CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-813

CHEMISTRY REVIEW(S)

NDA 50-813

Amoxicillin Extended Release Tablets

MiddleBrook Pharmaceuticals

(Advancis)

Shrikant Pagay, Ph.D.

ONDQA/OPS

The Chemistry Review for NDA 50-813

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability – Recommend to approve this NDA (NDA#50-813) from CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Amoxicillin is broad spectrum penicillin. It is used as a trihydrate in the proposed drug product. It is orally active. Amoxicillin trihydrate is a white to off white crystalline powder. It has slight odour, typically sulphur odour. It is manufactured from [redacted] Amoxicillin trihydrate is soluble in water; approximately 1 to 10 mg/mL depending on the pH. [redacted] It is lipophilic in nature since the [redacted]. Amoxicillin trihydrate solid state properties are well characterized through single crystal X-ray as well as powder X-ray diffraction. Amoxicillin in dilute solution, 0.4 to 4 mg/mL is more stable at pH 6.0 than in the acidic and alkaline regions. Amoxicillin is well absorbed when given orally with bioavailability between 74-92%. All studies for bioavailability are reported for immediate release formulations. Based on the GI transit time studies, amoxicillin has a narrow window of absorption indicating challenges in developing a once or 2 times a day dosing.

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Drug Product

The drug product is intended to be used as once a day dosing for the treatment of tonsillitis and/or pharyngitis secondary to Streptococcus pyogenes (S.pyogenes) in adolescents and adults. The drug product is a film coated printed oval tablet and weighs 1.5 grams (exact 1497.6 mg). Each tablet contains 775 mg amoxicillin trihydrate which is divided into 3 portions; one portion of amoxicillin (45% drug) formulated as immediate release granulation designated as Pulse 1; a second portion (30% amoxicillin) formulated as delayed release pellets targeted to release the drug at [redacted] (based on in-vitro testing) designated as Pulse 2; and a third

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portion (25% amoxicillin) formulated as delayed release pellets targeted to release the drug at —— (based on in-vitro testing) designated as Pulse 3 (see the tablet design below). Although, the individual delayed release components meet USP criteria as delayed release components, i.e., no release of the drug below certain pH and 100% release when the pH triggered where coated pellets dissolve, the finished drug product is an extended release tablet. The formulation is complex in a sense that it contains —— the manufacturing process involves manufacturing —— The drug product was developed taking into consideration both pharmacokinetic and formulation aspects for this once a day therapy. The technology was deemed as pulsatile formulation. The term may be appropriate from in-vitro data but not necessarily in-vivo data. The tablets are available in —— bottles and in blister cards. Twenty-four months stability data is provided in the submission for the first 3 batches (primary stability batches) and 3 other batches manufactured at the proposed production site. Twelve months stability data for 2 of these stability batches are provided and lesser data for the third batch.

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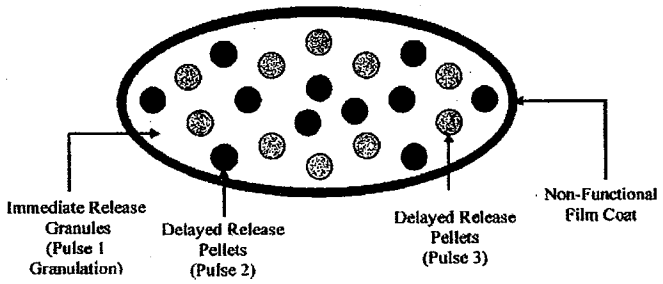

B. Description of How the Drug Product is intended to be used

The tablets are administered with food once a day for 10 days. Although the tablet size is large, it is easy swallow due to its shape and smooth surface. The tablet is not to be chewed.

