CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208083Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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PLLR Labeling Review

Date: February 26, 2017 **Date consulted:** August 29, 2016

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Office of Antimicrobial Products /Division of Anti-Infective Drug Products (OAP/DAIP)

Drug: Clindamycin in 0.9% Sodium Chloride Injection

Class: Lincosamide

NDA: 208083

Applicant: Celerity Pharmaceuticals LLC

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication(s)
Clindamycin is indicated for the treatment of the following:

- Serious infections caused by susceptible anaerobic bacteria
- Infections Due to Susceptible Strains of Streptococci, Pneumococci and Staphylococci
- Lower Respiratory Tract Infections

- Skin and Skin Structure Infections
- Gynecological Infections
- Intra-abdominal Infections
- Septicemia
- Bone and Joint Infections.

Materials Reviewed:

- October 17, 2016, applicant's response to Information Request (IR)
- September 12, 2016 Division's IR for a summary of all available published literature and pharmacovigilance database to support the PLLR format of the labeling,
- August 29, 2016, OAP/DAIP's request to DPMH-MHT for labeling review

Consult Question: Assist with Pregnancy and Lactation Labeling

INTRODUCTION

On August 29, 2016, this original 505(b)(2) application for Clindamycin in 0.9% Sodium Chloride Injection, NDA 208083, was submitted. The referenced listed drug (RLD) is Cleocin Phosphate in Dextrose 5% in Plastic Container, NDA 050639, approved on August 30, 1989. The proposed indications for this 505(b)(2) are the same as for the RLD (Cleocin). Clindamycin is a lincosamide antibacterial indicated for the treatment of serious infections caused by susceptible anaerobic bacteria.

The Division of Anti-Infective Drug Products (DAIP)) consulted the Division of Pediatric and Maternal Health (DPMH) on August 29, 2016, to provide input for appropriate labeling of the pregnancy and lactation sections of Clindamycin in 0.9% Sodium Chloride Injection labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND

Regulatory History

The applicant, Celerity Pharmaceuticals LLC, submitted with this application, a "preliminary" labeling review amendment in response to the FDA's Filing Communication of September 12, 2016 informing the applicant that the prescribing information (PI) must comply with the Pregnancy and Lactation Rule (PLLR) content and format requirements:

"The submission should include

- a review and summary of the available published literature regarding drug use in pregnant and lactating women and females and males of reproductive potential,
- a review and summary of reports from the applicant's pharmacovigilance database, and
- an interim or final report of an ongoing or closed pregnancy registry (if applicable)".

Cleocin (Clindamycin Phosphate) for injection has been approved for treatment of infections in human for over 40 years [the RLD (Reference Listed Drug) Cleocin Phosphate, NDA 050441 was first approved on October 2, 1972]. The non-clinical information of the active ingredient clindamycin phosphate, for injection has been reviewed by the FDA for the RLD Cleocin Phosphate in Dextrose 5% in Plastic Container (Pharmacia and Upjohn, NDA 050639, approved on August 30, 1989). The applicant has not performed any clinical studies in support of its proposed product Clindamycin in 0.9% Sodium Chloride Injection in GALAXY Container. The applicant is relying on the FDA's findings on safety and efficacy for the RLD NDA 050639 to support this NDA.

Approval of NDAs:

- October 2, 1972 NDA 050441
- August 30, 1989 NDA 050639

Submissions

- June 30, 2016, NDA 208083 an "original" 505(b)(2)
- October 17, 2016 amendment submission incorporating the responses to IR regarding PLLR labeling and PLLR labeling

Drug's Characteristics

Clindamycin

Clindamycin in 0.9% Sodium Chloride Injection in the GALAXY plastic container for intravenous use is composed of clindamycin phosphate equivalent to 300, 600, and 900 mg of clindamycin premixed with 0.9% sodium chloride as a sterile solution. Clindamycin is a lincosamide antibacterial and a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin. The molecular weight is 504.96 Daltons. The serum elimination half-life of active clindamycin is about 3 hours in adults.

PLLR

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. [1] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

Current Labeling for RLD Cleocin Phosphate[2]

[1] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

[2] Pharmacia and Upjohn. Approved Labeling for Cleocin Phosphate, in Dextrose 5% in Plastic Container, NDA 050639. November 17, 2016.

The approved labeling for the RLD shares labeling with Cleocin Phosphate, NDA 050441, and is not in Physician Labeling Rule format.

Pregnancy

Pregnancy Category B

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. Clindamycin should be used during the first trimester of pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (2.1 and 1.1 times the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (0.9 and 0.5 times the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity. Cleocin Phosphate Sterile Solution contains benzyl alcohol. Benzyl alcohol can cross the placenta. See WARNINGS.

Nursing Mothers

Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers.

