CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022462Orig1s000

OTHER REVIEW(S)

DRAFT

November 9, 2010 Supplemental Review Memo to Review Memos dated May 4, 2010, April 16, 2010 and July 12, 2010

The following supplemental memorandum finalizes CDRH's position regarding the drug / device stability testing for implanted infusion pump systems, based on the September 2, 2010, meeting among the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Office of Combination Products. This memorandum is an addendum to the previous CDRH consults dated April 16, 2010, May 4, 2010, and July 12, 2010, regarding this topic.

During the September 2, 2010, meeting and teleconference, CDER provided additional information to address CDRH's concerns regarding the manufacturing process and specifications for Gablofen. Specifically:

1) CDER stated the Sponsor's clarification that the solubilization time of Gablofen (b) (4) CDRH was originally concerned that Gablofen (b) (4) in order to achieve the necessary solubilization.

2) CDER demonstrated that the specifications of Gablofen, including pH, osmolality and impurity levels, while slightly wider than those for Lioresal, did not appear to present any additional risk in terms of use with implantable pumps using currently approved for use with Gablofen.

3) CDER demonstrated that minor differences in the Gablofen specifications are similar to observed lot-to-lot variability of Lioresal, which were based on the annual report from Medtronic dated on August 16, 2000 and July 26, 2001.

4) CDER demonstrated that the Sponsor had provided the tests of degradation product (b) (4) as well as all chromatography data in Gablofen, as well as Lioresal.

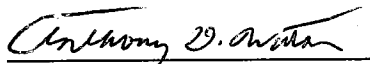
The basis for CDRH's requirement for additional testing was the lack of clear identity between Lioresal and Gablofen. Based on the updated information provided by CDER, CDRH believes the additional premarket and post market testing that we requested in previous memoranda is not necessary for the Gablofen product (up to the 2 mg/mL strength) because it appears that they are for all intents and purposes identical.

The following concerns are mine alone and are related to but separate and distinct from the aforementioned drug-device testing decision. I have several outstanding concerns that have not been addressed adequately at the time of this review. Some concerns relate to future changes to the device that might affect the drug and do not affect this version of the drug with the present version of the device. Specifically, my concerns are:

1. Medtronic has reported over 20,000 MDRs since 1986. Most of these MDRs do not have a root cause. Very few of the explanted pumps are actually returned because they are retained for litigation, discarded or otherwise destroyed during explantation. However, over the past 6 or 7 years, Medtronic has undertaken a series of actions to abate use of off-label drugs, including compounded drugs, in their pumps. These drugs, containing untested and often unknown formulations of drugs, cause various problems with the pumps resulting in pump failures. Although these problems appear to only be a result of compounded and off-label drugs, it speaks to the need for tight supply chain control. Since CNS and Medtronic do not have any business relationship, supply chain control is nonexistent.

2. Devices change materials frequently for a number of reasons (e.g., cost, usability, manufacturing efficiencies, etc.). Although most of these changes do not affect the drug, it would be shortsighted not to consider how to address possible changes to the device materials that could affect the drug. Since the drug sponsor and the device sponsor are not working together, there exists the real possibility that the device manufacturer makes a change to the device materials that would require a change to the drug formulation. This change would not be known to the Gablofen manufacturer but would be known to the Lioresal manufacturer because the device manufacturer owns the rights to Lioresal. Even if the drug changes would require a public change to the formulation, this would require the Gablofen manufacturer to find out through third-party channels, submit a formulation change, and await approval. In the meantime, an incompatible and possibly unsafe formulation of Gablofen would be used in the pump. I requested an answer to this issue during meetings on June 18, 2010, July 1, 2010 and September 2, 2010. No one from any of the Offices and Centers present, including (b) (5) OCP, and staff and managers from several CDER and CDRH offices, could adequately address this issue. Instead I was told that it was a postmarket issue that would be addressed at a later date.

