CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review - Addendum

Date	November 16, 2010
From	Eric Bastings, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-462
Applicant	CNS Therapeutics
Date of Submission	March 27, 2009
PDUFA Goal Date	April 27, 2010
Proprietary Name / Established (USAN) names	Baclofen Injection (intrathecal) (Gablofen)
Dosage forms / Strength	Intrathecal injection / 0.05 mg/ml, 0.5 mg/ml, 2.0 mg/ml (b) (4)
Proposed Indication(s)	Spasticity
Recommended:	*Approval for Gablofen 0.05 mg/ml, 0.5 mg/ml, 2.0 mg/ml;* (b) (4)

For over a year there has been an on-going dialogue between CDER and CDRH regarding whether the formulations of Gablofen up to 2 mg/ml (i.e., 0.05 mg/ml, 0.5 mg/ml, 2.0 mg/ml) are the same as those of the reference drug, Lioresal. CDER previously concluded that the formulations of Gablofen up to 2 mg/ml are qualitatively and quantitatively the same as those of Lioresal. In other words, the formulations are identical. CDER also concluded that the minor differences in pH and osmolality specifications between Gablofen and Lioresal are not clinically significant, and are acceptable. Therefore, Gablofen is expected to perform the same as Lioresal under the conditions of use described in labeling, and is expected to have the same compatibility profile as Lioresal with respect to the devices approved for its administration. CDRH previously believed that there was insufficient information to conclude that Gablofen and Lioresal were identical, and that further testing of Gablofen with the device indicated for its administration was necessary for approval. In sum, CDRH now agrees that Gablofen up to 2 mg/ml is identical to Lioresal and that no additional testing of Gablofen with the device indicated for its administration is necessary before approval.

In my original Cross-Discipline Team Leader Review (CDTL) memorandum dated July 16, 2010, I discussed that no alignment had been reached between CDRH and CDER up to that date regarding the testing necessary to support approval of Gablofen up to a concentration of 2 mg/ml, and that CDRH's final recommendations were pending. The purpose of this memorandum is to clarify certain statements in my CDTL memorandum dated July 16, 2010, and to document resolution of the issues between CDRH and CDER.

Clarifications to CDTL memorandum dated July 16, 2010

I have clarified below certain aspects of my July 16, 2010, CDTL memorandum:

- My July 16, 2010, CDTL memorandum provides an overview of the proposed Gablofen product approval and summarizes the history of communications between

CDER and CDRH regarding the sameness of the formulations and whether additional testing for Gablofen was needed. At this time, CDER (b) (4) intends to approve Gablofen up to a concentration of 2 mg/ ml (i.e., 0.05 mg/ml, 0.5 mg/ml, 2.0 mg/ml). (b) (4)

- As noted above, my July 16, 2010, CDTL memorandum summarizes CDRH's previous communications regarding the sameness of the formulation and whether additional testing was necessary. (See e.g., pages 5-13.) I indicated in a number of instances in the memorandum that CDRH's rationale for certain testing was not clear to me. (See e.g., p. 6, 7, 9). To clarify, my view is that the additional testing proposed by CDRH was not necessary because the formulations of Gablofen and Lioresal (up to 2 mg/ml) were the same and the minor differences in pH and osmolality specifications were not clinically significant, and found to be acceptable. The compatibility profile of Gablofen with pumps approved for its administration, for example, would be expected to be the same as that of Lioresal under the conditions of use described in labeling.

- My July 16, 2010, CDTL also alludes to certain labeling issues which have since been considered thoroughly and addressed. FDA concluded that the proposed Gablofen labeling -- taking into account either the "old" Medtronic device labeling or the "new" Medtronic device labeling for which an approval order was issued on October 6, 2010 -- is acceptable. Gablofen -- when used with pumps approved for its administration -- is safe and effective under the conditions described in its labeling.

Resolution of CDER and CDRH issue

As noted above, I discussed in my July 16, 2010, CTDL memorandum that no alignment had been reached between CDRH and CDER up to that date regarding the testing necessary to support approval of Gablofen up to a concentration of 2 mg/ml. Further discussions have taken place since that time, and alignment was reached between CDER and CDRH to approve Gablofen up to a concentration of 2 mg/ml without further testing. CDRH summarized in two memoranda its concurrence with the approval of Gablofen (up to a concentration of 2 mg/ml) and the basis for its conclusion. (Appended to this document are the September 13, 2010, memorandum (appendix 1) from Steven K. Pollack, Director of the Office of Science and Engineering Laboratories (OSEL), Dinesh Patwardhan, Director of the Division of Chemistry and Materials Science, OSEL, and Ji Guo, Senior Staff Fellow, Division of Chemistry and Materials Science, OSEL, and the November 9, 2010, memorandum (appendix 2) from Anthony Watson, Director of the Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices, Office of Device Evaluation, Center for Devices and Radiological Health).[1] In summary, the two memoranda together explain that, based upon

[1] The full title of this memorandum is "November 9, 2010 Supplemental Review Memo to Review Memos dated May 4, 2010, April 16, 2010 and July 12, 2010." Upon further clarification with CDRH, we note the following: This memorandum was inadvertently finalized with the word "draft" in the header. The May 4, 2010, memorandum referenced in the title does not include the date on the memorandum itself and the April 16, 2010, memorandum referenced in the title is actually dated April 28, 2010.

updated information provided by CDER, CDRH now agrees that the formulation of Gablofen (up to a concentration of 2 mg/ml) is identical to that of Lioresal and that CDRH believes the additional premarket and post market testing requested in previous memoranda are not necessary for Gablofen (up to a concentration of 2 mg/mL). In his memo, Mr. Watson also discusses additional personal concerns. I have addressed his concerns below.

First, Mr. Watson comments about the large number of adverse events reported by Medtronic for its pumps, and about the steps that Medtronic has taken to abate off-label use of drugs (and use of compounded drugs) with its pumps. Mr. Watson further comments that the use of untested and often unknown formulations of intrathecal drug can result in pump failures, which in his view calls for a tight supply chain control. He then notes that since CNS and Medtronic do not have a business relationship, supply chain control is nonexistent.

Although I agree with Mr. Watson's concerns about the off-label use of drugs and use of compounded products with intrathecal pumps, I do not believe that these concerns are relevant to the current application for Gablofen (up to a concentration of 2 mg/ml) for a number of reasons. The formulations of Gablofen (up to a concentration of 2 mg/ml) are identical to those of Lioresal. The manufacturing process for Gablofen is well known, has been reviewed by CDER, and found acceptable. Gablofen would be indicated and approved for use with certain pumps based on appropriate testing, and, therefore, use of Gablofen as described in its approved labeling would not be an off-label use. Also, Gablofen (up to a concentration of 2 mg/ml) would not be a compounded drug. This situation is very different from that of unapproved products, including compounded products, which may have inadequate quality control. Here, CDER has found Gablofen to be safe and effective and has found that there is adequate quality control.

Second, Mr. Watson expresses a concern regarding what might happen in the future if the device manufacturer, i.e. Medtronic, makes changes to the device materials that would require a change to the Lioresal formulation. Mr. Watson is concerned that this change may not be known to CNS therapeutics, and would require CNS therapeutics to find out through third-party channels, submit a formulation change, and await approval. He states that, in the meantime, an incompatible and possibly unsafe formulation of Gablofen could be used in the pump. That issue was discussed with CDRH during the review cycle, and is also discussed in my original memorandum dated July 16, 2010, the latter of which Mr. Watson had not reviewed before finalizing his November 9, 2010, memorandum. This issue, as Mr. Watson acknowledges, does not implicate the current approval of Gablofen at this time. I was unaware, however, until I reviewed Mr. Watson's November 9, 2010, memorandum that he continued to have concerns regarding this issue.