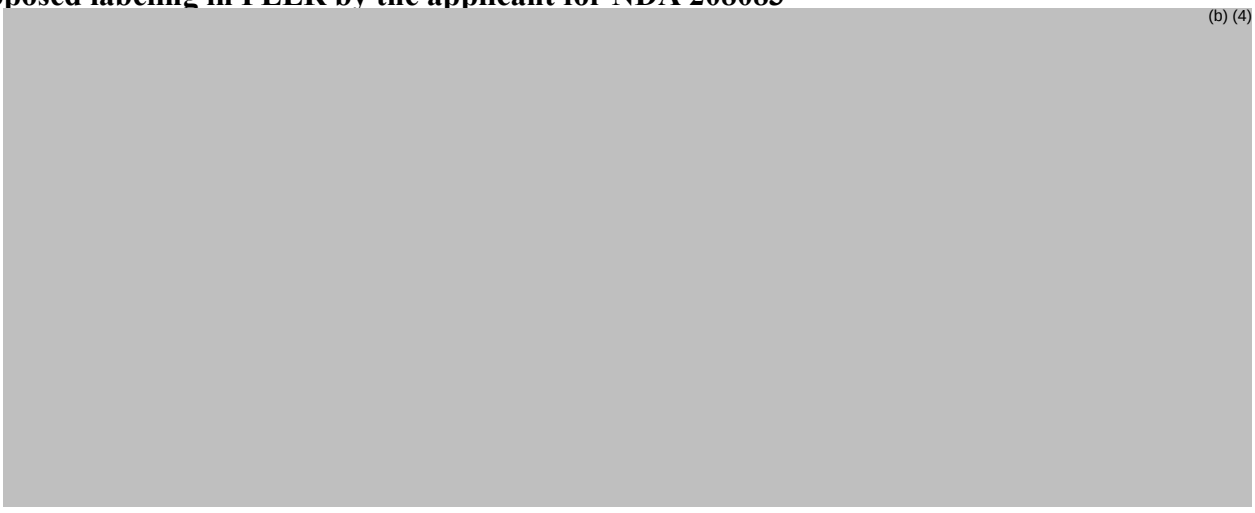
Warnings and Precautions

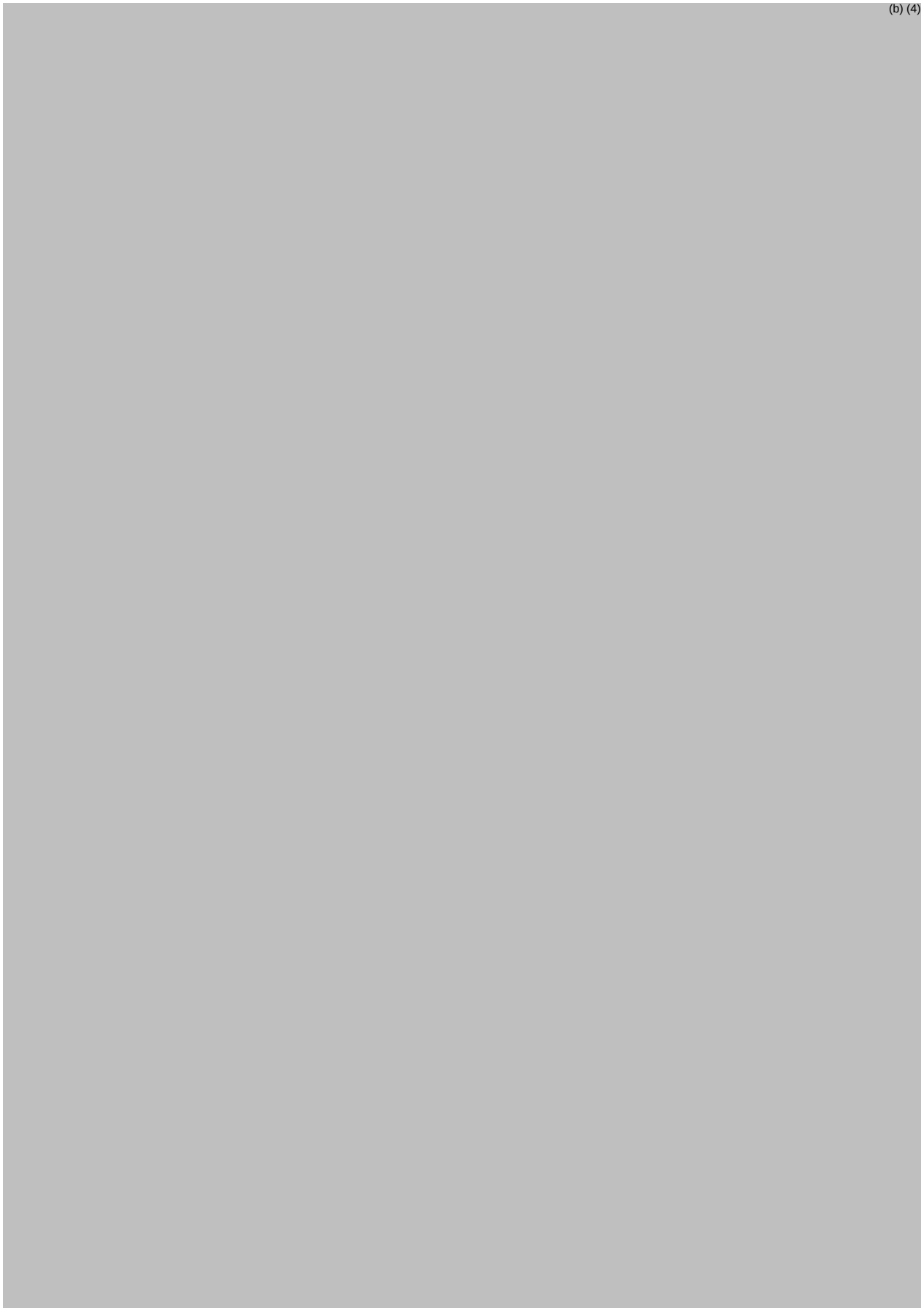
Benzyl Alcohol Toxicity in Pediatric Patients ("Gasping Syndrome")

This product contains benzyl alcohol as a preservative. The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Premature and low birth weight infants may be more likely to develop toxicity.

Proposed labeling in PLLR by the applicant for NDA 208083

(b) (4)




(b) (4)

Summary
The findings from the nonclinical data on clindamycin have been previously reviewed under the RLD and remain unchanged.

Review of Literature
The applicant has not performed any clinical studies in support of its proposed product Clindamycin in 0.9% Sodium Chloride Injection in GALAXY Container and is relying on the FDA's findings on safety and efficacy for the RLD (Cleocin Phosphate) to support this NDA.

Applicant's Review
A literature search of PubMed was performed with terms including "clindamycin AND pregnancy", "clindamycin AND lactation", "clindamycin AND breast feeding", and

[3] Applicant's response to IR, October 17, 2016
[4] Berezhinskaia VV, Dolgova GV, Egorenko GG, Svinogeeva TP, Shterel'man LA, Zebrev AI et al. [Study of general toxic and organotropic properties of clindamycin in long-term experiments]. Antibiot Khimioter 1992; 37(3):18-20.
[5] Lee SI, Lee JH, Lee SC, Lee JM, Lee JH. Calcium and neostigmine antagonize gentamicin, but augment clindamycin-induced tetanic fade in rat phrenic nerve hemidiaphragm preparations. J Anesth 2008; 22:385-390.

"clindamycin AND milk". The search included publications from July 1, 2014 till September 20, 2016, because the applicant considered the latest approved labeling for Cleocin (RLD) that was updated in 2016, and as such previous literature findings had been reviewed and incorporated into the labeling. All relevant abstracts were also reviewed for pertinent findings. In addition, the applicant searched the Toxnet database for any additional information. The search yielded 10 relevant publications.

In a single, randomized controlled study of 276 women by Meaney-Delman *et. al*., parenteral clindamycin was given for 6 weeks in the 2nd and 3rd trimester of pregnancy. Pharmacokinetic analysis demonstrated transplacental passage of clindamycin to the amniotic fluid and to fetal tissues. Similar rates of "congenital malformations" were reported among in utero exposed (3.9%) and unexposed infants (4.4%), and no differences in birth weight were observed.[6]

In a review article, it is noted that major congenital malformations were observed in 31 of 647 infants (4.8%) whose mothers were given prescriptions for clindamycin during the 1st trimester of pregnancy; "expected rate was 4.3%". No congenital malformations were observed among 16 "children" of women treated with clindamycin during the 1st trimester of pregnancy for attempted prevention of recurrent miscarriage. For women treated with clindamycin during the 2nd or 3rd trimester of pregnancy, it has been demonstrated that there are no increases in the rate of major congenital malformations in 104 women treated with clindamycin for the prevention of preterm delivery. Additionally, no increased rates of congenital malformations were observed in 65 infants born to women who received clindamycin and quinine during the 2nd or 3rd trimester of pregnancy for the treatment of malaria.[7]

DPMH Review

In addition to the search of published literature performed by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases[8] for clindamycin and use in pregnancy. The search yielded 8 relevant publications.

Williams *et. al*., in an abstract, reported that using a highly sensitive and specific high-pressure liquid chromatographic (HPLC) analytic method, did not find that clindamycin was transferred to the fetus or was measureable in the amniotic fluid,[9] while others reported that clindamycin crosses the placenta at term.[10,11] Ou MC *et. al*.[12] treating 16 women for prevention of recurrent abortions during the early first trimester and treated with amoxicillin and clindamycin, reported

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[6] Meaney-Delman D, Rasmussen SA, Beigi RH, Zotti ME, Hutchings Y, Bower WA et al. Prophylaxis and Treatment of Anthrax in Pregnant Women: A Systematic Review of Antibiotics. Obstet Gynecol 2013; 122(4):885-900.

[7] Nahum GG, Uhl K, Kennedy DL. Antibiotic Use in Pregnancy and Lactation: What Is and Is Not Known About Teratogenic and Toxic Risks. Obstet Gynecol 2006; 107(5):1120-1138.

[8] TERIS and ReproTox databases, Truven Health Analytics, Micromedex Solutions, 2016.