   In a subsequent e-mail exchange with Dr. Eric Bastings of CDER, he further clarified to me that any such change to the formulation would result in a public recall of the existing formulation of Lioresal. Therefore, it would be known to CNS that they had to change the formulation of Gablofen. Although I can appreciate the public nature of this process, I am still not convinced that this method of notification is either efficient or adequate. In addition, this process appears to be speculative in how it will unfold. The timing of changes, in my opinion, is very undefined and ad hoc. Having said that, I am not certain anything other than tight supply chain control will alleviate my concern. Therefore, I will just note that my concern still stands and defer to my CDER colleagues who have faith in this process. I do not wish to delay a signed final memo any longer as CDER cannot take action without it.



Anthony D. Watson, BS, MS, MBA
Director
Division of Anesthesiology, General Hospital,
Infection Control, and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

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/s/

ERIC P BASTINGS

11/09/2010

This review is checked on behalf of Anthony Watson, from CDRH, who does not have access to DARRTS

Date:

September 13, 2010

To:

Anthony D. Watson
Director, Division of Anesthesiology, General Hospital,
Infection Control, and Dental Devices
Office of Device Evaluation

From:

Steven K. Pollack
Director
Office of Science and Engineering Laboratories

Dinesh Patwardhan
Director, Division of Chemistry and Materials Science
Office of Science and Engineering Laboratories

Ji Guo
Senior Staff Fellow
Division of Chemistry and Materials Science
Office of Science and Engineering Laboratories

Subject:

Equivalence of Gablofen and Liorasel

On September 2nd meeting, CDER addressed the following concerns from CDRH, regarding Gablofen manufacture and specifications.

1. CDER updated that solubilization time of baclofen in [redacted] (b) (4) This issue was cleared by a short consult of CDER to the sponsor.

2. CDRH agreed that the specifications of Gablofen, including pH, osmolality and impurity levels, while slightly wider than those for Liorasel, did not appear to present any additional risk in terms of use with implantable pumps using currently approved for use with Gablofen.

3. CDER demonstrated that minor differences in the Gablofen specifications are similar to observed lot-to-lot variability of Liorasel, which were based on the annual report from Medtronic dated on 8/16/2000 and 07/26/2001.

4. CDER indicated that they have requested the tests of degradation product [redacted] (b) (4), as well as all chromatography data and found Liorasel and gablofen to be equivalent based on this analysis

Per all the updated information from CDER, CDER has demonstrated that Gablofen is identical to that of Liorasel up to 2 mg/mL strength.

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/s/

ERIC P BASTINGS

09/13/2010

This review is checked on behalf of Steven K. Pollack, Dinesh Patwardhan, and Ji Guo, who do not have access to DARRTS.

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-462	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Gablofen Established/Proper Name: baclofen Dosage Form: intrathecal Strengths: 0.05 mg/ml, 0.5mg/ml, 2 mg/ml (b) (4)		
Applicant: CNS Therapeutics, Inc.		
Date of Receipt: 3/30/09		
PDUFA Goal Date: 4/30/10 (10mos+3 mos)	Action Goal Date (if different): DNP will target June 30, 2010	
Proposed Indication(s): Spasticity		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20-075 Lioresal	Clin Pharm, Non-Clinical, Clinical

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Proposed product is qualitatively and quantitatively identical to the referenced product for the lower dose strengths.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Lioresal (baclofen)	NDA 20-075	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new concentration (4mg/ml) of baclofen intrathecal formulation.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical*

compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☒ NO ☐

*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): generic tablets

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

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/s/

LANA Y CHEN
07/09/2010

ERIC P BASTINGS
07/13/2010

July 12, 2010 Supplemental Review Memo to Review Memos dated May 4, 2010 and April 16, 2010

The following supplemental memorandum is designed to further clarify CDRH's position regarding the drug / device stability testing for implanted infusion pump systems, which was stated in previous memoranda dated April 16, 2010 and May 4, 2010. During an intra-agency discussion on July 8, 2010, CDRH was asked to provide a rationale as to why additional drug / device stability testing was required for the Gablofen / SynchroMed II system. CDRH has provided this additional rationale, as well as further specified the premarket and postmarket testing for the Gablofen / SynchroMed II system.

