluated doses of 2.5 mL, 5.0 mL, and 7.5 mL of SABER Bupivacaine in healthy volunteers, as well as in patients undergoing appendectomy, open hernia repair, and shoulder surgery. Altogether, 286 patients have been exposed to SABER Bupivacaine. Drug has been injected (into the subacromial space or subcutaneously) or instilled directly onto the wound site. Studies have compared the pharmacokinetics of injected and instilled drug.

Only one study, CLIN-803-006-0006, had pre-specified a systematic evaluation for potential cardiovascular effects of SABER Bupivacaine. In this trial, PK assessments and 24-hour telemetry and PK monitoring were performed in a subset of patients. The cardiovascular results of this evaluation were not included in the meeting package. All other completed Phase 2 trials either did not include ECG testing or recommended that ECGs be done “as indicated.” This extent of evaluation of potential cardiovascular effects of SABER Bupivacaine is not considered adequate.

Your Phase 3 protocols should include pre-specified and systematic evaluations of the cardiovascular and neurological effects of SABER Bupivacaine beyond Tmax and throughout the anticipated duration of analgesic effect.

DURECT Response (9-13-07)-

As a pre-specified and systematic evaluation of cardiovascular effects of SABER™-Bupivacaine in the Phase 3 protocols, we will collect 12-lead ECGs at screening, and approximately at 24, 48, 72-hr, and 14-day post-surgery for independent and centralized evaluation. Observed neurological symptoms, including early signs of CNS toxicity, will be reported as adverse events and incidence analyzed per treatment group.

Discussion

Dr. Roca stated that the sponsor will need to provide a rationale for their time point selection.

With respect to the proposed Phase 3 dosing of 5 mL, Dr. Roca noted that the 5-mL dose had yielded drug levels approaching 800 ng/mL (up to 1000 ng/mL in some cases) in some of the patients studied to date and that information available in the literature suggested that QT segment prolongation could occur near these levels. The sponsor stated that they had follow-up EKG data in 60 patients they could share with the Agency, noting that the data consisted of 12-lead readings as needed, based on alarms when patients were connected to continuous telemetry. The sponsor stated that, based on these data, they felt the concern regarding QT prolongation could be addressed. Dr. Roca stated that the Division would need to review the data before we could agree.

Question 9 (8.3.2.1)—Phase 3 Study Design

Area Under the Curve for pain (on movement and at rest), as well as total opioid analgesia supplementation (in Morphine Equivalents) were pre-specified efficacy endpoints in the Phase 2 studies that showed clinically meaningful results. Does the Agency agree that the choice of endpoints as specified in the Phase 3 Study are adequate as primary efficacy endpoints?

FDA Response

Your proposed study, CLIN-803-007-001, is a randomized, double-blind, placebo-controlled, 12-week study comparing the effects of placebo versus 5.0 mL SABER Bupivacaine, instilled over the surgical wound site.

We agree with the use of a primary endpoint that is based on a measure of pain intensity. An area under the curve (AUC) analysis of efficacy over 1-72 hours post-dose is acceptable. Pain on movement represents patients' worst pain, and is acceptable.

An assessment of the total amount of opioid used (in morphine equivalents) of the use of would provide supportive evidence of the analgesic efficacy of SABER Bupivacaine. The mean total opioid dose used during the 1 to 72 hours post-surgery time period is an acceptable assessment.

However, because SABER Bupivacaine is intended for concomitant use with opioids, a reduction in opioid use alone may not have clinical significance unless additional benefit can be demonstrated, such as fewer opioid-related adverse events. Therefore, the efficacy analysis should include an evaluation of the effect of treatment on opioid-related adverse events.

DURECT Response (9-13-07)-

CLIN-803-007-0001 is a 2-week study, not 12-week study.

Question 10 (8.3.2.2)

DURECT will be using the Opioid-Related Symptoms Distress Scale (SDS) and Activities Assessment Scale (AAS), as measurements of safety and patient functional status. Does the Agency concur with the use of these validated instruments?