[9] Williams M, Colombo DF, Augustine JM, Fan-Havard P: Lack of maternal-fetal transfer of clindamycin in cord blood and amniotic fluid. J Soc Gynecol Investig 2004;11(2 Suppl):192A

[10] Weinstein AJ, Gibbs RS, Gallagher M: Placental transfer of clindamycin and gentamicin in term pregnancy. Am J Obstet Gynecol 124:688-91, 1976

[11] Philipson A, Sabath LD, Charles D: Transplacental passage of erythromycin and clindamycin. N Engl J Med 288:1219-21, 1973

[12] Ou M-C, Pang C-C, Chen F-M et al: Antibiotic treatment for threatened abortion during the early first trimester in women with previous spontaneous abortion. Acta Obstet Gynecol Scand 80:753-756, 2001.

that no malformations were observed among the 16 exposed offspring. Other publications reported on investigations for the inhibition of fetal membrane weakening and subsequent preterm birth caused by uterine microorganisms.[13,14] McCormack *et. al.* found treatment with clindamycin in the second or third trimester of pregnancy had no effect on birth weight of newborns to mothers treated with clindamycin for mycoplasma or Ureaplasma.[15] In a randomized trial that involved 485 women with abnormal vaginal flora and vaginosis who received clindamycin early in the second trimester, antibiotic treatment was found to have significantly fewer miscarriages or preterm deliveries (13/244) than did those in the placebo group (38/241; percentage difference 10.4%, 95% CI 5.0-15.8, p=0.0003). Clindamycin also reduced adverse outcomes across the range of abnormal Nugent scores, with maximum effect in women with the highest Nugent score of 10.[16] No increase in the incidence of other adverse outcomes was noted, but the incidence of congenital malformations was not the primary focus of this trial.

Review of Pharmacovigilance
The applicant has not established a pharmacovigilance program because the applicant has not performed clinical studies with Clindamycin in 0.9% Sodium Chloride Injection and the drug has not been marketed yet.

Summary

Overall, there are limited reports of exposure during different trimesters to clindamycin use during pregnancy. No clinical studies have reported findings to inform any potential risk of major congenital malformation or miscarriage. Because there are limited reports on exposure during different trimesters in pregnancy, even though no increased risk of major malformation or miscarriages are reported, for now DPMH recommends maintaining current pregnancy recommendations and restructuring labeling to the PLLR format.

LACTATION
Animal Data
No information exists for the presence of clindamycin in animal milk.

Human Data
The current RLD labeling states that clindamycin has been detected in breast milk in the range of 0.7 to 3.8 mcg/mL following maternal administration at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for serious adverse reactions like alteration to normal intestinal flora, anaphylactic and severe hypersensitivity reactions, toxic epidermal necrolysis and Stevens-Johnson syndrome in nursing infants, clindamycin should not be taken by nursing

[13] McGregor JA, JN Schoonmaker, BD Lunt: Antibiotic inhibition of bacterially induced fetal membrane weakening. Obstet Gynecol 76:124-128, 1990
[14] Larsson PG, Fahraeus L, Carlsson B, Jakobsson T, Forsum U: Premature study group of the Southeast Health Care Region of Sweden. Late miscarriage and preterm birth after treatment with clindamycin: a randomized consent design study according to Zelen. BJOG 2006;113:629-37
[15] McCormack WM, Rosner B, Lee YH, Munoz A, et al.: Effect on birth weight of erythromycin treatment of pregnant women. Obstet Gynecol 69:202-207, 1987
[16]Ugwumadu A, ManyondaI, Reid F, Hay P: Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomized controlled trial. Lancet 2003;361:983-88.

mothers.

Review of Literature
Small amounts of clindamycin is present in human milk.[17,18] Following oral doses of 300 mg every 6 hours, the breastmilk levels averaged 1.0 to 1.7 mg/L at 1.5 to 7 hours after dosing. In a study of 15 women who received 600 mg clindamycin intravenously, levels of clindamycin in milk averaged 1.03 mg/L at two hours following the dose.[19] There was a case report of an infant who developed bloody stools in association with exposure to clindamycin in milk[20]; however, a causative relationship cannot be established based on this report. The American Academy of Pediatrics classified clindamycin as compatible with breastfeeding[21] based on drug levels in human milk and/or infant serum, possible adverse effects (reported sign or symptoms) on breastfeeding infants, and potential effects on lactation. Review of Lactmed and *Medication's and Mother's Milk* by Thomas Hale report similar findings as above. There is no published information on infant levels. There is no relevant published information on the effects of clindamycin on milk production.

Review of Pharmacovigilance
The applicant has not established a pharmacovigilance program because the drug has not been marketed yet.

Summary
Clindamycin is present in breast milk in small amounts. As such, it has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora. If oral or intravenous clindamycin is required by a breastfeeding woman, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. The American Academy of Pediatrics classified clindamycin as compatible with breastfeeding.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Animal Data
Fertility studies in rats treated orally with up to 300 mg/kg/day (equivalent to the highest recommended adult human dose based on a body surface area comparison) revealed no effects on fertility or mating ability.[2]
Fertility studies in rats treated orally with up to 300 mg/kg/day (equivalent to the highest recommended adult human dose based on a body surface area comparison) revealed no effects on fertility or mating ability.[2]

Review of Literature
There are no reports of adverse effects of clindamycin on the fertility of females and males of reproductive potential in the published literature (identified by either the applicant or this reviewer).

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[17] Smith JA, Morgan JR, Rachlis AR: Clindamycin in human breast milk. Can Med Assoc J 112:806, 1975.
[18] Steen B, Rane A. Clindamycin passage into human milk. Br J Clin Pharmacol. 1982;13:661-4.
[19] Zang Y, Zhang Q, Xu . Tissue and body fluid distribution of antibacterial agents in pregnant and lactating women. Zhonghua Fu Chan Ke ZaZhi.1997;32:288-92
[20] Mann CF: Clindamycin and breast-feeding. Pediatrics 66:1030-1, 1980
[21] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics 108:776-89, 2001

Summary
There is no human information regarding infertility in females and males of reproductive potential. As discussed above, animal studies revealed no effects on fertility or mating ability.[2] Contraception and pregnancy testing are not recommended because clindamycin is not genotoxic and, with the available information on its use in pregnant women, there is no increase in major congenital malformations or miscarriages. Section 8.3, Females and Males of Reproductive Potential will be omitted from labeling because there is nothing to be reported.

CONCLUSIONS
Clindamycin labeling has been updated to comply with the PLLR. No new safety information about any major congenital malformations or pregnancy related complications was identified during the current review.

The Pregnancy and Lactation sections of clindamycin labeling were structured to be consistent with the PLLR as follows:

- Pregnancy, Section 8.1
  The "Pregnancy" section of clindamycin labeling was formatted in the PLLR format to include: "Risk Summary", and "Data" sections.
- Lactation, Section 8.2
  The "Lactation" section of clindamycin labeling was formatted in the PLLR format to include the "Risk Summary" and "Clinical Considerations" sections.
- Females and Males of Reproductive Potential, Section 8.3
  Females and Males of Reproductive Potential, Section 8.3 is omitted because there is nothing to be reported regarding effects on fertility. Contraception and pregnancy testing are not recommended.
- Patient Counseling Information, Section 17
  The "Patient Counseling Information" section of labeling was updated to correspond with sections 8.1 and 8.2 of labeling.

RECOMMENDATIONS
The below recommendations include DPMH revised sections 8.1, 8.2, and 17 of Clindamycin in 0.9% Sodium Chloride Injection labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling.