C. Basis for Approvability or Not-Approval Recommendation

CMC recommendations for approvability are based on the following factors:

Satisfactory resolution of all FDA Comments

Acceptability by Compliance of all manufacturing and control facilities

Adequate in-process and finished drug product controls – see note below:

Note: The drug release specifications for the finished drug product are finalized and will be included in a follow up review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Bloc

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

119 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-1

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/s/

Shrikant Pagay
1/1/2008 06:23:35 PM
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Norman Schmuff
1/1/2008 08:23:41 PM
CHEMIST

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division:	Division of Anti-Infectives and Ophthalmology Drug Products
NDA:	50-813
Applicant:	Advancis Pharmaceutical Corporation
Stamp Date:	14-Dec-06
PDUFA Date:	14-Oct-07
Trademark:	Not given
Established Name:	Amoxicillin
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* in adolescents and adults
PAL:	Rapti D. Madurawe, Ph.D.
	YES NO
ONDQA Fileability:	☐ ☒
Comments for 74-Day Letter:	☐ ☐ N/A

Summary and Critical Issues:

A: Summary

NDA 50-813 provides for amoxicillin tablets, 775 mg (anhydrous). Amoxicillin, is a well-established β-lactam antibiotic with a long history of usage in many dosage forms. In this amoxicillin NDA, a "pulsatile release formulation (Pulsys®)" is used to achieve drug release in different regions of the gastrointestinal tract for once-a-day dosing. The pulsatile formulation contains a mixture of immediate-release amoxicillin granules and two delayed-release (enteric coated) amoxicillin pellets. The formulation is intended to deliver 45% of the dose as an immediate release, 30% of the dose as delayed-release at approximately — and 25% of the dose as delayed-release at approximately — b(4)

NDA 50-813 is cross-referenced to the applicant's corresponding amoxicillin pulsatile INDs, IND 62,576 (tablet) — b(4)

Drug Substance

The drug substance (DS) is powder grade Amoxicillin, USP. The DS is manufactured as a trihydrate by — A letter of authorization is provided to refer to DMF — for Amoxicillin Trihydrate held by —. DMF — has been reviewed and found adequate multiple times; most recently in Oct-2005. An Annual Report has been submitted since the date of last review. As the DS is the subject of an adequate DMF and is used in other US-approved drug applications, the DS is not reviewed here. Properties relevant to the drug product formulation and function are briefly discussed below and the proposed DS specifications are provided in Table 1. The proposed DS specifications appear to be the USP requirements with a — Assay range of — (USP is 900-1050 µg/mg) and additional tests for related impurities, residual solvents and particle size. b(4)

Amoxicillin trihydrate has a single crystal structure and is not polymorphic. The trihydrate form is not hygroscopic. Dehydration at high temperatures results in a hygroscopic anhydrous form which reabsorbs water to a greater extent than in the trihydrate form. DS particle size is controlled by [redacted] b(4)
[redacted] during manufacture. Specification for particle size is [redacted] NMT [redacted] The median equivalent diameter is stated to be typically [redacted]. The DS manufacturer provides to the applicant a detailed particle size distribution on an informative basis. The DS is slightly soluble in methanol and ethanol, but insoluble in solvents such as diethylether and chloroform. The DS solubility in water is 4 mg/mL. Aqueous pH solubility profile is U-shaped with a trough (< 10 mg/mL) around pH 3-7. Minimum solubility is at pH 4. Amoxicillin degrades in acidic and basic solutions and in alcohols, polyols, etc (containing –OH groups). Solution degradation is catalyzed by phosphate, di- and mono-hydrogen citrate ions. Optimum stability is in a pH 5.8 - 6.5 citrate buffer

Table 1: Proposed DS specifications

Test	Method	Acceptance Criteria
Appearance	[redacted]	
Identification		
Crystallinity		
pH		
Water		
[redacted]		
Assay		
Related Impurities		
Residual Solvents		
Particle Size		

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The DS manufacturer certifies that the DS is stable at room temperature through 60 months when stored at controlled room temperature in the original packaging [redacted] b(4)

DS stability data is referenced to the DMF.

Drug Product

The commercial DP is manufactured by Clonmel Healthcare Ltd. in County Tipperary, Ireland. The drug product (DP) is a blue, film coated, biconvex, oval shaped, printed tablet. It contains 775 mg amoxicillin, anhydrous basis. The tablet target weight is 1498 mg. DP is packaged 30-count per bottle, blister of 1 tablet, and blister card of 10 tablets. The DP is code named APC-111 MP Tablet.