FDA Response

Use of the SDS as a measure of opioid-related effects poses some challenges because of the complexity in which each symptom and, subsequently, each dimension is scored. Interpretation of any observed difference in scores is, therefore, difficult.

A labeling claim of fewer opioid-related adverse effects would require replicated evidence of this finding, as well as demonstration of analgesic efficacy of SABER Bupivacaine and reduced opioid use.

We will consult SEALD (Study Endpoints and Labeling Development) regarding whether the AAS is valid and reliable measures of functional status in patients who have had surgery.

DURECT Response (9-13-07)-

We appreciate the Agency's input on the complexity of the SDS scale and will take this into consideration. Please inform us of any outcomes from the discussion with SEALD regarding the AAS scale.

Discussion

The sponsor stated that they understand that the SDS is a complex and challenging scale, noting that their choice was driven by it being a validated tool, and inquired if the Division could provide any further input on their approach to this issue. Dr. Roca stated that once the Division received a response from the SEALD team, it would provide the details to the firm.

Question 11 (8.3.2.3)

Does the Agency concur with the Phase 3 study statistical analysis methodology as described in the Information Package?

FDA Response

The statistical analysis section of the protocol should be revised to reflect advice provided in the response to Question 9.

The mean pain intensity will be analyzed using an analysis of covariance model with site and treatment as factors. You state, "Additional covariates such as baseline characteristics may be included to evaluate their impact on the main ANCOVA findings." Any covariates that are to be included in the primary efficacy analysis should be pre-specified. Additional covariates may be evaluated as exploratory analyses.

Complete details regarding the strategy to handle missing data should be included in the protocol and the Statistical Analysis Plan (SAP). In addition, you should address how you will handle the use of rescue medication in the analysis of pain intensity.

Lastly, in the synopsis for protocol CLIN-803-007-0002, you propose using an adaptive design. However, no details are provided regarding the design. A complete protocol (specifying statistical decision rules) should be submitted for discussion and advice.

Question 12 (8.3.3)

Is the Safety and Efficacy Database as projected in the Information Package adequate to support an NDA package?

FDA Response

Due to the systemic availability of instilled and injected SABER Bupivacaine, you must more adequately evaluate the neurological and cardiovascular safety of the drug beyond T_{max} and over the anticipated period of analgesic effect (approximately 72 hours). Refer also to the response to Question 8.

The size of your proposed safety database, 600 total exposed, is acceptable. However, a larger safety database may be required if there is a new or significant cardiovascular and neurological signal, or a signal regarding an adverse effect of SABER Bupivacaine on wound healing or scar formation (as based on your ongoing 6-month follow-up study to the hernia study, CLIN-803-006-0006).

Currently, your safety database includes very few women and older persons (aged > 65 years). This may have implications for product labeling and a justification for those deficiencies should be provided.

Discussion

The firm stated that they planned to conduct two studies of 300 patients each to reach the 600 total exposed level. However, they stated that, in a December 2006 letter, the Agency had mentioned that 400 patients would be acceptable for the safety database for the extra-articular locations, so they requested clarification on the apparent discrepancy. Dr. Roca stated that the Division would need to refer back to our December 2006 letter before being able to provide the requested clarification.

However, Dr. Rappaport stated that, if the sponsor decided not to conduct one of their 300-patient studies, the minimum required numbers would need to be re-discussed. He stated that it was, however, unlikely that the Agency would find it acceptable that the sponsor could conduct only one pivotal study (as mentioned in the firm's opening statement), so the planned two 300-patient studies (for a total of 600 patients exposed) should yield more than the required minimum number of patients.

Question 13 (8.3.4)

Does the Agency agree that the Clinical Program as outlined supports the below indication:

SABER™-Bupivacaine is indicated (b) (4)

FDA Response

The exact language describing the indication is determined upon review of the NDA.

You propose two Phase 3 trials, one in patients undergoing hernia surgery, and the other in patients undergoing extra-articular shoulder surgery. The majority of your Phase 2 trials were also in patients who underwent hernia surgery. Furthermore, the extent of the surgical area that can be dosed is limited to the volume of drug (5 mL). Provide your rationale as to how these surgeries are sufficiently similar to each other and to other types of surgeries that an indication for use of SABER Bupivacaine across a broad range of surgeries (e.g., laparotomy, thoracotomy) is appropriate.