PRESCRIBING INFORMATION

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In limited published clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of major birth defects. The limited published data on use of clindamycin in pregnant women with exposure during the first trimester are insufficient to inform a drug-associated risk of pregnancy-related adverse outcomes *(see Data)*. In animal reproduction studies, no evidence of any adverse developmental outcomes was observed when oral or subcutaneous doses of clindamycin were administered to pregnant rats and mice during organogenesis at doses half to twice the highest clinically relevant dose based on body surface area comparison *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

In limited published trials in pregnant women administered clindamycin during the first trimester of pregnancy, there was no difference in the rate of major birth defects reported among in utero exposed infants compared to unexposed infants. From these observational data, it is not possible to draw any conclusions on the rate of specific major birth defects associated with clindamycin. These data cannot definitely establish or exclude any clindamycin-associated risk during pregnancy.

Animal Data

Reproduction studies performed during organogenesis (gestational days 6-15) in pregnant rats and mice that were administered oral doses of clindamycin up to 600 mg/kg/day (twice or equivalent to the highest recommended adult human dose based on a body surface area comparison, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (equivalent to or half the highest recommended adult human dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

8.2 Lactation

Risk Summary

Clindamycin is present in breast milk in small amounts. There is no information on the effects of clindamycin on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breastfed child from clindamycin or from the underlying maternal condition.

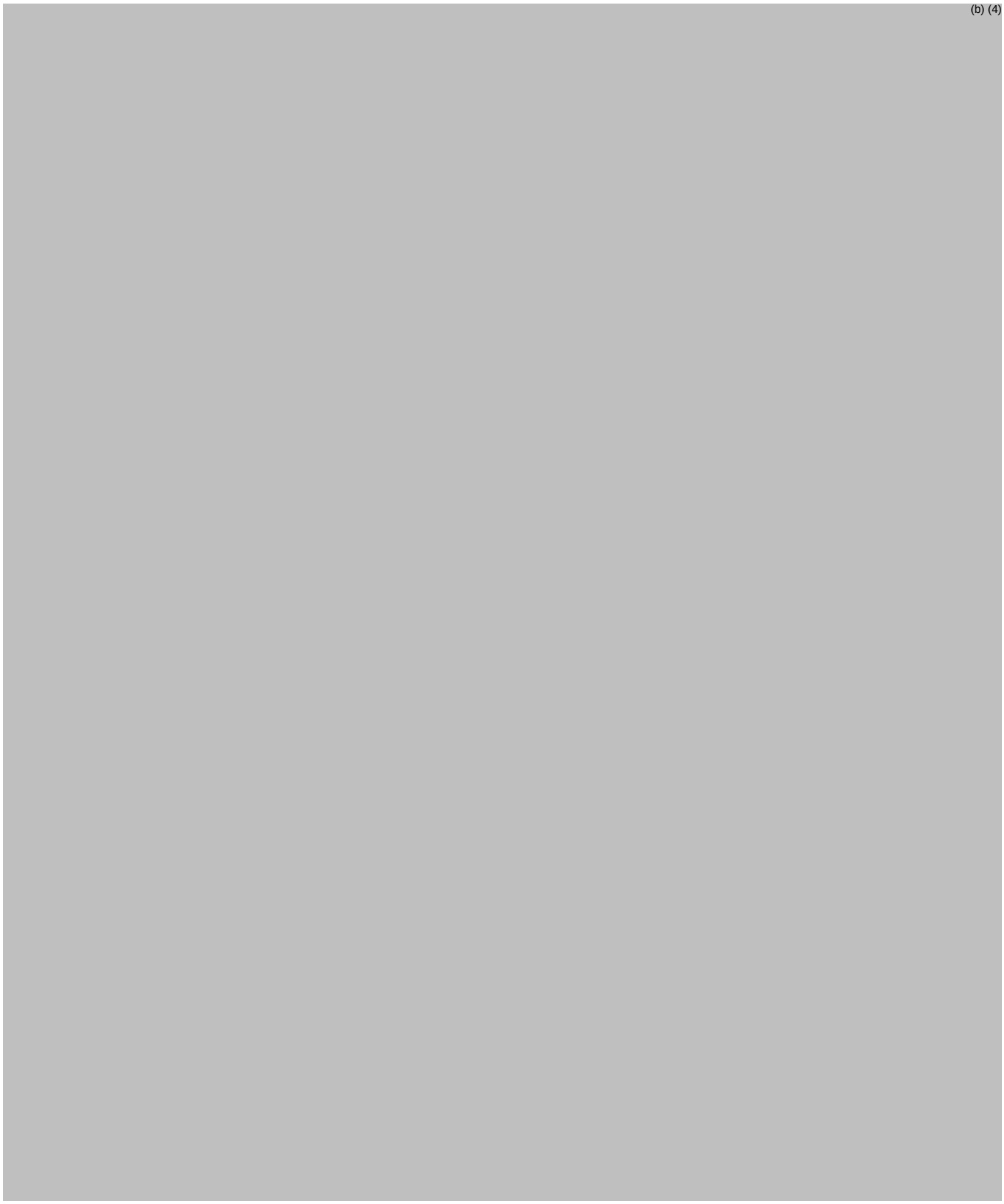
Clinical Considerations
Clindamycin may cause intestinal flora alteration. Advise a woman to monitor the breastfed infant for diarrhea and bloody stools.

17. PATIENT COUNSELING INFORMATION

- Lactation: Advise a woman to monitor the breastfed infant for diarrhea and bloody stools.

Appendix 1
Applicant's proposed labeling for Clindamycin in 0.9% Sodium Chloride Injection

(b) (4)




(b) (4)

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

/s/

CHRISTOS MASTROYANNIS
04/04/2017

TAMARA N JOHNSON
04/05/2017

LYNNE P YAO
04/05/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 3, 2017
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 208083
Product Name and Strength:	Clindamycin in 0.9% Sodium Chloride Injection in Galaxy Container, 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL
Submission Date:	March 22, 2017
Applicant/Sponsor Name:	Celerity Pharmaceuticals, LLC
OSE RCM #:	2016-2505-1
DMEPA Primary Reviewer:	Deborah Myers, RPh, MBA
DMEPA Team Leader (acting):	Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container labels and carton labeling for Clindamycin in 0.9% Sodium Chloride Injection in Galaxy Container (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

The March 22, 2017 Labeling Amendment submitted by Celerity Pharmaceuticals provides responses to the FDA's February 22, 2017 labeling recommendations. A point-by-point response to each of the identified labeling recommendations was included in this March 22, 2017 submission and is provided (Appendix B).

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

[a] Myers, D. Label and Labeling Review for Clindamycin (NDA 208083). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 FEB 01. 23 p. OSE RCM No.: 2016-2505.

We submitted an Information Request (IR) to Celerity on March 10, 2017 requesting clarification regarding Celerity's February 24, 2017 email (Appendix C) that did address all of our labeling recommendations. Celerity provided their response in an email dated March 13, 2017 (Appendix D). After several emails and as requested, on March 22, 2017 Celerity submitted updated labeling (Appendix A), as well as a point-by-point response to each of our identified labeling recommendations (Appendix B).