As Mr. Watson notes, Medtronic could make changes to the device many of which would not affect the drug Lioresal or Gablofen. The above issue raised by Mr. Watson would only arise if Medtronic made certain changes to the device and those changes were incompatible with the current formulation of Medtronic's Lioresal (and therefore Gablofen).

There are a number of legal authorities under the Federal Food, Drug, and Cosmetic Act (the Act) that could be invoked as appropriate based on relevant facts and circumstances (e.g.,

sections 505 (o), 505-1, and 505 (e) of the Act). In the event CDER approves for Medtronic's Lioresal certain labeling statements regarding the compatibility or lack thereof with certain versions of the pump, CDER could immediately notify CNS that similar safety labeling changes for Gablofen are warranted, and ultimately require that such changes be made. CDER could also require CNS to implement certain risk evaluation and mitigation strategies as appropriate. CDER could immediately begin proceedings to withdraw Gablofen from the market if need be. In sum, there are a number of legal authorities that could be invoked to require CNS to make certain labeling changes or withdraw the drug from the market if need be.

I further note that, in the unlikely situation in which Medtronic changed its device and then decided to change the formulation of Lioresal to make it compatible with modifications to its pump, Medtronic would have to address all of the lots of the "old" formulation of Lioresal that would still be in various pharmacies and hospitals, as the old lots would no longer be compatible with the new pumps. In addition, the situation would be complicated by the fact that all of previously implanted patients would still have the previous (unmodified) pump type, which would not be compatible with the new formulation of Lioresal. Therefore, Medtronic would have to be very public about the transition, recall the lots of the "old" Lioresal formulation, and/or provide instructions to pharmacies and labeling to specify what formulation of Lioresal could go with what pump (old or new model). Considering the confusion this could create, I believe that this scenario is extremely unlikely.

Should it occur, however, this issue would be evident to CNS therapeutics, as it would be reflected in the labeling for both Lioresal and Medtronic's pump. Additionally, there would be a transition period during which the original formulation of the drug and existing (unmodified) pumps would remain on the market, which would allow adequate time for CNS therapeutics and CDER to take the appropriate course of action (if Gablofen became incompatible with a modified pump, the product would become misbranded). CDER asked CNS to address the issue of ensuring continued compatibility. CNS expressed its willingness to cooperate with the agency and conduct certain monitoring for changes to the formulation of Lioresal and/or changes to the SynchroMed pump.

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/s/

ERIC P BASTINGS
11/19/2010

Cross-Discipline Team Leader Review

Date	July 16, 2010
From	Eric Bastings, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-462
Applicant	CNS Therapeutics
Date of Submission	March 27, 2009
PDUFA Goal Date	April 27, 2010
Proprietary Name / Established (USAN) names	Baclofen Injection (intrathecal) (Gablofen)
Dosage forms / Strength	Intrathecal injection / 0.05 mg/ml, 0.5 mg/ml, 2.0 mg/ml (b) (4)
Proposed Indication(s)	Spasticity
Recommended:	*Approval for Gablofen 0.05 mg/ml, 0.5 mg/ml, 2.0 mg/ml;* (b) (4)

1. Introduction

Oral baclofen (10 and 20 mg) has been marketed for several decades in the United States for the treatment of spasticity, first under the tradename Lioresal, and later on as a generic. An intrathecal formulation of baclofen (Lioresal Intrathecal) was later developed for the management of severe spasticity, as a 0.05 mg/mL, 0.5 mg/mL, and 2 mg/mL solution. The Lioresal Intrathecal NDA (20-075) is owned by Medtronic, who also is the sponsor for one of the pump systems (SynchroMed) used for administration of the product. Another pump (Codman) is also approved for intrathecal administration of baclofen. No generic product has yet been approved for baclofen injection.

CNS Therapeutics submitted a 505 (b)(2) application for four concentrations of baclofen injection: 0.05 mg/mL, 0.5 mg/mL, 2 mg/mL (same as currently approved) (b) (4)

CNS Therapeutics is proposing the tradename Gablofen for their product, and I will use that name to describe CNS Therapeutics's baclofen for the rest of this document.

2. Background

A pre-IND meeting was held with CNS therapeutics on April 30, 2008. At that meeting, CMC, non clinical and clinical requirements for a 505(b)(2) applications were discussed. (b) (4)

(b) (4)

The division agreed that pharmacokinetic data would not be needed, and informed CNS therapeutics that if they intended 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, they 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).

3. CMC/Device

CMC

Dr. Akm Khairuzzaman conducted the CMC review.

Dr. Khairuzzaman notes that (b) (4) strengths (0.05 mg/ml, 0.5 mg/ml and 2 mg/ml) of Gablofen are qualitatively and quantitavely identical to that of reference product, Lioresal Injection (NDA 20-075). (b) (4)

(b) (4)

Importantly, Dr. Khairuzzaman notes that the Gablofen proposed pH specifications (5.5 to 7.0) are the same as those of Lioresal. Table 1, copied from Dr. Khairuzzaman's review, shows that the pH of samples of Lioresal (purchased by the sponsor) and Gablofen were essentially identical. I agree with Dr. Khairuzzaman. I also note that the Synchromed pump labeling also list as a contraindication "drug formulations with pH < 3", which I interpret as indicating that the pH of Gablofen is not a problem.

Table 1: Comparison of Lioresal and Gablofen

Test Date	Sample	Lot#	pH Results
7-16-2008	Lioresal® 0.5 mg/mL (10 mg/20 mL)	CS0058A	6.7 – 6.7
7-16-2008	Lioresal® 2 mg/mL (40 mg/20 mL)	DS0028	6.7 – 6.7
7-30-2008	Lioresal® 2 mg/mL (10 mg/5 mL)	BS0046	6.6 – 6.7
12-2-2008	CBL/CNS 0.05 mg/mL (50 mcg/1 mL)	2155-101	6.5 – 6.6
9-3-2008	CBL/CNS 0.5 mg/mL (10 mg/20 mL)	2118-101	6.4 – 6.5
(b) (4)			

Dr. Khairuzzaman also notes that the Gablofen osmolality specifications (b) (4) are slightly wider than those of Lioresal (b) (4). Dr. Khairuzzaman recommends that the osmolality range should comply with the actual physiological range of cerebrospinal fluid, but overall found the specifications acceptable. As CSF osmolality in normal subjects was reported as 283±20 mOsm/kg[1], and considering the low volume of drug infused over 24h, I believe that the differences in osmolality specifications (centered on the physiologic range for both products) between Gablofen and Lioresal are not clinically significant.

Dr. Khairuzzaman describes that a drug product-pump compatibility study was performed with the FDA approved pump systems for baclofen intrathecal injections: Johnson & Johnson Codman 3000 and Medtronic SynchroMed II. Dr. Khairuzzaman notes that the Codman 3000 pump was found to be incompatible, as the major degradation product (b) (4) increased significantly, as shown in Figure 1, copied from his review:

[1] Harrington et al. *Headache* 2006;46:1128-1135

(b) (4)

Dr. Khairuzzaman notes that Gablofen was found to be stable over six months in the Medtronic SynchroMed II pump. (b) (4)

He additionally notes that after the 180 day stability test in the pump, no leachates were identified at levels that were a concern.

(b) (4)

Dr. Khairuzzaman also discusses that a drug product-pump catheter (model 8711) compatibility study has been conducted in which three lots of catheters were exposed for 117 hours to two Gablofen formulations (0.5 mg/ml (b) (4)). The drug solution was tested for assay, pH, organic extractable and silicon. Dr. Khairuzzaman found the results of that test acceptable.

Dr. Khairuzzaman also recommended that the sponsor evaluate the physical stability of the drug product inside the pump/catheter under a flow condition that simulates actual use. (b) (4)

(b) (4)

Finally, the sponsor conducted a short term precipitation study of Gablofen 2 (b) (4) mg/ml with Infumorph 500 (25 mg/ml morphine) for 48 hours in a sterile glass container. Three lots of each products were examined. Analytical data showed no precipitation.

Dr. Khairuzzaman concludes that all strengths of Gablofen were stable for a period of 6 months into the pump to be used in actual clinical condition. Dr. Khairuzzaman notes that the

pump is approved for an implant life of 7 years or more and as a result, the stability data derived from a six month period of time (from the drug-pump compatibility study) may not be truly reflective of what could happen after several years once the pump has been implanted, as the pump environment may change over time.

Dr. Khairuzzaman further adds that there is some controversy on baclofen's aqueous solubility (precipitation occurs above 2 mg/ml concentration) that is reported in some literature, particularly a white paper published by Novartis/Medtronic. (b) (4)

(b) (4)

CDRH

Dr. Lana Shiu conducted the CDRH review. My discussion of her review is based on a review document dated September 29, 2009 and on several follow-up emails (dated 12/17/2009, 1/13/2010 and 4/5/2010).

Dr. Shiu notes that CNS' intention is to seek approval of Gablofen as a drug product, and not a drug-device combination product. Dr. Shiu also notes that Gablofen has a wider range osmolality of (b) (4) when compared to Lioresal's tighter range of osmolality ((b) (4)). Dr. Shiu emphasizes that solutions for intrathecal infusion are supposed to be isotonic to the CSF which has an osmolality of approximately 300 mOsmol/kg. Of note, base on a literature search, the physiologic CSF osmolality range is reported at 280-310 mOsmol/kg[2], and I found a study in healthy subjects in which the observed osmolality was 283±20 mOsm/kg[3]. Lioresal osmolality specifications, according to Dr. Khairuzzaman, are 280-300 mOsm/kg. Moreover, Ziconotide (NDA 21-060), another product "thoroughly tested by Medtronic" and listed in the Synchromed II labeling for use with that pump has a pH specification of 4-5, and does not have any osmolality specification. The Synchromed pump, according to Medtronic's specifications, is compatible with a pH of 4-8, which far exceeds the specifications of Gablofen (and Lioresal). In my opinion, the differences of osmolality specifications between Gablofen and Lioresal are not clinically significant.

Dr. Shiu discusses that Lioresal is a baclofen formulated specifically for the Medtronic SynchroMed Intrathecal Pump and that the maximum concentration that can be safely used [according to Medtronic] is 2mg/ml. Dr. Shiu believes that Gablofen may emulate the Lioresal baclofen at lower concentration strengths (b) (4)

Regarding the testing on products for intrathecal administration, Dr. Shiu discusses that *"the fluid dynamics of the pump system, pump in combination with the catheter affect the location*

[2] Salvador et al. *Min Invas Neurosurg 2007; 50:51-55.*
[3] Harrington et al. *Headache* 2006;46:1128-1135

of the infusion solution and receptor solution interaction site. Depending on the fluid dynamics of the pump system and attached catheter the mixing site could occur in the following locations; in the lumen of the catheter, in the catheter outlet holes, and/or in the CSF space (receptor space). Understanding the chemistry/biochemistry at this mixing site is also critical. For intrathecal infusion, a physiologically significant change in pH or concentration between the fluid delivered by the infusion system and the receptor fluid (CSF) which could result in denaturation, adsorption and aggregation of available protein in the distal lumen of the catheter and around distal catheter ports. This has been observed from returned Medtronic SynchroMed Catheter device analysis. Analysis of dark material at the intrathecal end of the catheter lumen and infusion holes (ports) from returned product analysis showed CSF protein, beta trace and heme protein. In some cases it led to total occlusion of the intrathecal catheter, cessation of therapy and in the case of intrathecal baclofen, it can be life threatening/fatal because of withdrawal. Therefore it is critical to evaluate the chemistry/physiological biochemistry interactions of the infusate, the device, the catheter, and the biological interface (receptor solution, i.e. CSF) over the entire pathway of drug delivery from the device reservoir, through inner pump tubing, and finally to the intrathecal delivery site."

Dr Shiu believes that Gablofen drug-device compatibility testing was inadequate, for several reasons.

First, Dr. Shiu notes (in a 1/13/2010 email) that the testing provided by the sponsor was under static condition (with the drug in the reservoir for 6 months), which *"does not delineate whether this drug will have adverse interactions with the pump device"*. Dr. Shiu adds that *"there has to be actual flow of the drug through the pump in order to verify if any drug particles may clog the pump filter and if the high concentration of the drug will drive the permeation of ions across the pump silicone tubing to invade the gear assembly and corrode the gears over time. Corrosion of the gears will eventually stall the pump which can be fatal for the patient."*

The rationale for the need of actual pump flow is not entirely clear to me, as the static testing allowed for contact between the pump reservoir and Gablofen. Gablofen was stable under the conditions of testing for a duration of 6 months. The composition of the inner pump tubing which was not exposed to Gablofen during this stability testing is the same than that of the external catheter that connects to the pump, and that was the object of a separate testing (see CMC above), (b) (4), and a small difference in thickness (0.4 mm for the catheter vs. 0.3mm for the pump inner tubing). The catheter is also (b) (4). As Gablofen ingredients and specifications are very similar to those of Lioresal, the basis for a genuine concern regarding a different permeation of ions between Gablofen and Lioresal, or a differential compatibility between Gablofen and the external catheter versus the inner pump tubing is unclear to me, at least up to the 2mg/ml concentration. (b) (4).

Second, Dr. Shiu noted in a 12/17/2009 email that there are multiple catheters that can be used with the SynchroMed pump for intrathecal infusion, but the sponsor only tested one. Dr. Shiu

describes in that email that "*CNS only tested model 8711; Medtronic has additional catheter Models 8703, 8703W, 8709, 8731, 8709SC, 8731SC that can be used with Synchromed Pump. The catheter designs are 1 or 2 piece segments and also vary from single end hole (open tip) to closed ends with side exit holes which will impact on the flow. The tips can also change from open tip to* (b) (4) *(90/10). Model 8703 is not marketed in the U.S. any longer but that does not mean there are not patients out there who are still implanted with this catheter. If the sponsor does not intend to test the other models of the Synchromed catheters then the labeling for this CNS Baclofen should be very clear and specific in that only 8711 can be used with the drug and the other catheters are not to be used with the CNS baclofen because their safety and efficacy has not been evaluated with this particular drug".*

As the material for these various catheters is identical (silicone), the rationale for testing each of them is unclear to me.

Third, Dr. Shiu notes that intrathecal pumps can stay implanted in the body up to 7 years, but that the testing done by CNS was much shorter. Dr. Shiu notes that *"many adverse interactions have identified when unknown drugs have been filled into the pump and upsets the delicate balance leading to fatal events … These adverse interactions between the drug and the device may not be apparent at the beginning of its use but could be seen as the device nears its longevity mark but the clinical effect on the patient from the malfunction is catastrophic nevertheless. Thus, CNS Baclofen must be able to submit its own stand-alone safety testing to ensure the safe and effective use of this drug product with the Medtronic SynchroMed pump over the lifetime of this device w/o basing its arguments on how similar this product is to Lioresal".* Similarly, Dr. Shiu notes that there is no data to show that prolonged infusion through the various Medtronic catheters does not leachables, degradants or particulate matter.

I disagree that the similarity between Gablofen and Lioresal should not be factor in deciding what compatibility testing should be required. It seems reasonable to me that if a new product has the same ingredients, same concentration, and the same or nearly identical pH specifications compared to a reference drug, the extent of studies needed to support the new product may be less than those needed for an entirely new product. In addition, the requirement for data covering the lifetime of the pump appears impracticable to me. For chronically administered drugs, it is typical to extrapolate safety data from a limited but practical duration of use (typically up to 1 year) to support chronic use. It is recognized that some safety issues with late onset may not be identified by such testing, but it is generally accepted that on practical standpoint, a compromise must be made between the extent of safety data available at the time of approval and the duration of development program for new products.

Fourth, Dr. Shiu notes that the sponsor studied only simulated CSF in vitro, which could not get to the root of the problem of protein aggregation (in the distal catheter or at the catheter end) if the study did not include also in-vivo testing in an appropriate animal model (preferably sheep) of long enough duration with actual dynamic flow to simulate the fluid dynamics of the drug through the whole device system. (b) (4)

(b) (4)

Fifth, Dr. Shiu believes that as Lioresal is supplied in refill kits specifically designed for refill with the SynchroMed System, the refill kit should be thoroughly tested with the CNS baclofen in terms of compatibility as well as reliability of the (b) (4) Needle insertion into the pumps port. Dr. Shiu is concerned about coring (embolism of the core into CSF flow) and leaking over the life time of the pump. That concern is valid. (b) (4) The approach adopted by CNS therapeutics for pump refills is, in my opinion, satisfactory.

Sixth, Dr. Shiu commented on the issue of intrathecal masses (further discussed below), and noted that recent literature suggests that these masses may represent concentrated baclofen unable to adequately mix with CSF flow, leading to precipitation at the catheter tip. Dr. Shiu further notes that Novartis did explain in a "white paper" that higher concentrations of Lioresal (3 and 4 mg/ml) form precipitates over time, which may lead to inaccurate dosing or potential clogging of the pump filter by precipitate. She adds that Novartis stated in a meeting that highly concentrated compounded baclofen into the lower thoracic or lumbar spine does not mix well with CSF because the of relatively stagnant flow in this area, which can result in drug precipitate/drug mass at the catheter tip.

I agree that *in vitro* testing can not address the issue of drug precipitation in the CSF or at the catheter tip, and that in vivo data are needed to address the issue. Also, I agree that 28-day studies (as conducted by CNS therapeutics) appear too short to adequately assess the issue. I am not convinced that 3-month non clinical studies would by themselves be entirely sufficient to rule out formation of such precipitates with long term use, as I am not aware of good data regarding the timing of development of these drug precipitates. (b) (4) . At the best of my knowledge, available post-marketing clinical data from compounded baclofen used with the intrathecal pump are insufficient to address the issue, as I can not judge the extent of such compounding, and I expect a vast under-reporting of problems with a compounded preparation (among other reasons because of a risk of liability for prescribers).

Dr. Shiu concludes that CNS Therapeutics has not adequately demonstrated that their formulation of baclofen (b) (4) can be used safely and effectively with the Medtronic SynchroMed Pump and the various catheters through longevity of the pump (approximately 7 years). Dr. Shiu believes that to support the safety and efficacy of the drug to be used with the pump, animal as well as human clinical data will be needed.

(b) (4)

Also, the basis for further testing (e.g. under flow conditions) in order to support the 0.5mg/ml and 2mg/ml formulation is not clear to me.

(b) (4)

Because of the risks that Medtronic would be taking on as the pump manufacturer if CNS' baclofen comes to market (since it is only compatible with the SynchroMed pump), Dr. Shiu believes that CNS therapeutics should contact Medtronic to allow Gablofen to be indicated for use with the SynchroMed pump. Dr. Shiu also believes that in order to ensure the safe use of Gablofen with the SynchroMed intrathecal pump, CNS therapeutics and Medtronic will have to work together to resolve labeling discrepancies so that Gablofen can be cross-labeled with the SynchroMed pump. I agree that a collaboration between CNS therapeutics and Medtronics may address most of the issues described above; however, it is also understood that the companies are commercial competitors, and that reference listed drug NDA holders are under no obligation to collaborate with sponsors of generic drugs, and probably generally have an incentive not to. FDA has no authority to require such collaboration.

Finally, Dr. Shiu notes that CNS Baclofen was not stable with the Codman Pump but stable in the SynchroMed pump. However, Dr. Shiu observes that the label does not have any warning for the CNS Baclofen not to use the Codman pump. I believe that this can be addressed by labeling.

As discussed below, (b) (4) the OND review team (DNP and CMC) considered approval of the 2 mg/ml formulation and 0.5mg/ml formulation (b) (4).

In a follow-up memorandum (3/31/2010), Dr Shiu expressed the following additional concerns regarding the 2 mg/ml and 0.5mg/ml dosage strengths:

"If Gablofen and Lioresal are identical in terms of pH, concentration, and excipients then their permeation properties along the fluid path could be similar. However, at this point, we do not have data on the effect of manufacturing residual chemicals that may cause a different permeation profile of the drug in the along the fluid path including internal pump tubing. To this date, the sponsor has only provided test data on one particular intrathecal catheter under static conditions but no dynamic testing with the actual drug flowing in all of the fluid path. They have only tested one catheter model instead of providing tests for all of the possible

catheter models based on their reasoning that all catheters are of the same length and are made of silicone. However, what the sponsor has not taken into account is that the tip of the catheters are designed differently with open-end vs. many side holes which can impact on the fluid dynamics of the drug flow thus ultimately impacting on the interaction of the drug to CSF boundary layer creating varying protein adhesions to the catheter.

Whether Gablofen formulations will lead to higher protein deposition has not been investigated by the sponsor and there are no long term testing performed using the drug with the pump.

At this time, we have no information on how the Gablofen will interact in the CSF because the sponsor only provided minimal testing in artificial CSF which is inadequate. (See CDRH Comments from January 23, 2010) Limitations of testing using this technique are: the simulated CSF is an electrolyte solution without proteins; the lack of complex in-vivo fluid dynamics; lack of a full compliment of CSF constituents which can vary based on the location of the catheter tip within the neuraxis; and the lack of interaction of the catheter tip with subarachnoid anatomical structures such as meninges, spinal nerve roots, and dentate ligaments that may affect CSF flow as well as the local chemical environment in proximity to the catheter tip.

Public data in the form of white papers show: Certain drugs form neutral ion pairs which can permeate through the internal pump tubing to corrode the pump gears causing pump stalls thus resulting in under-dosing of baclofen which can potentially lead to fatal Baclofen Withdraw Syndrome. To clearly understand the drug's long term effect on the pump, Medtronic performs numerous proprietary tests in which contact with drug to help determine the infusion system survivability/durability/reliability."

Therefore, Dr. Shiu recommended the following:

"Medtronic Synchromed Pump can stay implanted in the body for over 7 years and at this time Gablofen sponsor has not provided adequate test protocol or test data to show that the new drug up to 2 mg/ml (although very similar to Lioresal) is completely compatible with the implanted pump over the life time of the device and does not cause device failures. Medtronic has developed many proprietary tests over the last 20+ years to ensure that indicated drugs developed by their pharmaceutical partners for the Synchromed pump undergo rigorous testing to ensure compatibility and reliability. Gablofen's sponsor would have to either design their own comparable validated test methods or they need to send their drug product to Medtronic to be tested thoroughly with the device. Since the Gablofen sponsor has no binding agreement with the Medtronic pump manufacturer then any minor changes in the materials or design of the pump could lead to severe adverse events in the patients receiving Gablofen due to drug/device incompatibility resulting in public health safety issues.

Baclofen has a narrow therapeutic range where pumps stalls or catheter occlusions from drug/device incompatibility can result in patient mortality from Baclofen Withdrawal Syndrome. Thus, I believe it is in the best interest of the public health that the drug sponsor collaborates with the device manufacturer in testing during pre and post approval to assure continued safe and effective use of the drug in the delivery device."

The concerns expressed by Dr. Shiu in the 3/30/2010 memorandum are similar to those expressed in earlier documents. Considering the identical ingredients and similar pH specifications of Lioresal and Gablofen, the division was not convinced that any additional testing is needed to support approval of Gablofen 2 mg/ml and 0.5mg/ml, and further discussions with CDRH ensued.

Dr. Anthony Watson, provided final CDRH recommendations in a 4/16/2010 memorandum. In that memo, Dr. Watson expresses a concern that there is not *"enough information on the performance of the device with the drug showing reasonable safety and effectiveness. Specifically, we do not have enough information to say that Gablofen will not perform differently than Lioresal in the device over time."*

Dr. Watson provided the following updated recommendations:

Labeling

- *For the purposes of approving a stand-alone PMA, without a concurrent NDA submission, we require device labels to conform to the currently approved drug label of interest. This is of special significance, given that the labeling for SynchroMed pumps specifically state that Lioresal (intrathecal baclofen) is the only drug to be delivered for the treatment of chronic spasticity. Further, the product labeling clearly states that users should not deliver other drugs through the device than the ones identified.*
- *Our recommendation is also based on our experience that some drugs used in devices cleared through the 510(k) process (i.e. analogous to generic device) are in fact incompatible with the drug even though the device has used similar drugs without problems. For example, in 2008, Cardinal Health had submitted a 510(k) for the ReadyMed Elastomeric Infusion Pump,* (b) (4) *. CDRH noted that the drug manufacturer Cubist Pharmaceuticals (manufacturers of Cubicin (daptomycin for injection)) had issued a safety alert in 2008 stating that Cubicin interacted with pump's, drug fluid pathway to release an impurity, 2-mercaptobenzothiazole (MBT). Cubist Pharmaceuticals stated that cutaneous exposure to MBT has been associated with dermal sensitization, and chronic administration of MBT to laboratory rodents has been associated with an increased risk of certain tumors. As FDA has not received other safety alerts like this and Cubicin is one of many other antibiotics used in this device, this data further supports that each drug is unique with respect to the drug/device interaction.*
- *In addition, CNS Therapeutics has tested the stability of Gablofen through Codman's implantable infusion pump and determined that the drug was not stable at 1 month. In review of Codman's PMA, P890055, the drug Lioresal was tested in the Codman pump and approved for use. This suggests that there may be slight differences between Gablofen and Lioresal that could result in serious adverse events.*

Bench Data

- *We would expect the sponsor to provide an in-use stability test at 37C while the pump system (e.g., pump and catheter(s)) is being used under the expected flow rates with the proposed drug concentration(s). Samples of the solution that are collected from the effluent at various time points under these conditions should be analyzed for Assay, Impurities/Degradants, and Leachables, Sterility, Endotoxins, and Foreign Particulates.*
- *The duration of the in-use study should be commensurate with the expected range of time the drug solution is expected to be present in the pump. This should be cycled with at least one or two refills of the pump. The purpose of including multiple refill cycles into the evaluation is to assess the potential for cumulative levels of impurities/degradants and the risk for leakage of these degradants to the patient over the use-life of the pump system.*
- *The test report will assess any risks associated with interaction of impurities/degradants with the pump in use (e.g., adsorption of impurities/degradants and impairment of the pump performance and function, and/or conversion of the degradants to other chemical species).*
- *Extractable/Leachables and Impurities/Degradants should be sufficiently characterized and assessed as per ICH Q3B(R).*

Animal Data
If the Extractable/Leachable or Impurity/Degradant levels exceed ICH Q3B thresholds, animal data will be required to qualify the safety of the drug/pump combination.

Post-Approval Study
We would expect to see a post-approval study (PAS) to assess the long-term affects of drug/device interaction throughout the entire life of the pump system (i.e., 8 or more years). The PAS will include protocols for an in-vitro, in-use stability study, (e.g., using the highest and lowest flow rates) over refills of the pump for the intended use period, which can be eight or more years. The protocol will characterize the long-term profile of extractable/leachable and impurities/degradants and will address any impairment of pump system function. Sampling should occur at the end of each refill cycle, or once per year.

Manufacturing Quality
In addition to the scientific data requirements, one aspect of particular importance for safety is manufacture of the device and drug products and potential post-approval modifications. Additionally, it is also our experience from observing the adverse events reports from the use of compounded drugs that are supposed to be similar to the approved drugs for use in the pump that they can have a profound impact on performance, causing the pump to fail. Although we do not always have direct evidence that the drug quality is at fault, it is the most likely conclusion. We can only conclude that some of the ingredients or components used in the preparation of the drug might be different somehow. Knowing that Medtronic has reported to us how well they maintain tight control over the supply chain of all of their components, including the drug components, it seems to us that supply chain management is particularly important and that agreements between the device and drug sponsors are important to ensure safe and effective combinations.

Additional meetings between CDRH, CDER/OND, OCC and OCP were held between May and early July 2010. No alignment was reached between the centers up to this day (July 16, 2010). CDRH final recommendations are pending. My opinion at this time is that no additional testing should be required to support approval of Gablofen at doses up to 2mg/ml. (b) (4)

(b) (4)

4. Nonclinical Pharmacology/Toxicology

Dr. D. Charles Thompson conducted the non clinical pharmacology/toxicology review. Dr. Thompson is recommending approval provided CMC quality and stability standards have been met. Dr. Thompson discusses that the proposed limit of NMT (b) (4) exceeds the ICH qualification threshold, but notes that this issue has subsequently been adequately addressed to the satisfaction of CMC reviewers.

Dr. Thompson notes that the sponsor conducted the following studies:

- 069-001: "Maximum Tolerated Dose (MTD) Toxicity Study of Baclofen Via Continuous Intrathecal Administration in Beagle Dogs"
- 069-002: "28-Day Safety Study of Baclofen Via Continuous Intrathecal Lumbar Administration in Beagle Dogs"
- 069-003: "28-Day Safety Study of High Concentration Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs"
- 069-004: "28-Day Safety Study of High Concentration Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs".

Dr. Thompson notes that the reason stated by CNS therapeutics for conducting three separate 28-day dog studies is that pyogranulomatous inflammation was observed in all dose groups of the first two studies (including vehicle and untreated device controls) at a high incidence (~50%). For that reason, the sponsor tested a different intrathecal catheter system in each of the three 28-day studies, connected to an external syringe pump (and not to an implanted pump as proposed for clinical use). This means that the non clinical data have not been generated utilizing either the Medtronic Synchromed II pump or the Medtronic Indura IT catheter (model 8711) proposed for clinical administration of Gablofen.

I will briefly discuss the key results of the 28-day studies, as described by Dr. Thompson:

In the first study **(**069-002), dogs either received 0.9% saline, Gablofen 2mg/ml (reportedly at the rate used in studies supporting approval of Lioresal), Gablofen 4mg/ml (at half the infusion rate of the 2mg/ml dose), and catheter alone. Dr. Thompson notes pyogranulomatous inflammation at the catheter tip in all groups, including the catheter controls. I reproduce below (Table 2) a table copied from Dr. Thompson's review, that summarizes the granulomatous inflammation findings in Study 069-002:

Table 2: Lesions at the catheter tip in Study 069-002

Incidence and Severity of Pyogranulomatous Lesions at the Catheter Tip

Study Group/Sex	Test/Control Article	Dose mg/day (Concentration)	Pyogranulomatous Lesion at Catheter Tip Incidence and Severity (number of animals)				
			none	minimal	mild	moderate	severe
1/M	Vehicle	0 (0 mg/mL)	3		1		
1/F	Vehicle	0 (0 mg/mL)	1		1	1	1
2/M	IT baclofen	2 (2 mg/mL)	1			1	2
2/F	IT baclofen	2 (2 mg/mL)	1	1	1		1
3/M	IT baclofen	2 (4 mg/mL)		1	1		2
3/F	IT baclofen	2 (4 mg/mL)			2	2	
4/M	Device control	-	1				1
4/F	Device control	-		1			1

In the second 28-day study (069-003), dogs either received 0.9% saline, Gablofen 2mg/ml, Gablofen 4mg/ml (half rate), Lioresal 2 mg/ml, or device placement with no infusion. Again, pyogranulomatous inflammation at the catheter tip was present in all groups, including the catheter controls. Table 3, copied from Dr. Thompson's review, summarizes the findings:

Table 3: Lesions at the catheter tip in Study 069-003

Summary of Microscopic Findings: Pyogranulomatous Inflammation (CT)*

		Group 1		Group 2		Group 3		Group 4		Group 5	
Spinal Cord Section	Sex	Inc	Avg Severity	Inc	Avg Severity	Inc	Avg Severity	Inc	Avg Severity	Inc	Avg Severity
Catheter Tip	M	4/4	3.75	2/4	1.75	3/4	2.25	2/2	3.00	1/1	5.00
	F	2/4	1.75	1/4	0.25	3/4	2.25	2/2	4.50	1/1	5.00
Caudal to Cath Tip	M	2/4	1.50	1/4	1.00	1/4	0.75	1/2	1.50	-	-
	F	1/4	1.25	1/4	0.25	-	-	1/2	2.50	-	-
Cauda Equina	M	1/4	1.00	1/4	1.00	-	-	-	-	-	-
	F	-	-	-	-	-	-	-	-	-	-

* Inc = incidence; - = not observed; Average severity = 5.00 maximum

Group 1 = vehicle; Group 2 = Gablofen 2mg/ml; Group 3 = Gablofen 4mg/ml (half rate); Group 4 = Lioresal 2mg/ml; Group 5 = device control.

In the third 28-day study (069-004), dogs either received 0.9% saline, baclofen 2mg/ml, baclofen 4mg/ml (half rate), Lioresal 2 mg/ml, or device placement with no infusion[4]. Again,

[4] Not examined microscopically

the incidence of pyogranulomatous inflammation was similar across groups. Dr. Thompson created the following table from the study results:

Table 4: Lesions at the catheter tip in Study 069-004

Summary of Microscopic Findings: Pyogranulomatous Inflammation (CT)*

		Group 1		Group 2		Group 3		Group 4	
Cord Section		**Inc**	**Avg Severity**	**Inc**	**Avg Severity**	**Inc**	**Avg Severity**	**Inc**	**Avg Severity**
Catheter Tip	M	1/4	1.25	2/4	2.25	1/4	0.75	0/4	-
	F	1/4	0.75	1/4	0.75	1/4	0.50	0/4	-
Catheter Insertion Point	M	0/4	-	0/4	-	1/4	0.75	0/4	-
	F	0/4	-	2/4	1.5	0/4	-	0/4	-
Cauda Equina	M	0/4	-	0/4	-	0/4	-	0/4	-
	F	0/4	-	0/4	-	0/4	-	0/4	-

* Inc = incidence; - = not observed; Average severity = 5.00 maximum
Group 1 = vehicle; Group 2 = Gablofen 2mg/ml; Group 3 = Gablofen 4mg/ml (half rate); Group 4 = Lioresal 2mg/ml; device control (Group 5) was not examined microscopically in this study.

Finally, Dr. Thompson notes that drug precipitation was not reported at necropsy in any these studies. Table 5, copied from Dr. Thompson's review, summarize the catheter sizes and compares beagle dogs and human spinal anatomy.

Table 5: Comparison of beagle dogs and human spinal anatomy

	Beagle	Human
Average Spinal Canal Diameter	0.8 cm	1.0 cm
Area	48 mm2	75 mm2
Average Subarachnoid Space	1 mm	2.5 mm
Medtronic Catheter (O.D./I.D.)	---	1.4/0.53 mm
Sims Deltec (dog study catheter) (O.D./I.D.)		---
Study 069-002	0.9/0.5 mm	
Study 069-003	1.0/0.38 mm	
Study 069-004	0.9/0.5 mm	
Catheter ratio (size relative to space)*	1.1	1.7

*Dog study represents worst case due to smaller relative space

Dr. Thompson identifies a number of limitations of the studies: 1) the dose range-finding study was inadequate based on inclusion of only two male animals and absence of any control group; 2) the dose groups and the numbers of animals was not uniform across the three 28-day studies, such as an RLD-dosed group being absent in the first 28-day study (069-002), present with only 2 dogs/sex in the second study (069-003), and present with 4 dogs/sex in the third study (069-004); 3) only spinal cord tissue was examined; 4) the 28-day study duration was sub-optimal based on current state of the science for a chronic IT dog study; 5) a 'Device Control' group was only included in the first two studies as an afterthought, by protocol amendment, while such a 'Device Control' group was included by original protocol design in

the third study (069-004), but then the spinal cord tissue from these animals was not even examined microscopically; and 6) adequate sampling to conduct a thorough kinetic analysis of baclofen levels in CSF, or even plasma, was not included in any of the studies. Despite these limitations, Dr. Thompson concludes that "it a reasonable interpretation of the reported study data that there is no meaningful difference between the two in this regard [regarding neurotoxicity] ". Dr. Thompson also comments that the reported analyses of plasma baclofen levels, across all three studies, appear to indicate that levels are comparable among all drug-treated groups after both 24 hours and 28 days of continuous infusion.

Dr. Thompson concludes that taken as a whole, the nonclinical data package is deficient in providing positive assurance of safety for the specific proposed drug product formulation and drug infusion system combination product. However, the submitted nonclinical data do appear to support a conclusion that there is no meaningful difference in biological response within the intrathecal space of the dog chronically administered either the RLD or the proposed drug product formulation. Dr. Thompson adds that "therefore, provided CMC review determines the proposed drug product quality and stability to be acceptable, this reviewer has no objections from a nonclinical perspective with a clinical review team decision in favor of approval."

Dr. Freed, supervisory pharmacologist, is concerned that the potential toxicity of the highest concentration of IT baclofen, 4 mg/mL, has not been adequately characterized, because the pivotal 28-day IT study in dog (Study #069-004) is not of adequate duration and did not test the clinical delivery system. Dr. Freed notes that large animal models have been demonstrated to be more sensitive to morphine-induced granuloma formation at the catheter tip than humans, but there are no data to suggest a similar interspecies difference for baclofen, since baclofen-induced granulomas have not been definitively detected in either animals or humans.

(b) (4)

5. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology/biopharmaceutics information in this (505)(b)(2) application.

6. Clinical Microbiology

Denise Miller conducted the clinical microbiology review, and is recommending approval from a quality microbiology standpoint.

7. Clinical/Statistical- Efficacy

There was no new efficacy information in this (505)(b)(2) application. The application relies of FDA's prior finding of efficacy of intrathecal baclofen, and proposes to use the same total daily dose.

(b) (4)

8. Safety

The sponsor did not conduct any new clinical trial, and is proposing to largely rely on the prior finding of safety of intrathecal baclofen by the Agency.

This application however includes a higher concentration dosage strength (4mg/ml), which poses unique safety issues, that are discussed under section 3 (CMC and CDRH) and section 11 (Medtronic white papers). Briefly, there are two concerns related to the higher concentration of baclofen: a potential for increased local toxicity at the site of infusion, and a possibility of precipitation of the drug, either in the pump, or at the site of intrathecal infusion.

Local toxicity

A theoretical potential for increased local toxicity does exist if tissues at the site of infusion are exposed to a higher concentration of drug. (b) (4)

Drug precipitation

As discussed above in the CMC/Device review section, and below in the Medtronic's white papers summary, Medtronic believes that concentration of baclofen higher than 2mg/ml will lead to drug precipitation, and possible occlusion of the pump filter. (b) (4) While 28-day animal studies did not identify any case of catheter occlusion, the short duration of the study is unable to assess a possible progressive narrowing

of the catheter due to local precipitation of Gablofen in contact with the CSF. (b) (4)

9. Advisory Committee Meeting

No advisory meeting was held for this 505(b)(2) application.

10. Pediatrics

PREA is not triggered by this 505(b)(2) application.

11. Other Relevant Regulatory Issues

Office of Combination Policy and Office of Chief Counsel opinion
Because this product is administered intrathecally through an implanted pump, the office of combination policy (Dr. Patricia Love) participated to the review of this product.

OCP made the following comments documented in a January 13, 2010 internal meeting minutes document:

- "Lioresal Intrathecal (baclofen) is considered as a combination product that inadvertently has one-way labeling with the SynchroMed pump. Specifically, Lioresal 2-mg/ml (the only currently approved baclofen) is approved for use only in pumps specifically approved for use with Lioresal. The SynchroMed pump is only approved for use with Lioresal. The SynchroMed pump labeling states that the maximum concentration of Lioresal in the pump is 2-mg/ml; and it contains express warnings against using other baclofen formulations because of the clinical adverse events and device malfunction at higher concentrations".

(b) (4)

- "It is possible that Medtronic could make changes to its pump in the future that render the pump unsafe and/or ineffective with Gablofen. Since there is no business

agreement between the CNS Therapeutics and Medtronic, Medtronic does not have to inform CNS of the changes to their pumps. The incompatibility between the revised pumps and Gablofen could cause serious injury to the patients."

- "Medtronic reported that the numbers of adverse events associated with the compounded drugs is increasing. In addition, it is crucial to be sure Gablofen can be used safely and effectively in the SynchroMed pump and that users can clearly understand how each drug (CNS Therapeutics' Gablofen (b) (4) vs. Medtronic Lioresal at 2-mg/ml) is to be used with the SynchroMed pump. (For example, it would be important to avoid labeling confusion that would cause a user to be uncertain and therefore select a compounded drug or a different incompatible pump)."
- "The technology and assay methodology expertise to ensure use of the appropriate testing to demonstrate compatibility of the drug in the pump resides with Medtronic's and not CNS."
- "Since the two labels are inconsistent, how would a user know which label to follow? How might a hospital purchasing department respond? For example, might the Hospital order a different pump that is not compatible with Gablofen and thereby make the wrong pump available to the Hospital? Could an end-user prescribe the wrong pump because of the label differences?"
- "What if Medtronic's updated its label to warn/contraindicate the use of their device with Gablofen and provide data to support their claim? This would create an untenable situation. We need both labels to be clear and to avoid misleading information."

OCP meeting minutes (b) (4) final recommendations regarding these various issues:

(b) (4)

2. OCP, based on current information, recommends that the labeling for Gablofen and the SynchroMed pump should be consistent for the safety and effectiveness reasons discussed above. The requirement of labeling consistency does not necessarily mean that the product meets the definition of a combination product in the context of mutually conforming labeling.

Finally OCP recommended the following steps:

(b) (4)

Determine if CNS has a mechanism in place for detecting the changes to the SynchroMed pump

- Determine if the labeling inconsistencies could be reasonably addressed in one label (Gablofen) or whether more specific cross-labeling is needed to protect the public health by minimizing inconsistencies. For example, in making the approvability determination of safety and effectiveness, consider whether the proposed labeling or reasonable modification is sufficient

- If concerns about undue user confusion persist that could resolved with without SynchroMed relabeling, then the centers could consider whether a Human Factors/User comprehension study would be of benefit to address outstanding concerns.

(b) (4)

We asked CNS therapeutics to address the concern of ensuring continued compatibility of Gablofen with the Synchromed pump. CNS therapeutics noted that "*it is very unlikely that the PMA holder, Medtronic, would modify the SynchroMed pump to a configuration that was not compatible with the current Lioresal formulation (which is the same as, and is expected to be interchangeable with CNS' formulation), due to safety concerns and consequent liability concerns. These factors lead to the conclusion that were any such change in the pump to be made it would be accompanied by prominent labeling and warnings to avoid inadvertent use of incompatible products."* CNS therapeutics adds that *"in the event that Medtronic intended to make changes to the SynchroMed pump that could affect compatibility, Medtronic would be required to file a prior approval supplement (l80-Day Supplement) to its approved PMA. The supplement would need to include data confirming that the modified pump remains compatible with the drugs which it is approved to deliver, including Lioresal, and would result in a labeling change for the pump. Since the formulation of CNS's generic concentrations of baclofen is identical to the formulation of the same concentrations of Lioresal, any compatibility data generated by Medtronic in support of a pump modification would also support the use of CNS' product in the modified pump."* As situation of concern to the division was that of a concurrent modification of the SynchroMed pump and reformulation of Lioresal. CNS however belies that this situation would be transparent the healthcare community, and CNS, and would *"afford the opportunity for CNS to take swift action to address potential safety issues. CNS believes that concurrent modification of the pump and reformulation of Lioresal is a highly unlikely scenario. However, if this were to occur, it would be evident in the labeling for both Lioresal and the SynchroMed pump. Additionally, there would be a transition period during which the original formulation of the drug and existing (unmodified) pumps would remain on the market. In the event that the reformulated drug product was not compatible with the existing pumps or if the modified pumps were not compatible with the original formulation of Lioresal, Medtronic would need to initiate recalls or send a letter to the medical community advising of these non-compatibilities. While this scenario would be consequential to CNS' Gablofen product, it would be transparent, and would afford CNS the opportunity to promptly take action to address any potential safety issues. Such action would be coordinated with the Agency and would be consistent with the action being taken by Medtronic. While we believe that the highly unlikely scenario described in this section would be very transparent to CNS, we will commit to monitor CDER and CDRH web sites for*

changes to the formulation of Lioresal and/or changes to the SynchroMed pump." I believe that the response of CNS therapeutics to the continued compatibility concern is acceptable.

(b) (4)

[redacted]

Medtronic "white papers"

Medtronic released white papers regarding three topics relevant to this 505(b)(2) application:

http://professional.medtronic.com/interventions/intrathecal-drug-delivery/clinical-outcomes/index.htm

1. Intrathecal Distal End Catheter Occlusions as a Result of pH & Salt Concentration Gradients Between Delivery Solution & Cerebrospinal Fluid (CSF)

In that white paper, Medtronic is claiming that they have "confirmed through engineering analyses that the use of indicated and nonindicated drug formulations can result in collection of protein in the catheter lumen, distal end. Although this may occur with any drug, nonindicated drug formulations can result in significant collection of material in the catheter lumen resulting in complete occlusion of the catheter, loss of patency, and therapy cessation. CSF proteins have been identified in returned catheters with occlusion at the distal end."

Of note, Gablofen is indirectly targeted by this white paper, as Medtronic adds that "Nonindicated formulations are not approved for use with the infusion systems. Use of nonindicated drugs or fluids may result in increased risks to the patient due to permanent damage to the catheter requiring surgical replacement and a loss or change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug under-dose. Nonindicated drug formulations include drugs not listed in the Indications labeling, admixtures, compounded drugs, and unapproved drug concentrations. Indications labeling is provided with the pump and catheter systems."

Medtronic provides as an mechanism for these occlusions that "Mixing of the drug and cerebrospinal fluid (CSF) normally occurs in and around the distal end of the intrathecal catheter. High salt concentration gradients and pH gradients between the drug and CSF in this mixing area can result in an environment that promotes more precipitation and aggregation of available proteins within the distal portion of the catheter, ultimately leading to complete occlusion of the distal catheter lumen and ports."

Medtronic also mentions in this paper that "The pH of lumbar CSF is 7.3,* and all drugs indicated for intrathecal infusion have a pH greater than pH 4.0."

Considering that the pH and osmolality specifications of Gablofen are very similar to those of Lioresal, I strongly doubt that the product differences between Gablofen and Lioresal could lead to this type of issue. No catheter occlusion was noted in non clinical studies conducted by CNS therapeutics. I agree, however, that it is certainly possible that compounded formulations may reach pH levels outside of the range of specifications of Gablofen or Lioresal, and therefore may possibly be subject to the risks described in this white paper.

2. SynchroMed® EL & SynchroMed II Pump Corrosion from Nonindicated Drug Formulations Resulting in Permanent Pump Stalls

In that white paper, Medtronic states that they have "confirmed through engineering analyses that the use of nonindicated drug formulations can compromise the performance of the SynchroMed® EL and SynchroMed® II infusion systems." Medtronic states that "corrosive agents originating from nonindicated drug formulations can permeate the pump tubing as neutral ion pairs between drug species and counter ion (e.g., chloride, sulfur). After permeating through the pump tubing, the neutral ion pair can dissociate and cause corrosion to the pump's internal components. Neutral ion pair formation can be caused by drug formulation conditions such as pH. Mixing drug solutions or compounding drugs are some of the mechanisms that can result in adjustments to the formulation pH. The concentration of ion pairs in solution is affected by (but not limited to) the following: additives, impurities, pH adjustments, and concentration adjustments."

Medtronic adds that "Labeled Lioresal® Intrathecal (baclofen injection) at formulation pH 6 is highly dissociated from the chloride ion (corrosive agent). At labeled formulation the permeation rate of chloride associated with drug is negligible over the life of the pump. If the pH is adjusted below the formulation pH (nonindicated), the formation of ion pairs with baclofen increases. The amount of permeation across the pump tube over the implant life of the pump increases as well. It is the chloride carried by baclofen that causes the pump corrosion." Again, considering the similarities between Gablofen and Lioresal, I do not believe that this issue applies to Gablofen. In addition, the material used for the internal tubing and all external catheters – silicone - is the same. Therefore, it is in my opinion reasonable to assume that compatibility testing of Gablofen with catheters applies to the internal tubing of the pump, and that corrosion of the pump is not expected for Gablofen. The problem is also apparently less of an issue with small molecules, and more frequent for peptides.

3. Solubility and Stability of Intrathecal Baclofen Solutions at High Concentrations: Implications for Chronic Use in the SynchroMed Infusion System

In that white paper, Medtronic states that "solubility and physical stability of 3 and 4mg/mL aqueous baclofen solutions were evaluated in a study undertaken by Novartis Pharmaceuticals Corporation, manufacturer of Lioresal Intrathecal (baclofen injection), to determine if a formulation of baclofen at concentrations higher than those commercially available is a safe, viable option for further development. The results of the study demonstrate that precipitation occurs in concentrations above 2mg/mL, independent of several variables evaluated in the study. Consequently, there are numerous unsubstantiated risks associated with formulation of

intrathecal baclofen above the commercially available 2mg/mL concentration. Of particular concern are the unknown risks associated with inaccurate dosing due to an altered concentration of the drug solution in the pump or potential clogging of the pump filter by precipitate. Given the unknown nature of these risks, use of intrathecal baclofen solution with SynchroMed® Programmable Drug Infusion Systems at concentrations higher than the commercially available 2mg/mL is unadvisable." The white paper describes CMC testing of 3 and 4mg/ml preparation, and states that "After 24 hours storage at room temperature and at 8°C, both the 3 and 4mg/mL concentrations started to form a small part of insoluble particulate matter, whereas a 2mg/mL control formulation manufactured in the same manner remained clear and free of particulate matter."

(b) (4)

12. Labeling

The proposed tradename, Gablofen, was found acceptable by DMEPA.

(b) (4)

Of note, the sponsor proposed specific language to address the Gablofen labeling contradiction with the Synchromed pump labeling regarding use of baclofen concentrations above 2mg/ml (this issue is also discussed above by OCP). Specifically, the Synchromed pump labeling states that it is approved for "The chronic intrathecal infusion of Lioresal Intrathecal (baclofen injection) in the management of severe spasticity. The maximum approved concentration is 2 mg/mL". The Medtronic white paper described above further adds that "use of intrathecal baclofen solution with SynchroMed® Programmable Drug Infusion Systems at concentrations higher than the commercially available 2mg/mL is unadvisable"

(b) (4)

(b) (4)

(b) (4)

13. Recommendations/Risk Benefit Assessment

I recommend approval of Gablofen up to a concentration of 2mg/ml.

(b) (4)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

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

/s/

ERIC P BASTINGS
07/16/2010