1 Page(s) Withheld

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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-2

[redacted]

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The commercial DP container closure systems are: (a) [redacted] packaged 30-count per bottle; (b) blister with [redacted] packaged 1- and 10-tablets per blister. The proposed expiration dates are [redacted] for blisters stored at 25°C (77°F) and [redacted] for bottles stored at USP controlled room temperature. "Primary" stability data provided are 18-months long-term (25°C/60%RH) and 6 months accelerated (40°C/75% RH) data for 3 [redacted] DP batches packaged [redacted] bottles and [redacted] blister strips. Site-specific (Clonmel) stability data are provided DP packaged [redacted] bottles and [redacted] blister strips. Long-term and accelerated data provided are respectively, 12- and 6-months for 2 batches, and 3- and 4- months for a 3rd batch. Secondary stability data are provided for [redacted] These packaging configuratons are different from the commercial configuratons as the 10-day course of therapy was established after initiating the stability studies. Both [redacted] Clonmel packaging are said to have the same well/bottle volumes and container closure materials. Appearance, drug release, assay, degradants and water are tested under stability. Blisters showed a 5% decrease in assay value over 6-month under accelerated storage, but were stable with no significant trends under long-term and intermediate (12-months, 30°C/65% RH) storage. Bottles met specification under all test conditions. Stability data are said to be comparable between manufacturing sites. Stress studies indicate the tablet is not light sensitive and high humidity/high temperature conditions accelerate degradation.

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The 3 DP batches used for primary stability and Phase 3 clinical studies (study 111.301, 111.302 and 111.115) were manufactured by [redacted] Formulation development has gone through several development changes, but the actual differences in toxicology, IVIVC and clinical study batches are not clearly identified. The proposed commercial formulation is said to be identical to that used in the pivotal Phase 3 efficacy study, 111.302. All DP batches appear to have used the [redacted] amoxicillin USP drug substance. "Evaluation protocols" *(comparability studies?)* have been executed for 3 smaller-scale Clonmel batches for commercial site qualification and bioequivalence. Bioequivalence information is not presented in the CMC portion of the NDA.

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The applicant states that several of the commercial processes have not yet been scaled-up and optimized. The proposed commercial-scale and the current process-scale are given in Table 5 below. The commercial scale equipment differs in size and manufacturer, but is said to operate using the same principles. Many process parameters for the commercial process, including those for critical processes, are not defined in Module 3.2.P.2. Batch records are not submitted for the commercial process. Batch records are submitted for smaller scale processes at Clonmel [redacted]

Table 5: Process-scale comparison

Product/Component Name	Batch Size (kg)
APC-111 MP Tablet, 775 mg	
Amoxicillin Granules	
Amoxicillin Core Pellets	
Amoxicillin Pulse 2 Pellets	
Amoxicillin Pulse 3 Pellets	

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B: Review, Comments and Recommendation

1. The commercial-scale manufacturing process is not fully defined. Therefore, the quality of the commercial-scale DP is not known. Batch records submitted are for a smaller scale process and not for the commercial-scale processes. Two critical and complex intermediate processes — are currently at development-scale and require scale-up by a — No scale-up plan is outlined. Without a process batch record for commercial-scale manufacture, facility cGMP inspection would potentially be unacceptable. The above issues were discussed with the applicant in a teleconference date 06-Feb-07. The applicant stated the commercial process is expected to be ready by April/May 2007, but scale-up has not yet begun for key processes. b(4)
2. There is no direct linkage of the clinically tested DP to the commercial DP. Bioequivalence and stability data submitted are for DP made by the smaller-scale process. There is no stability data for the commercial packaging configurations. Slightly different packaging configurations were used in the stability studies. Available stability data may not be indicative of commercial-product stability as the packaging changes unfavorably impact factors that promote degradation (air volume, blister sealing, etc). When all the above issues are viewed collectively, the quality, stability, consistency and bioequivalency of the commercial DP become uncertain. These are potentially significant review issues for NDA approval.
3. [redacted] b(4)
4. The applicant refers to the tablet as Extended Release. Data shows that the drug concentration in plasma is very low at ~8 hours. The appropriate dosage form should be established as the tablet appears to be in between an extended-release and delayed-release formulation.
5. The dissolution specification has only 3 time points representing the end of each pH stage. This specification allows for various drug release rates at each pH stage as long as the final value is obtained. — Dissolution specifications should include additional time points. b(4)
6. The dissolution specification has wide drug release values — and values overlap with the next stage. The ranges should be tightened. Should overlaps be eliminated?
7. Blister packs failed the Assay criteria under accelerated storage conditions. Accelerated storage testing shows greater degradation for Clonmel compared to — blisters. The Clonmel — kg blisters appear to be less stable than the — blisters. Are the blisters adequately sealed, particularly in the 10 tablet card? The dimensions of the 10-card should be compared with that of the cards used in stability. Should — be used to reduce moisture? b(4)
8. [redacted] b(4)