Celerity's response (Appendix D) to our March 10, 2017 IR (Appendix C) provides clarity that since the lead time for labeling is 8 weeks, Celerity has previously ordered container labels consistent with the proposed labeling included in their June 30, 2016 labeling submission. Celerity forecasts that the already ordered container labels will be on the market (b) (4) for the 900 mg strength and (b) (4) for the 600 mg strength product. The submitted supply forecast is only applicable to the units used for (b) (4) manufacturing batches. (b) (4)

Additionally, in Celerity's response (Appendix D) to our March 10, 2017 IR (Appendix C) they provide information (b) (4)

(b) (4)

(b) (4)

Along with Celerity's March 22, 2017 updated labeling submission (Appendix A), they included a point-by-point response to each of our identified labeling recommendations (Appendix B). We are in agreement with Celerity regarding:

All Container and Carton Labeling

- FDA Recommendation 1 to change the font of the "300 mg per 50 mL (6 mg/mL)" strength statement. Celerity has agreed on both the container and carton to change the (b) (4) text to black text on a white background with black outline around the white box to aid in readability and help decrease the potential for wrong strength medication errors. We find this acceptable.
- FDA Recommendation 2 to change the statements "For Intravenous Use" to read "For Intravenous Infusion Only", remove the statement "Not for rapid injection of Intravenous push", and increase the font of the statement "For Intravenous Infusion Only". Celerity commits to make these changes immediately upon completion of manufacturing of the first three (b) (4) batches of the 600 mg and 900 mg strengths. In addition, Celerity has agreed to implement the above changes for the 300 mg strength carton and container. We find this acceptable. However, we note that our previous February 22, 2017 recommendation to consider moving the statement, "For Intravenous Infusion Only", up prior to the container size (50 mL), was not addressed. As this placement is consistent with the RLD container label, we have again included this recommendation to the Applicant in Section 3 for their consideration.
- FDA Recommendation 3 to add the intended location of the lot number and expiration date. Celerity has stated that the intended location for the lot number and expiration date has been included on both the container and carton labeling for all three strengths. We find this acceptable.
- FDA Recommendation 4 to revise the product code (middle 3-4 digits) of the National Drug Code (NDC) number to not be sequential. Celerity agrees and the product code for all three strengths has been revised to no longer be sequential and we find this acceptable. (b) (4)

(b) (4)

- FDA Recommendation 5 to insert the Centigrade symbol (C) and Fahrenheit symbol (F) within the storage statement. Celerity commits to make these changes immediately upon completion of manufacturing of the first three (b) (4) batches of the 600 mg and 900 mg strengths. In addition, Celerity has agreed to implement the above changes for the 300 mg strength carton and container. We find this acceptable.

Container Label

- FDA Recommendation 1 to increase the prominence of the product name, "Clindamycin in 0.9% Sodium Chloride Injection". Celerity determined that increasing the font size would result in part of the product name shifting to the next line and not allow space for the remaining text to fit within the die line. Therefore, Celerity proposes that this change not be implemented for all three strengths. We agree with this rationale and find this acceptable.
- FDA Recommendation 2 to incorporate (b) (4)
- FDA Recommendation 3 to increase the prominence by moving the statements "Caution: Do not add supplementary medication. Must not be used to series connections. Check for minute leaks and solution clarity." to precede the statement "Each 50 mL contains: Clindamycin phosphate USP…". Celerity commits to make these changes immediately upon completion of manufacturing of the first three (b) (4) batches of the 600 mg and 900 mg strengths. In addition, Celerity has agreed to implement the above changes for the 300 mg strength container labels. We find his acceptable.
- FDA Recommendation 4 to revise the NDC package codes (last 1-2 digits) to be the same for all three strengths in representing their identical (50 mL) container size. Celerity agrees and the NDC package codes have been appropriately changed to "-05" for all three strengths and we find this acceptable (b) (4)

Carton Labeling

- FDA Recommendation 1 to insert a comma between "clindamycin" and "9 mg" on the Right Panel of the proposed 900 mg carton labeling so that It reads "…900 mg

clindamycin, 9 mg sodium…". Celerity has inserted the comma as requested. We find this acceptable.

- FDA Recommendation 2 to clarify and submit appropriate changes regarding the discrepancy between the carton labeling indicating 12 containers per carton and Section 16. *How Supplied/Storage and Handling* of the Full Prescribing Information indicating 24 containers per carton. Celerity provided an explanation and we find their rationale acceptable.
- FDA Recommendation 3 to revise the NDC package codes (last 1-2 digits) to be the same for all three strengths in representing their identical carton size. Celerity agrees and has revised the package code for all three strengths to "-24" on the carton labeling. Additionally, the package insert has been revised to reflect these new NDC numbers. We find these changes acceptable.

3 RECOMMENDATIONS FOR CELERITY PHARMACEUTICALS, LLC

The revised container labels and carton labeling that have already been ordered for Clindamycin in 0.9% Sodium Chloride Injection in Galaxy Container are acceptable from a medication error perspective. Due to the time constraints involved with printing updated labels, we agree with the following:

Additionally, we have the following recommendations:

A. The Agency previously recommended (February 22, 2017):

> *To provide clarity and decrease the potential of wrong technique or rate of administration medication errors, revise all of the statements "For Intravenous Use" to read "For Intravenous Infusion Only". We also recommend that you consider moving this statement, "For Intravenous Infusion Only", up prior to the container size (50 mL) and description (Single-Dose Container) or increase the prominence of this important information. In addition, we recommend removing the statement "Not for rapid injection or Intravenous push" due to post-marketing reports that negative statements (e.g., do not) may have the opposite*

of the intended meaning because the word "not" can be overlooked and misinterpret the warning as an affirmative action.

To which Celerity responded (March 22, 2017):

Since the recommended changes for the statements [redacted] (b) (4) *and "* [redacted] (b) (4) *are also currently present in the RLD labeling (CLEOCIN; NDA 50639), we believe chances of potential wrong technique or rate of administration medication errors seems uncommon.*

Celerity acknowledges the Agency's recommendation as further enhancement and commits to make the change immediately upon completion of manufacturing of the first three [redacted] (b) (4) *batches of 600 mg and 900 mg strength.* [redacted] (b) (4)

- *Change "For Intravenous Use" to read "For Intravenous Infusion Only"*
- *Increase the "For Intravenous Infusion Only" statement font*
- *Remove the statement "Not for rapid injection or Intravenous push"*

Celerity agrees to implement above changes for 300 mg strengths carton and container labeling.

We again recommend that to increase the prominence of this important information that you additionally consider moving this statement, "For Intravenous Infusion Only", up prior to the container size (50 mL), which is consistent with the Reference Listed Drug (RLD) container label.

B. [redacted] (b) (4)

C. [redacted] (b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX B. POINT-BY-POINT RESPONSE TO FDA LABEL AND LABELING RECOMMENDATIONS

RESPONSE TO FDA QUESTIONS

Celerity is submitting this response as requested in the email dated 2017 FEB 22. For ease of review, the Agency recommendations provided in Clindamycin Carton and Container Recommendations email dated 2017 FEB 22 are listed below in **bold** followed by Celerity's responses.

All Container Labels and Carton Labeling

FDA Recommendation 1

The font of the strength statement "300 mg per 50 mL (6 mg/mL)" appears to be a (b) (4) **font which is difficult to read. To aid in readability and help to decrease the potential for wrong strength medication errors, we recommend changing the text "300 mg per 50 mL (6 mg/mL)" to more prominent font and/or color that does not overlap with that used for the proprietary name and differentiates compared to the 600 mg and 900 mg/50 mL strengths.**

Celerity's Response

Celerity agrees with the Agency and per the recommendation, the font for the "300 mg per 50 mL (6 mg/mL)" strength statement on both the container and carton was changed (b) (4) to a black text on a white background with a black outline around the white box to aid readability and help decrease potential for wrong strength medication errors.