Rationale for Requiring Drug / Device Stability Testing:

CDRH requires infusion pump manufacturers to demonstrate drug / device compatibility by performing a premarket assessment of the interaction between the "drug fluid pathway" within the device and the drug that is proposed to be delivered through the device. CDRH defines the "drug fluid pathway" delivery pathway for the drug, beginning at the drug reservoir and ending at the point of delivery into the patient (usually the distal tip of various implanted catheters). Additionally, CDRH requires implanted infusion pump sponsors to conduct postmarket surveillance and bench testing of the device to assess "real-time" drug stability over the device's operational lifecycle.

CDRH's review of the Medical Device Reports (MDRs) that have been submitted to the Center regarding external and implanted infusion pumps, and coupled with testing performed by implanted infusion pump manufacturers, suggest that there is an evolution of the drug delivery profile over several drug re-fill cycles. CDRH has also noted that implanted infusion pump manufacturers have recently submitted changes to the drug fluid pathway of their devices to mitigate corrosion, or degradation of the materials of construction due to observed interactions between the device and the drugs delivered through them.

CDRH has worked with CDER's Office of New Drugs and Quality Assurance (ONDQA) to develop the premarket drug / device stability testing requirement for device manufacturers.

In the case of CNS Therapeutics, the drug manufacturer is proposing to deliver its drug Gablofen (intrathecal baclofen) through the SynchroMed II implantable infusion pump system. SynchroMed II is specifically indicated to deliver Lioresal (intrathecal baclofen) based on extensive premarket and post market testing performed by the device manufacturer regarding the drug / device interaction between SynchroMed II and Lioresal.

A review of the drug / device interaction studies performed by CNS Therapeutics has revealed that the Sponsor performed the following drug stability testing with Gablofen and the SynchroMed II pump:

- (b) (4)
- Additional drug stability testing was performed on one lot of the 2 mg/mL and 0.5 mg/mL Gablofen products by loading each drug into a SynchroMed II pump for three months.
- The Sponsor performed a stability test between Gablofen and Medtronic's Indura Catheter (Model 8711) catheter by exposing the catheter for 117 hours (5 days) to the 0.5 mg/mL (b) (4) Gablofen products and then verifying that the drug meets the assay and pH specifications, as well as demonstrates the absence of organic leachables.

The drug stability testing performed by CNS Therapeutics does not adequately assess drug / device stability for the entire "drug fluid pathway" of the SynchroMed II pump. For this device, the drug fluid pathway includes:

1) the titanium drug reservoir
2) the internal tubing connected to the reservoir, that travels around the pump head (which provides the peristaltic action to drive the flow of therapy though the drug fluid pathway), and eventually connects to the catheter connection (which leads to the epidural catheter).
3) the catheter that is implanted into the patient.

Figures 1 and 2, below illustrate the drug fluid pathway. Figure 1, below, shows internal components of the SynchroMed II pump. The drug fluid pathway elements have been circled in Red. Figure 2 shows an assembled SynchroMed II pump with the attached epidural catheter.

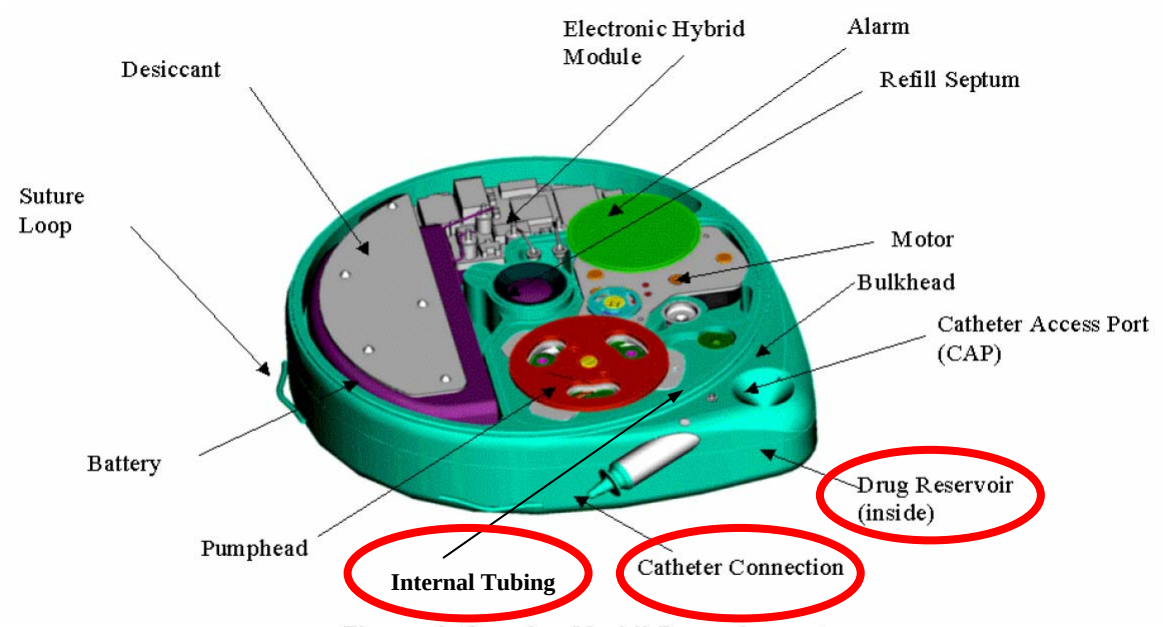


Figure 1. SynchroMed II Pump Layout

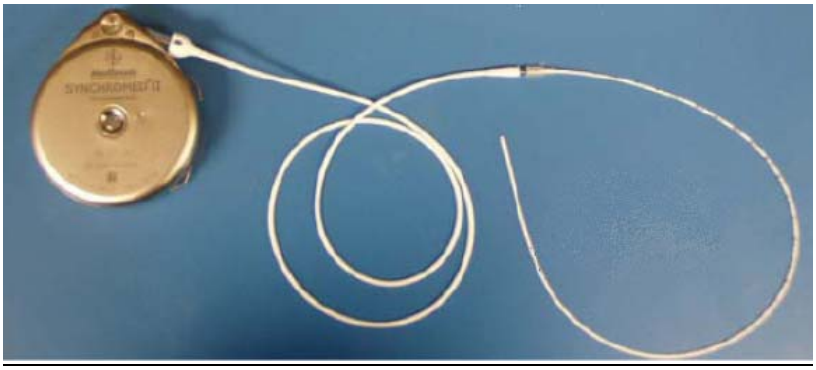


Figure 2. SynchroMed II Pump with Catheter

CDER has stated in several discussions that Gablofen is "identical" to Lioresal. CDRH noted that Gablofen is manufactured at a higher temperature than Lioresal, and also there are noteworthy differences between pH and osmolality between the two products. We questioned the "identical" nature of these two drug entities, if such differences (in the manufacturing process, or the chemical properties of the drugs) existed.

On July 1, 2010, CDRH asked CDER to provide a side by side comparison of two drugs, Gablofen (CNS Therapeutics) and Lioresal (Novartis Pharmaceutical), during the discussion of NDA 22-462 on July 1st. On July 9, 2010, CDER provided a document listing the specifications of Gablofen and Lioresal, prepared by CDER ONDQA, as shown below. The comparisons included batch data of pH, osmolality and impurities of two drugs.

Table 3. F.P. Actual data (pH and osmolality)

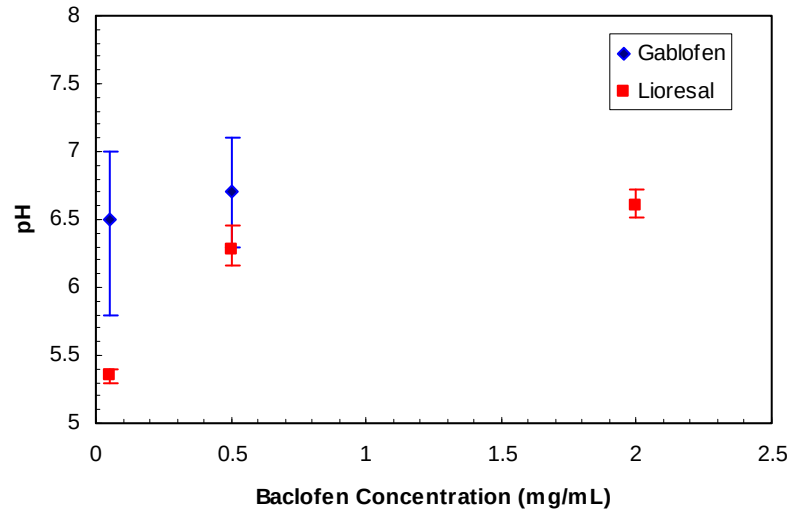
	CNS Products (3 Registration batches)	Lioresal (6 commercial batches)
pH		
0.05 mg/ml	**6.5** (median), n=28 (Range: 5.8-7.0)	5.3, 5.4, 5.4, 5.3, 5.3, 5.4 **Median: 5.35** (Range: 5.3-5.4)
0.5 mg/ml	**6.7** (median) n=38 (Range: 6.3-6.7)	6.1, 6.3, 6.3, 6.4 Median: **6.28** (Range: 6.1-6.4)
2 mg/ml	NT	6.7, 6.6, 6.7, 6.6, 6.6, 6.5 **Median: 6.61** (Range: 6.5-6.7)
		(b) (4)
Osmolality (mOsmol/kg)		
0.05 mg/ml	283 (median), n=100 (Range: 268-297)	287, 286, 286, 289, 289, 290 **Median: 287.8** (Range: 286-290)
0.5 mg/ml	282 (median), n=110 (Range: 266-309)	287, 289, 287, 291 **Median: 288.5** (Range: 287-291)
2 mg/ml	NT	296, 296, 297, 296, 297, 298 **Median: 296.6** (Range: 296-298)
		(b) (4)

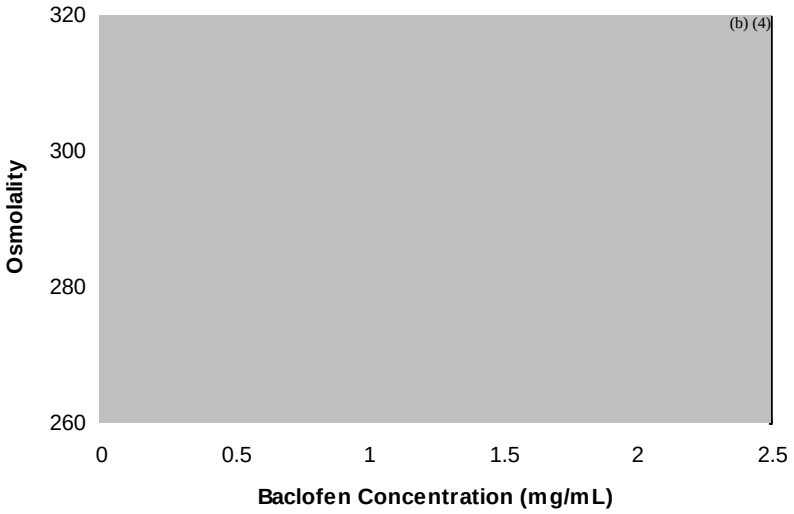
CDRH's Office of Science and Engineering Laboratories (OSEL) reviewed CDER's comparison and had the following observations:

1. Three batches of CNS products and 6 batches of Lioresal were summarized in Table 3. The pH and osmolality results for each batch of Lioresal were reported. However, no data for individual batch of Gablofen were presented; instead a median and range were provided. It is difficult to draw information on batch-to-batch variation from this limited data. In addition, it is unclear of the physical meaning of "n", which varies from 28 to 110.

   CDRH requests pH and osmolality results of each batch for Gablofen, including drug strength 2mg/mL.

2. The pH and osmolality for Gablofen and Lioresal were plotted below, using the data summarized in Table 3.





It is apparent that Lioresal has a very tight specification range for each drug formulation batch. However, the range of pH and osmolality of Gablofen is significantly larger than Lioresal. For example, the span of pH for Gablofen with strength of 0.05 mg/mL is 1.2 (from 5.8 to 7.0), compared to 0.1 (from 5.3 to 5.4) for Lioresal. The span of osmolality for Gablofen with strength of 0.05 mg/mL is 29, compared to 4 for Lioresal.

The pH specification range for Lioresal was set from 5.0 to 7.0, for the coverage of three drug dosages. In addition, the pH of Lioresal increased with increasing drug dosage. However, Gablofen did not demonstrate the same trend as Lioresal. These observations suggest an underlying difference between Gablofen and Lioresal. CDRH is concerned of possible pH & osmolality disparity of Gablofen from batch to batch or even within different parts in the same batch.

3. In the December 18, 2009, CMC review from CDER, CNS presented pH results of three Gablofen lots with strength 0.05 mg/mL, labeled as 2155-101, 2155-102 and 2155-103. On page 40, the pH values of these three lots were listed as 5.9, 5.9 and 5.8, respectively.

   However, the pH result of batch 2155-101 was reported as 6.5-6.6 on page 20.

   The pH values of these three lots reported in Table 3 were 5.8-7.0 as shown below.

0.05 mg/ml	**6.5** (median), n=28 (Range: 5.8-7.0)	5.3, 5.4, 5.4, 5.3, 5.3, 5.4 **Median: 5.35**

		(Range: 5.3-5.4)

CDRH requests additional information of batch data, to help us to understand why one batch of Gablofen has different pH values.

(b) (4)

The General Hospital Devices Branch, ODE, CDRH has also developed requirements for implantable drug pump systems with respect to evaluation of drug stability and compatibility. Our bench data requirements were developed through consultation with the Office of New Drug Quality Assessment (ONDQA) within CDER's Office of Pharmaceutical Science.

CDRH Recommendation

We recommend that the drug sponsor, CNS Therapeutics, provide the information outlined below. Our recommendations are based on our experience with implantable drug pumps. Without these data, we are unable to make a determination of reasonable safety and effectiveness. Without baseline data, it will be difficult to conclude that changes in the drug or device do not impact the safety and effectiveness of the device. These are long-term, permanent implant devices, and the cumulative exposure of device/drug needs to be addressed.

On April 16, 2010, GHDB submitted a review memorandum to the Office of Combination Products that updated the original recommendations from our September 29, 2009, review. Since April 16, 2010, CDRH has further clarified requirements for the testing that should be performed to establish a baseline performance of the drug in the pump and ensure that it does not adversely affect the performance of either the pump or the drug. Our updated recommendation regarding this testing is identified below:

Specific Questions Regarding Gablofen / Lioresal Comparison:

1) CDRH requests batch data for each lot of Gablofen and Lioresal that was tested to try to understand why there are discrepancies between various characteristics for these two drug products (such as pH and osmolality).

Bench Data

2) We would expect the sponsor to provide an in-use stability test at 37°C 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.
3) The duration of the in-use study should be commensurate with the expected range of time that the drug solution is expected to be present in the pump. Typically, CDRH would request 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. In this case, CDRH is willinging to modify our premarket data requirements in the following manner:
    a) The duration of this study should be 6 months because the refill cycle for this device is indicated for 6 months.
    b) The Sponsor should assess the in-use stability of the SynchroMed II pump using the highest indicated strength of Gablofen (2.0 mg/mL) and the lowest (0.5 mg/mL), and through each catheter that is indicated for use with the device.
    c) The Sponsor will not be required to perform a refill cycle as part of the pre-market assessment. CDRH's rationale for eliminating this requirement stems from the fact that the refill cycle criterion

was more recently developed through collaborative effort with CDER/ONDQA. This criterion was not in effect when the CDRH and CDER began their collaborative review of Gablofen. Secondly, CDRH believes that having a refill cycle at a time point less than typical refill cycle for the pump (i.e. refill at 3 months as opposed to 6 months) may not offer a long enough time period for impurities/degradants to accumulate. Thus, the test might not be effective in assessing the accumulated impurities/degradants in the reservoir.

4) 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).
5) Extractable/Leachables and Impurities/Degradants should be sufficiently characterized and assessed as per ICH Q3B(R).

Animal Data

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

Post-Approval Study

7) 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

8) 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.

_____

Anthony D. Watson, BS, MS, MBA
Director
Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices
Office of Device Evaluation
Center for Devices and Radiological Health

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/s/

ERIC P BASTINGS

07/12/2010

This review is checked on behalf of Anthony Watson, from CDRH, who does not have access to DARRTS.

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-462
APPLICANT	CNS Therapeutics, Incorporated
DRUG NAME	GABLOFEN (baclofen intrathecal injection)
SUBMISSION DATE	March 30, 2009
SEALD REVIEW DATE	April 26, 2010
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

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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

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/s/

DEBRA C BEITZELL
04/26/2010
SEALD comments sent to DNP on 4/26/10.

LAURIE B BURKE
04/26/2010

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH/ODE/DAGID/GHDB
Division: General Hospital Devices Branch
Mail Code: HF Z-480
Consulting Reviewer Name: Alan Stevens
Building/Room #: WO66 RM2561
Phone #: 301-796-6294
Fax #:
Email Address: Alan.Stevens@fda hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: HFD-120/ DNP
Mail Code: HFD-120
Requesting Reviewer Name: x_____ Eric Bastings, MD
Building/Room #: WO22, 4353
Phone#: 301-796-1056
Fax #:
Email Address: lana.chen@fda hhs.gov
RPM/CSO Name and Mail Code: Lana Y Chen HFD-120
Requesting Reviewer's Concurring Supervisor's Name: Eric Bastings, MD

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: _____

Requested Completion Date: 3/30/10

Submission/Application Number: NDA 22-462
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: March 27, 2009

Official Submission Due Date: NDA 10+3 mo goal date is 4/30/10

Name of Product: baclofen intrathecal

Name of Firm: CNS Therapeutics

Intended Use: Spasticity

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Please see NDA amendment dated January 28, 2010 and review as appropriate. Paper desk copies attached (2).

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary)

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

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/s/

LANA Y CHEN
02/18/2010

ERIC P BASTINGS
02/19/2010

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Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

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Center: CDRH/ODE/DAGID/GHDB
Division: General Hospital Devices Branch
Mail Code: HF Z-480
Consulting Reviewer Name: Alan Stevens
Building/Room #: WO66 RM2561
Phone #: 301-796-6294
Fax #:
Email Address: Alan.Stevens@fda hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: HFD-120/ DNP
Mail Code: HFD-120
Requesting Reviewer Name: x_____ Eric Bastings, MD
Building/Room #: WO22, 4353
Phone#: 301-796-1056
Fax #:
Email Address: lana.chen@fda hhs.gov
RPM/CSO Name and Mail Code: Lana Y Chen HFD-120
Requesting Reviewer's Concurring Supervisor's Name: Eric Bastings, MD

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: _____

Requested Completion Date: 3/30/10

Submission/Application Number: NDA 22-462
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: March 27, 2009

Official Submission Due Date: NDA 10+3 mo goal date is 4/30/10

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Type of Request: ☑ Consultative Review ☐ Collaborative Review

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/s/

Eric Bastings

6/1/2009 05:40:25 PM