DURECT Response (9-13-07)-

Our rationale is based on our planned 505(b)(2) application, which will include the extensive body of literature on the use of continuous infusion of bupivacaine via elastomeric pumps for post-surgical pain control. This literature establishes the systemic adverse event profile and analgesic activity of sustained local delivery rates of bupivacaine (10 mg/hr), similar to SABER™-Bupivacaine, in a broad range of surgeries (including thoracotomy, cholecystectomy, lymph node dissection, hysterectomy and others).

Discussion

Dr. Rappaport stated that a reply to this response was part of the whole decision process involving if one or more studies would be required for approval of the product, noting that the Division would get back to the sponsor once a decision had been reached on this point.

Question 14 (8.3.5)

Does the Agency agree that (b) (4) *the Phase 1 and 2 Clinical Program as outlined supports the below indication:*

SABER™-Bupivacaine is indicated (b) (4)

FDA Response

In general, we do not recommend indications based on limited development programs.

However, a narrow indication for SABER Bupivacaine may be possible due to the relatively novel route of administration, and if there is evidence of substantial safety concerns that result in an acceptable risk-benefit analysis only in this limited condition of use.

Note that an indication for (b) (4) would require demonstration of efficacy in at least two adequate and well-controlled trials.

DURECT Response (9-13-07)-

We are in agreement with the Agency that two adequate, well-controlled trials

(b) (4)
(u) (4)
would be required to support the above indication
.

Discussion

Dr. Roca stated that the Division does not generally recommend the pursuit of such a narrow indication. Dr. Rappaport stated that the sponsor will need to provide a rationale that would merit limiting the indication in such a manner. He also noted that the Division will need to review what the firm has completed so far in their development program, other information available and our standards for a 505(b)(2) application before being able to provide complete feedback on this issue.

The sponsor stated that they understood the need for two studies and the need for a confirmatory study if the indication goes beyond pain (e.g., opioid-sparing, etc.). The sponsor indicated that they would provide the Division with their new position statement.

Question 15 (8.3.6)

Is the use of the FDA preferred term, (b) (4) (FDA[CDER Manual] code (b) (4), appropriate for the proposed route of administration?

FDA Response

At this time, we do not consider (b) (4) to be an appropriate term that captures both the injection and instillation routes of administration that will be studied in the Phase 3 trials. The product label will, therefore, reflect the route that was utilized in each surgery type.

Clinical Comments

- 1. Regarding study CLIN-803-007-0001 (a 12-week efficacy trial in patients undergoing hernia surgery)**

DURECT Response (9-13-07)-

CLIN-803-007-0001 is a 2-week study, not a 12-week study.

- a. The protocol should specify the timing of patients' pain assessments relative to their use of rescue analgesia.**

DURECT Response (9-13-07)-

Patient reported outcomes of pain on movement and rest are collected by electronic diaries at specified timepoints throughout the day for efficacy analysis. Additionally, pain severity is recorded at the time of administration of rescue analgesia to ensure absence of prophylactic use.

Discussion

Dr. Roca confirmed that the sponsor's proposal in this regard was sufficient.

- b. As previously communicated to you in our letter dated December 27, 2006, it will be necessary to define the length and extent of surgical wounds that are suitable for analgesic management with SABER Bupivacaine, and how any limitations on use will be communicated to health care providers.**

DURECT Response (9-13-07)-

Wound length data will continue to be collected in Phase 3. According to surgeons who participated in CLIN-803-006-0006 and CLIN005-0010, all doses were generally contained within the hernia wound.

Discussion

Dr. Roca stated that the sponsor will need to clarify the term "generally contained" with specific data. The sponsor indicated that they collected data on the incision and would provide it to the Division and will continue to collect information on the wound site in an attempt to develop appropriate language for the package insert (PI).

- 2. We note that your Phase 3 trials will include foreign sites. Information will be required regarding how the surgical and clinical management of patients in those countries compares to standard U.S. practices.**

The sponsor summarized their understanding of the meeting as follows (includes action items)

1. The sponsor understands that they will need to provide a rationale for time selections of EKGs.
2. The sponsor understands that the Division cannot agree to a 5-mL dose at this time and will provide data and analysis of their recent study to include the C_{max} , T_{max} , AUC, etc. of the product.
3. The Division will provide further information on the SAS/SDS after receiving input from the SEALD team. Dr. Rappaport stated that the Agency does not recommend any specific *instrument* to collect opioid AEs, just that the firm collect a *profile*, looking at all three issues, i.e., pain, dose and AEs, and determine if, overall, the product made a difference.

He stated that the Division can assist the sponsor in defining appropriate analyses to evaluate this data.

4. The sponsor understands that it is unlikely that the Division will accept one study for approval of the product, but will submit information on this position for the Division to review.
5. The sponsor understands that the Division does not recommend a limited indication for the product, but that the Division will consider this with additional information the sponsor will provide on this issue.
6. The Division feels that the sponsor's response to Question 1, Agency Response number 2 d is reasonable, but depends on the data in the NDA.
7. Regarding [REDACTED] (b) (4), the sponsor understands that they need to provide a justification of the selection of this technique and also that the Agency has seen problems when this technique was employed in the past.
8. The sponsor will address the novel excipients SAIB and BA in their NDA submission.
9. The sponsor understands that they need to provide a rationale/justification for tests of the Drug Substance for impurities and genetic toxicology. Dr. Mellon emphasized that the Division recommends that the sponsor test the *isolated impurity*, and that they provide a justification to the Division if there is some reason they cannot do this.
10. Regarding repeat-dose toxicology, the sponsor understands that they should consider the clinical use of the product (if it could be used in a repeated manner at all) and provide a rationale of how the product will be used and how this issue would be addressed in the labeling. Dr. Mellon clarified that ICH M3 states that 28-day toxicology in two species is normally required, noting that once an appropriate rationale for clinical use is submitted, the Division can work with the sponsor to appropriately adjust this requirement based on clinical use.
11. The sponsor is planning to conduct stability for leachables on three batches of product.
12. The sponsor will expand on the opioid-sparing language in their opening paragraph. Dr. Rappaport stated that the Division would look at the evidence in the trials that the sponsor has completed to date and whether efficacy could be established in just one trial. He also noted that since the object is to demonstrate a clinical benefit, they will need a patient reported outcome as the primary endpoint and full assessment of the opioid and bupivacaine related adverse events.

*****Post-Meeting Note-**

After internal discussions, the Division has determined that only one adequate and well-controlled trial will be required. However, the results of the trial should be robust and able to withstand sensitivity analyses.

Attachment A
(Prepared statement read by the sponsor at the beginning of the meeting)

DURECT Opening Statement

As you know, bupivacaine is the active component of two already marketed products used for local analgesia following various surgeries. DURECT plans to utilize the 505(b)(2) regulatory pathway for a broad claim of local analgesia for its SABER™-Bupivacaine product.

In addition, we plan to provide “independent substantiation” for “new use” using a new “dosage form” and “different clinical endpoint” of an approved product – for instance opioid-sparing and reduction of opioid-related side effects – based on guidance in the FDA’s May 1998 Guidance on Evidence of Effectiveness (Section C.2.a and C.2.g). This guidance states that at most one clinical trial is required to support such a new use. In order to provide “independent substantiation”, or “replication” as you have recommended, we propose that the already completed CLIN-803-006-0006 hernia surgery trial, coupled with a yet to be conducted Phase 3 trial in a non-hernia surgical model, will provide the needed replication of the opioid sparing and reduction of opioid-related side effects.

Apart from this approach to confirming effectiveness, we plan to provide adequate safety information as outlined by the Agency in the FDA correspondence in December 2006 stating 400 post-surgical patients who have received SABER™-Bupivacaine administered via local wound infiltration.

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/s/

Kimberly Compton
10/12/2007 07:12:40 PM