FDA Recommendation 2

To provide clarity and decrease the potential of wrong technique or rate of administration medication errors, revise all of the statements "For Intravenous Use" to read "For Intravenous Infusion Only". We also recommend that you consider moving this statement, "For Intravenous Infusion Only", up prior to the container size (50 mL) and description (Single-Dose Container) or increase the prominence of this important information. In addition, we recommend removing the statement "Not for rapid injection or Intravenous push" due to post-marketing reports that negative statements (e.g., do not) may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpret the warning as an affirmative action.

Celerity's Response

Since the recommended changes for the statements (b) (4)

(b) (4)

(b) (4)

Celerity acknowledges the Agency's recommendation as further enhancement and commits to make the change immediately upon completion of manufacturing of the first three (b) (4) batches of 600 mg and 900 mg strength. (b) (4) (b) (4)

- Change "For Intravenous Use" to read "For Intravenous Infusion Only"
- Increase the "For Intravenous Infusion Only" statement font
- Remove the statement "Not for rapid injection or Intravenous push"

Celerity agrees to implement above changes for 300 mg strengths carton and container labeling.

FDA Recommendation 3

The location for the lot number and expiration date is not provided on the proposed container label and carton labeling that was submitted. The lot number statement and expiration date are required on the immediate container and carton labeling per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively. Include the intended location for the lot number and expiration date on the container label and carton labeling.

Celerity's Response

Celerity agrees with the Agency and the intended location for the lot number and expiration date has been included on both the container and carton labeling for all 3 strengths. The lot number and expiration date are printed on the top of the bag at the time of production and so only a placeholder can be provided on the labeling.

FDA Recommendation 4

Our post-marketing experience indicates that similarity of the product code (middle 3-4 digits) of the National Drug Code (NDC) has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g. (b) (4)). If these numbers cannot be revised, increase the prominence of the middle digits by increasing their font size in

comparison to the remaining digits and putting them in bold type. As an example: [redacted] (b) (4)

Celerity's Response

Celerity agrees with the Agency and per the request, the middle digits of the NDC numbers on Celerity's container and carton labeling for all three (3) strengths (300 mg, 600 mg and 900 mg) were revised to be non-sequential. Table 1 below describes the proposed NDC numbers. This is the same table as provided in the email communication dated Monday, 2017 MAR 13 between Celerity and Naseya Minor, Regulatory Health Project Manager, FDA.

The insert was revised to reflect the new NDC numbers in HOW SUPPLIED/STORAGE AND HANDLING section. The only changes to the insert are the NDC numbers and version number. Refer to package insert.

FDA Recommendation 5

To provide clarity, revise the Storage statement by inserting the Centigrade symbol (C) after the 20° and Fahrenheit symbol (F) after the 68°, to read: "Store at 20°C to 25°C (68°F to 77°F)[see USP Controlled Room Temperature]. Avoid temperatures above 30°C."

Celerity's Response

Celerity acknowledges the Agency's comment and proposes that the storage statement remain as currently listed on the labeling. The statement currently reads "Store at 20° to 25°C (68° to 77°F)[see USP Controlled Room Temperature]. Avoid temperatures above 30°C." This statement was originally applied as written to match exactly the definition in the United States Pharmacopeia (USP) controlled room temperature definition. This also maintains consistency with the other Celerity labeling and aligns with other marketed product. Therefore, Celerity kindly requests to keep this statement unchanged for the first three [redacted] (b) (4) batches of 600 mg and 900 mg strength. Celerity commits to implement this change to the Agency in a subsequent annual report. Celerity agrees to implement this change for 300 mg strengths carton and container labeling.

Container Labeling

FDA Recommendation 1

To help decrease the potential of wrong drug medication errors, we recommend increasing the prominence of the product name, "Clindamycin in 0.9% Sodium Chloride Injection", so that it is the most prominent information on the principal display panels for all three strength presentations.

Celerity's Response

Celerity assessed this recommendation with respect to the width of the container die line. We concluded that it adds more clutter as the product name with the current font size and is a perfect fit within the die line. If we increase the font size, part of the product name will shift to the next line. As a result, it will not allow space for remaining text to fit appropriately within the die line. Hence, we would propose to not implement this change for all three strengths as the current font is the maximum size text that allows the product name to fit on the same line.

FDA Recommendation 2

(b) (4)

FDA Recommendation 3

To increase the prominence of this information and align with the Reference Listed Drug (RLD) container label consider moving the statements "Cautions: Do not add supplementary medication. Must not be used in series connections. Check for minute leaks and solution clarity." to precede the statement "Each 50 mL contains: Clindamycin phosphate, USP…"

Celerity's Response

Celerity prefers to keep the Cautions statement after the Dosage information based on our interpretation of the guidance document titled "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors". Per the guidance, the first portion of the statement "Do not add supplementary medication." is essential. The second portion "Must not be used in series connections. Check for minute leaks and solution clarity." is considered less essential. Therefore, we prefer to keep this Cautions statement after the Dosage information to make it easier for the physician to read. We acknowledge the Agency comment; however, we believe this would not affect the safety of the product in its current state. Therefore, Celerity kindly request to keep this statement unchanged for the first three (b) (4) batches of 600 mg and 900 mg strength. (b) (4) (b) (4) Celerity agrees to implement this change for 300 mg strength container labeling.

FDA Recommendation 4

The currently assigned NDC package codes (last 1-2 digits) are different (3, 6, and 9). As the last 1-2 digits are intended to represent the container size, we recommend that you consider revising these numbers to be the same for all three strengths in representing their identical (50 mL) container size.

Celerity's Response

(b) (4)

Table 1. Summary of NDC Numbers on the Labeling

Packaging Configuration	NDC No. on Celerity's Current Proposed Labeling referred to 02/27/2017	NDC No. on Celerity's Revised Proposed Labeling	(b) (4)
300 mg/50 mL container	(b) (4)	67798-306-05	
300 mg/50 mL carton		67798-306-24	
600 mg/50 mL container		67798-612-05	
600 mg/50 mL carton		67798-612-24	
900 mg/50 mL container		67798-918-05	
900 mg/50 mL carton		67798-918-24	

Carton Labeling

FDA Recommendation 1

To improve readability of the statement "…USP equivalent to 900 mg clindamycin 9 mg sodium…" that currently appears on the Right Panel of the 900 mg/50 mL carton labeling, we recommend inserting a comma between "clindamycin" and "9 mg" on the Right Panel of the proposed 900 mg carton label so that it reads "…900 mg clindamycin, 9 mg sodium…".

Celerity's Response

Per the Agency's request, a comma has been inserted between "clindamycin" and "9 mg" on the Right Panel of the proposed 900 mg carton label. This was provided in error on the carton labeling submitted in the original application dated 2016 JUN 30; however, the current printed label for 900 mg strength, the statement reads as "Clindamycin phosphate, USP equivalent to 900 mg clindamycin, 9 mg sodium chloride, USP".

FDA Recommendation 2

The carton labeling indicates inclusion of 12 containers per carton, however Section 16, How Supplied/Storage and Handling, of your proposed Full Prescribing Information indicates 24 containers per carton. This information will need to be clarified and appropriate changes submitted.

Celerity's Response

To provide clarification, the carton label information is printed two (2) times on one (1) adhesive label and is separable along a perforation. During production, the perforated adhesive label is placed so that it connects two (2) very small cartons (VSCs). Each VSC contains twelve (12) 50 mL GALAXY containers for the 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL strengths. When the VSCs are separated during use, one full label with complete information remains with each VSC. However, orders are placed twenty-four units (24) at a time for the 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL strengths. Two (2) VSCs make up a carton and cartons are one unit of sale. Thus, the How Supplied section of the package insert lists twenty-four (24) units for the 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL strengths and the carton labels list twelve (12) units.

FDA Recommendation 3

The currently assigned NDC package codes (last 1-2 digits) are different (4, 5, and 7). As the last 1-2 digits are intended to represent the carton size, we recommend that you consider revising these numbers to be the same for all three strengths in representing their identical (12 count) carton size. In addition, we recommend that this package code be different than the container label as the container label of one unit and the carton labeling of 12 units should have different NDC numbers.

Celerity's Response

As provided in the email communication dated Monday, 2017 MAR 13 between Celerity and Naseya Minor, Regulatory Health Project Manager, FDA, the already printed carton labels for 300 mg, 600 mg and 900 mg strength already includes this change. Celerity's carton labeling for all three (3) strengths (300 mg, 600 mg and 900 mg) were revised to be the same for all three strengths in representing their identical carton size. As explained in Celerity's Response above to FDA Carton Labeling Recommendation 2, we have used the package code (24) to represent 24 counts in a carton which is also different than the container label package code (05). The following Table 2 summarizes the NDC number changes:

Table 2. Summary of the NDC Number Change on Labeling

Packaging Configuration	NDC No. on Current Labeling	NDC No. on Revised Labeling
300 mg/50 mL carton	(b) (4)	67798-306-24
600 mg/50 mL carton		67798-612-24
900 mg/50 mL carton		67798-918-24

The insert was also revised with the new NDC numbers. The only changes to the insert are the NDC numbers and version number. Refer to package insert.

APPENDIX C. INFORMATION REQUEST (IR) SENT TO CLERITY MARCH 10, 2017

Information Request (IR) – Clindamycin in 0.9% Sodium Chloride Injection (NDA 208083)

We reference your February 24, 2017 email request regarding the Agency's February 22, 2017 Container Labels and Carton Labeling recommendations. Provide clarification for the following:

- We note that your email request specifically addresses three of our twelve Container Labels and Carton Labeling recommendations. What are your plans regarding our additional nine Container Labels and Carton Labeling recommendations?

- You state that "The films for all three configurations of the Clindamycin in 0.9% Sodium Chloride Injection have been already ordered with current label printed on it due to the long printing lead time." Clarify if the "current" carton labeling and container labels you have ordered are the same as the labels and labeling that are referred to in the Agency's February 22, 2017 Container Labels and Carton Labeling recommendations.

- What is the quantity of films for all three configurations of the Clindamycin in 0.9% Sodium Chloride Injection that you have already ordered? How does this translate into expected product use (b) (4) once on the market?

- When do you expect to print new labels and labeling with the implemented Agency revisions? In addition, when would you expect this product with the updated container label and carton labeling to be shipped?

Given our review timelines, we request a response no later than Monday, March 13, 2017.

APPENDIX D. CELERITY'S MARCH 13, 2017 RESPONSE TO OUR MARCH 10, 2017 IR

Thank you for looking into this. I copied and pasted the requests in your email, which are in **bolded blue text below followed by** Celerity's responses in black. For greater clarity, the order of the 1st two questions and responses are switched.

You state that "The films for all three configurations of the Clindamycin in 0.9% Sodium Chloride Injection have been already ordered with current label printed on it due to the long printing lead time." Clarify if the "current" carton labeling and container labels you have ordered are the same as the labels and labeling that are referred to in the Agency's February 22, 2017 Container Labels and Carton Labeling recommendations.

Celerity's Response

(b) (4)

(b) (4)

All Container and Carton Labeling

1- Celerity agrees to change the font color of the 300 mg strength statement (b) (4) to black on a white background with a black outline around the white box. When making this change for the 300 mg film, other recommendations as explained below will be included for the container and carton on the 300 mg strength. These changes will be submitted in the labeling amendment in response to the Agency's February 22, 2017 Container Labels and Carton Labeling recommendations. (b) (4)

2- See email to the FDA dated February 24, 2017 requesting clarification (Change statement to "Intravenous Infusion Only" and remove "Not for rapid injection or Intravenous Push").

3- The location of the expiration date and lot number will be depicted on the new labeling in the response to the February 22, 2017 Container Labels and Carton Labeling recommendations.

4- The middle 3 digits of the NDC numbers in the new labeling are non-sequential. For Celerity's new labeling submitted for approval, the NDC numbers are non-sequential (306, 612, and 918 for 300 mg, 600 mg, and 900 mg strengths, respectively). (b) (4)

(b) (4)

Container Label

1- See email to the FDA dated February 24, 2017 requesting clarification (prominence of drug product name in the principal display panel).

2- [redacted] (b) (4)

3- See email to the FDA dated February 24, 2017 requesting clarification (Move the cautions statement to precede the statement "Each 50 mL contains: ...").

4- [redacted] (b) (4) The packaging codes for cartons are all 24 to correspond with the number of units per carton. See Table 1 summarizing NDC numbers below.

Table 1. Summary of NDC Numbers on the Labeling-Middle Digits

Packaging Configuration	NDC No. on Celerity's Current Proposed Labeling referred to 02/27/2017	NDC No. on Celerity's Revised Proposed Labeling	NDC No. on Baxter's Already Ordered Labeling
300 mg/50 mL container	67798-3455-3	[redacted] (b) (4)	0338-9545-30
300 mg/50 mL carton	67798-3455-4		0338-9545-24
600 mg/50 mL container	67798-3456-6		0338-9549-60
600 mg/50 mL carton	67798-3456-5		0338-9549-24
900 mg/50 mL container	67798-3457-9		0338-9553-90
900 mg/50 mL carton	67798-3457-7		0338-9553-24

Carton Labeling

1- The new carton labeling for the 900 mg strength will be revised so that a comma is added between clindamycin and 9 mg and will be submitted in the response to the

February 22, 2017 Container Labels and Carton Labeling recommendations. (b) (4)

2- To provide clarification, the carton label information is printed two (2) times on one (1) adhesive label and is separable along a perforation. During production, the perforated adhesive label is placed so that it connects two (2) very small cartons (VSCs). Each VSC contains twelve (12) 50 mL GALAXY containers for the 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL strengths. When the VSCs are separated during use, one full label with complete information remains with each VSC. However, orders are placed twenty-four units (24) at a time for the 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL strengths. Two (2) VSCs make up a carton and cartons are one unit of sale. Thus, the How Supplied section of the package insert lists twenty-four (24) units for the 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL strengths and the carton labels list twelve (12) units.

3- The carton labeling for the 300 mg, 600 mg and 900 mg strength already includes this change. The last two digits are the same for each strength. See Table 1 for Response 4 under Container Label.

(b) (4)


(b) (4)

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/s/

DEBORAH E MYERS
04/03/2017

OTTO L TOWNSEND
04/03/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 13, 2017

To: Naseya Minor, MPH
Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Puja Shah, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Response
NDA 208083
CLINDAMYCIN IN 0.9% SODIUM CHLORIDE injection, for intravenous use

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As requested in DAIP's consult dated August 3, 2016, OPDP has reviewed the draft Package Insert (PI) and Carton and Container Labeling (CCL) for CLINDAMYCIN IN 0.9% SODIUM CHLORIDE injection, for intravenous use (Clindamycin). OPDP's comments are based on the substantially complete version of the labeling titled "NDA 208083 Revised PI 10-19-16.docx" which was accessed via http://sharepoint.fda.gov/orgs/CDER-OAP DAIP/Active%20Documents/NDA%20208083%20Revised%20PI%2010-19-16.docx on March 10, 2017.

Package Insert

Our comments on the draft PI are included directly on the attached copy of the labeling.

Carton and Container Labeling

OPDP reviewed the following proposed CCL received via email from DAIP on March 13, 2017:

- 300 MG CONTAINER LABEL
- 600 MG CONTAINER LABEL
- 900 MG CONTAINER LABEL
- 300 MG CARTON LABEL
- 600 MG CARTON LABEL

- 900 MG CARTON LABEL

The proposed CCL includes the following Dosage and Administration information:

- "Cautions: Do not add supplementary medication. Must not be used in series connections. Check for minute leaks and solution clarity."

By only including the above Dosage and Administration information on the CCL, it suggests that this is the only important Dosage and Administration information associated with the proper use of the drug, when such is not the case. Specifically, section 2.5 of the PI states the following (emphasis added):

> Check for minute leaks prior to use by squeezing bag firmly. . . Do NOT use unless solution is clear and seal is intact.
>
> Do NOT use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Furthermore, using the word "Cautions" to present important Dosage and Administration information may misleadingly imply that these are the only "cautions" (i.e., risks) associated with the drug, when this is not the case. Clindamycin is associated with several serious warnings and precautions, including a Black Boxed Warning of *Clostridium Difficile*-Associated Diarrhea and Colitis. We recommend either deletion of the word "Cautions" from the CCL and including a more comprehensive discussion of the important Dosage and Administration information, or deletion of the Dosage and Administration information from the CCL to avoid the implication that this is the complete Dosing and Administration information associated with the proper use of the drug.

We also note that the CCL includes the following Storage and Handling information:

- "Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Avoid temperatures above 30°C."

We note that section 16 of the PI also includes the following temperature excursions information:

> Excursions permitted to 15°C to 30°C (59°F to 86°F).

We defer to DAIP on whether this information is pertinent to include on the CCL.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

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/s/

PUJA J SHAH
03/13/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208083

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Clindamycin in 0.9 Sodium Chloride Injection in GALAXY for Injection 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL

Applicant: Celerity Pharmaceuticals, LLC

Receipt Date: June 30, 2016

Goal Date: August 29, 2016

1. Regulatory History and Applicant's Main Proposals

Clindamycin in 0.9% Sodium Chloride Injection in GALAXY Container (300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL) is for the treatment of serious infections caused by susceptible anaerobic bacteria. This formulation is therapeutically equivalent to the Reference Listed Drug (RLD) NDA 050639 CLEOCIN PHOSPHATE IV Solution (clindamycin injection in 5% dextrose) in the GALAXY plastic container (300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 3, 2016. The resubmitted PI will be used for further labeling review.

---

4. Selected Requirements of Prescribing Information

Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

NO 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment: *No horizontal line to separate the HL from Table of Contents (TOC)*

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *For the Highlights section, the preferred format for referencing is the numerical identifier in parenthesis [e.g., (1)] at the end of each summarized statement or topic.*

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI

Selected Requirements of Prescribing Information

• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.
Comment: *Highlights of prescribing information must be bolded and appear in all upper case letters.*

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

NO 12. All text in the BW must be **bolded**.

Comment: *All text in the boxed warning must be bolded.*

NO 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the

BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment: *The boxed warning summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning.*

NO 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment: *The following verbatim statement must be placed immediately following the heading of the boxed warning: "See full prescribing information for complete boxed warning."*

NO 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment: *The Boxed Warning in Highlights should contain a concise summary of the boxed warning described in the Full Prescribing Information (FPI), not to exceed a length of 20 lines.*

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

NO 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the Table of Contents in UPPER-CASE letters and bold type. See 21 CFR 201.56(d) and 201.57(b).*

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *The headings and subsection headings must be named and numbered in accordance with 21 CFR 201.56. The Boxed Warning heading is missing from the FPI. In Section 8 Use in Specific Populations the subsection heading for 8.5 should state Geriatric Use. In Secton 12 Clinical Pharmacology the subsection heading for 12.2 should state Pharmacodynamics. Subsection 12.3 should state Pharmacokinetics. Subsection 12.4 should state Microbiology.*

NO 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment: *The format of the cross-references need to be corrected throughout the PI. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in italics and enclosed within brackets. For example, "[see Boxed Warning]."*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

NO 35. All text in the BW should be **bolded**.

Comment: *The Boxed Warning must be included in the Full Prescribing Information as the first section heading and all text must be bolded. See 21 CFR 201.56(d)(1) and 21 CFR 201.57(c)(1).*

NO 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment: *The Boxed Warning must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box.*

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *Verbatim statement nor appropriate modification is listed.*

N/A

39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

    Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *No reference to any FDA approved patient labeling*

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

NASEYA N MINOR
09/13/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 208083
BLA#</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Animal Rule Confirmatory Study (SE10)</td></tr>
<tr><td colspan="3">Proprietary Name: N/A
Established/Proper Name: Clindamycin in 0.9 Sodium Chloride Injection in GALAXY Container
Dosage Form: Injection
Strengths: 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL</td></tr>
<tr><td colspan="3">Applicant: Celerity Pharmaceuticals, LLC.
Agent for Applicant (if applicable):</td></tr>
<tr><td colspan="3">Date of Application: June 30, 2016
Date of Receipt: June 30, 2016
Date clock started after Unacceptable for Filing (UN):</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: April 30, 2017</td><td>Action Goal Date (if different): April 28, 2017</td></tr>
<tr><td colspan="2">Filing Date: August 29, 2016</td><td>Date of Filing Meeting: August 22, 2016</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch
☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval)
☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s):</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☐ 505(b)(1)
☒ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic***	☒	☐		

archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☒	☐		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☒	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☒	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English)	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	Not applicable for this 505(b)(2) application
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☐		Not applicable for this 505(b)(2) application
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☐	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Field copy certification is not required for eCTD submissions
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☐	☒		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☐		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR)	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

format?[4]				
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☐		No EOP 2 meeting held
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** February 9, 2015	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			No SPA

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 22, 2016

BACKGROUND: Filing and Planning Meeting for NDA 208083 Clindamycin in 0.9% Saline Injection (300mg/50ML, 600mg/50mL, and 900mg/mL) in a GALAXY plastic container for treatment of serious infections caused by susceptible anaerobic bacteria.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Naseya Minor	Y
	CPMS/TL:	Maureen Dillon-Parker	Y
Cross-Discipline Team Leader (CDTL)			
Division Director/Deputy	Sumathi Nambiar		Y
Office Director/Deputy	Dmitri Iarikov (acting)		Y
Clinical	Reviewer:	Maria Allende	N
	TL:	Thomas Smith	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Jalal Sheikh	Y
	TL:	Lynette Berkeley	Y
Clinical Pharmacology	Reviewer:	Kunyi Wu	Y
	TL:	Seong Jang	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		

	TL:	Karen Higgins	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tessie Alapatt	Y
	TL:	Terry Miller (acting)	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Dorota Matecka	Y
	RBPM:	Navi Bhandari	N
• Drug Substance	Reviewer:	Suresh Pagay	N
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Adam George	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	A request for Waiver of In-vivo Bioavailability studies was included.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: 505(b)(2) NDA	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division Director **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): N/A **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

NASEYA N MINOR
08/31/2016