b(4)

9. Process parameters and process controls are not adequate for appropriate definition and monitoring for manufacturing process consistency.
10. Should drug product (tablet) expiration date be calculated from the earliest manufacturing date of the constituent pulses/core pellet instead of the tablet manufacturing date?
11. The drug substance particle size *distribution* should be adequately controlled. Control of only the upper limit (X_{100}) is not sufficient.
12. In addition to the drug substance DMF review, the application requires review of about 18 DMFs for excipients, dyes and container-closure systems.
13. Recommend consultation with the ONDQA dissolution and manufacturing groups.

C: Critical issues for review

1. Commercial-scale manufacture of drug product (as described in Section B).
2. Control of attributes for Pulse 1 and Pulse 2 coatings
3. Stability in commercial packaging is unknown. Blister pack data need careful assessment.
4. Linkage of clinical material to commercial-scale material.
5. Dissolution test and establishing bioequivalency of clinically tested and commercial material.

D. Fileability

The NDA is not fileable due to the following reasons:

- A master batch record for commercial lot manufacture of drug product or a comparably detailed description of the process is not included as required in 21 CFR 314.50(d)(1)(ii)(c).
- The commercial-scale process is not defined yet and is still under development. Key processes are still at development-scale (<1/10th commercial-scale). No plan is outlined for developing a commercial-scale process from the current process.
- Pharmaceutical/process development and controls information do not demonstrate sufficient process knowledge to assure successful manufacture of commercial material.

Rapti D. Madurawe _____
Pharmaceutical Assessment Lead

_____
Date

Norman R. Schmuff _____
Branch Chief

_____
Date

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/s/

Rapti Madurawe
2/20/2007 04:45:02 PM
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Norman Schmuff
2/22/2007 10:38:09 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 50813/000
Org Code : 520
Priority : S
Stamp Date : 14-DEC-2006
PDUFA Date : 23-JAN-2008
Action Goal :
District Goal: 15-AUG-2007

Sponsor: ADVANCIS PHARM
NO CITY, , XX

Brand Name : AMOXICILLIN / APC-11
1
Estab. Name:
Generic Name: AMOXICILLIN / APC-11
1
Dosage Form: (TABLET)
Strength : 775 MG

FDA Contacts: L. MULLINS ATHEY Project Manager (HFD-800) 30
1-796-2096
S. PAGAY Review Chemist 30
1-796-1429
R. MADURAWE Team Leader 30
1-796-1408

Overall Recommendation: ACCEPTABLE on 27-NOV-2007by S. FERGUSON(HFD-3
22) 301-827-

9009

Establishment : CFN : [redacted] FEI : [redacted]

b(4)

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-NOV-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

b(4)

DMF No: AADA:

Responsibilities:

b(4)

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-FEB-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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b(4)

DMF No: AADA:

b(4)

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-JAN-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

b(4)

DMF No: 13776 AADA:

b(4)

Responsibilities:

Profile : OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-JAN-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment :

DMF No:

AADA:

b(4)

Responsibilities: