CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206628Orig1s000

CHEMISTRY REVIEW(S)

NDA 206-628

Dexmedetomidine Hydrochloride Injection (Dexmedetomidine Hydrochloride)

HQ Specialty Pharma Corporation

Xiaobin Shen, Ph.D.
for
Division of Anesthesia, Analgesia and Addiction Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-628

2. REVIEW #: 1

3. REVIEW DATE: 05-Feb-2015 (filed first version);
11-Mar-2015 (filed with updates)

4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	12-May-2014
Amendment 0006	29-Sep-2014
Amendment 0009	22-Dec-2014
Amendment 0011	02-Feb-2015
Amendment 0012	05-Feb-2015
Amendment 0014	18-Feb-2015
Amendment 0016	06-Mar-2015

Other amendments dated older than the last listed do not have CMC related information for review.

7. NAME & ADDRESS OF APPLICANT:

Name: HQ Specialty Pharma Corporation

Address: 120 Route 17 North, Paramus, NJ 07652

Representative (Agent): Joseph Pizza, President
Address is the same as above

Telephone: 201-857-8290

Fax: 201-857-8291

Email: jsqueglia@hqspecialtypharma.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Dexmedetomidine HCl Injection
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(2)

10. PHARMACOL. CATEGORY: α2-adrenergic agonist

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 400 mcg/4 mL, 1000 mcg/10 mL

13. ROUTE OF ADMINISTRATION: Injection

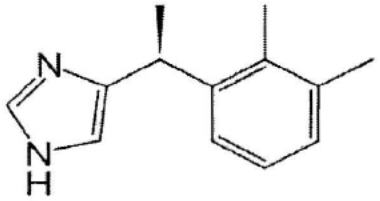
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: (S)-1H-Imidazole, 4-[1-(2,3-dimethyl-phenyl)ethyl]-, monohydrochloride
United States Adopted Name (USAN): Dexmedetomidine hydrochloride
Compendial name: Dexmedetomidine hydrochloride
Chemical structure:



Molecular Formula: $C_{13}H_{16}N_2 \cdot HCl$
Molecular Weight: 236.74

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETE	COMMENTS
(b) (4)	II	(b) (4)	Dexmede-tomidine HCl (b) (4)	3	Adequate	22-Jan-2015	
	III			4			USP Type I, no review needed.
	III			3	Adequate	24-Jan-2014	
	III			7			This DMF supports the microbiological aspect of DMF (b) (4).

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Approval	24-Feb-2015	Dr. Juandria Williams
Pharm/Tox	Acceptable with PMR	05-Feb-2015	Dr. Newton Woo
Biopharm	Acceptable	05-Feb-2015	Dr. Tien Mien Chen
Methods Validation	Not needed	23-Jan-2015	Dr. Xiaobin Shen
EA	Adequate	23-Jan-2015	Dr. Xiaobin Shen
Microbiology	Approval **pending a Complete Response to a Deficiency**	09-Mar-2015	Dr. Jessica Cole

The Chemistry Review for NDA 206-628

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for a **Complete Response**.

The applicant has not provided sufficient data to demonstrate the preservatives are effective at the minimum proposed preservative content.

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

The applicant is required to assess safety of possible leachables from the (b) (4) grey (b) (4) rubber stopper into the drug product. This PMR is initiated by pharm/tox, refer to details in pharm/tox review.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Dexmedetomidine hydrochloride is an α2-adrenergic agonist. It exists as an almost white or white (b) (4) powder. It is freely soluble in water and alcohol.

The dexmedetomidine hydrochloride drug substance is manufactured by (b) (4) in (b) (4) per DMF (b) (4). The DMF has been last reviewed by this reviewer on 22-Jan-2015 and deemed adequate. The drug substance manufacturer site EES status is acceptable.

Specifications for dexmedetomidine hydrochloride drug substance include both USP and ICH requirements. Collectively they include appearance, identification, assay, impurities, heavy metals, loss on drying, residue on ignition, residual solvents, microbial limits and bacterial endotoxin. The drug substance is packaged in (b) (4). The drug substance stability data was referenced to DMF (b) (4), which is adequate to support its use in the NDA. It has a retest date of (b) (4) months.

The drug product is available as 100 µg/mL injection solution filled as 4 mL (in 5 mL vial) and 10 mL (in 10 mL vial) packaging configurations. The excipients include methylparaben, propylparaben, and sodium chloride. All excipients are of compendial

grades. The vials are made of USP Type 1 tubular glass. The vials are stoppered with (b) (4) coated (b) (4) rubber stopper (non-drug contacting outside) that is secured with aluminum overseal containing a plastic lid. The drug product is manufactured by (b) (4). The drug product manufacturing site EES status is acceptable.

The drug product specifications include appearance, identification, pH, assay, degradation products, particulate matter, extractable volume, sterility and bacterial endotoxins. The drug product primary stability studies were conducted on 3 batches for each packaging configuration. Up to 24 months of stability data is provided for the product stored under long term (25°C/60% RH) storage conditions and 6 months of stability data is provided for products stored under accelerated conditions (40°C/75% RH). For the tested quality attributes, appearance, assay, API related impurities and degradation products, particulate matter, container closure integrity, sterility and bacterial endotoxins results remained relatively stable and showed no trend during the time periods studied for all product strength/packaging configuration combinations and under all storage conditions. pH stayed relatively unchanged under long term storage conditions, it decreased under accelerated storage conditions although it remained well within specification. The assay of the two preservatives decreased over time but still within specification by 24 months. Consequently, their degradation product (b) (4) (b) (4) increased over time and reached (b) (4)% by month 24 when stored at 25°C/60% RH. This is well within the specification of no more than (b) (4)% of the total preservatives and deemed acceptable by pharm/tox. Overall, the provided stability data supports the applicant's proposed 36 month product expiry.

The microbiology reviewer Dr. Jessica Cole deemed the NDA deficient because "The applicant has not provided data to demonstrate the preservatives are effective at the minimum proposed preservative content.", thus, she considers "these multi-dose vials have not been demonstrated to be safe for use and are not recommended for approval".

B. Description of How the Drug Product is Intended to be Used

The product is indicated for (b) (4). It should be diluted with saline or compatible solutions listed on the package insert before use. The dilution is described as either diluting 2 mL of the drug product with 48 mL of diluent to make a mixed solution of 50 mL or diluting 4 mL of the drug product with 96 mL of diluent to make a total of 100 mL. Dosing should be individualized and titrated to desired clinical response.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the dexmedetomidine hydrochloride

injection. From the CMC perspective, approval is recommended based on the following:

- The drug substance and product specifications provide adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use.
- Both drug substance and drug product are stable in the studied stability period and support the currently proposed expiry of 36 months for the drug product.

However, because the product is recommended as a Complete Response by the Microbiolgy reviewer, Dr. Jessica Cole, due to a preservative specification related deficiency, this NDA is recommended as a complete response pending resolution of the microbiology deficiency.

D. Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
		H, M, or L		The drug product is a simple injection solution, there is no apparent risk.	None

III. Administrative

A. Reviewer's Signature

See digital signature at end of document

B. Endorsement Block

Chemistry Branch Chief Name/Date: See digital signature at end of document

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Initially the carton label had a statement on the back panel saying that "The container closure is not made with natural rubber latex". This was inconsistent with the Agency's current viewpoint regarding the labeling of latex related information. Upon information request, the sponsor removed the statement.

Evaluation: Adequate. The labels have all required information from CMC perspective.

Package Insert

Refer to details of the package insert in Section 1.14.1.3 of the eCTD. The relevant edits and comments will be communicated to the applicant together with labeling comments from other review disciplines.

The SPL is provided with the required details.

Evaluation: Acceptable. The package insert's Sections 3, 11 and 16 have the information elements required per CFR 201.57.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The applicant requested categorical exclusion in accordance with 21 CFR25.31(a). There is no extraordinary circumstances exist.

Evaluation: Adequate. Categorical exclusion is granted.

III. EES Report

The overall establishment evaluation recommendation is approval.

Inspection Management - Overall Manufacturing Inspection Recommendation Status

Project	Project: Application Type	Project: Application Number	Project: Submission Type	Project: Submission Number	Task: Status	Task: Progress Status	Task: Assigned To	Task: Planned Completion Date	Project: Target Action Date	Facility Inspection - Overall Application Recommendation	Facility Inspection - Overall Application Re-evaluation Date	Task: Completion Date
Status: Complete(1)												
Facility Inspection - Overall Application Re-evaluation Date: Mar, 2016(1)												
NDA 205628-Orig1-NewNDA(1)	NDA	205628	Original	1	Complete	Late	Juandria Williams	7/25/14		Approve	3/27/16	2/24/15

Xiaobin Shen -A

Digitally signed by Xiaobin Shen -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaobin Shen -A, 0.9.2342.19200300.100.1.1=2000423313
Date: 2015.03.11 08:57:01 -04'00'

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.03.11 14:45:04 -04'00'

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

/s/

JULIA C PINTO
07/14/2014

TIEN MIEN CHEN
07/15/2014

TAPASH K GHOSH
07/16/2014

ERIC P DUFFY
07/16/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206628
2. DATES AND GOALS:

Letter Date: May 12, 2014	Submission Received Date : May 12, 2014
PDUFA Goal Date: March 12 2014	Granted Priority Review No

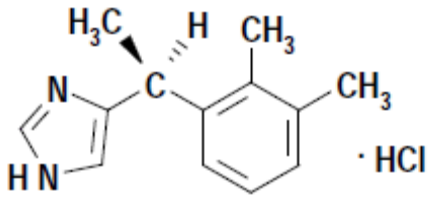
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Dexmedetomidine Hydrochloride Injection
Established or Non-Proprietary Name (USAN):	Dexmedetomidine Hydrochloride Injection
Dosage Form:	Solution
Route of Administration	IV Injectable
Strength/Potency	0.1mg/ml
Rx/OTC Dispensed:	Rx

INDICATION:

Dexmedetomidine Hydrochloride is formulated in a concentration of 100ug/ml (0.1mg/ml) in presentations of 4ml and 10ml vials. It is indicated for sedation of non-intubated patients prior to and/or during surgical.

DRUG SUBSTANCE STRUCTURAL FORMULA:



Dexmedetomidine Hydrochloride Injection MW: 236.74

1H-Imidazole, 4-[1-(2,3-dimethyl-phenyl)ethyl]-, monohydrochloride, (S)-

4. **NAME OF APPLICANT** (as indicated on Form 356h):

HG Specialty Pharma Corporation
120 Route 17 North
Paramus, NJ 07652

5. SUBMISSION PROPERTIES:

Review Priority:	Priority Review
Submission Classification (Chemical Classification Code):	
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAAAP

6. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		EES entered May 26, 2014 by J.Pinto/L.Riviera
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology Consult Sent: May 13, 2014 Jessica Cole, Ph.D. is the assigned Micro. Reviewer

Overall Filing Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes **X** No
CMC Filing Issues: **None**

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
Yes X No
CMC Comments for 74-Day Letter:
1. Microbial Testing should be included during stability at the 6 month and 12 months timepoints and yearly thereafter

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes X No
Biopharmaceutics Filing Issues: See Filing Review by Tien-Mien Chen, Ph.D.at the end of the CMC Filing Review.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
Yes No x
Biopharmaceutics Comments for 74-Day Letter:

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
Yes X No
Microbiology Filing Issues: None
See Filing Review in DARRTs by Jessica Cole, Ph.D.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes	No X
Suggested expertise for team:		

Summary of Critical Issues and Complexities

Initial Quality Assessment

The drug product is formulated as an aqueous solution and is (b) (4) sterilized. Perservatives are added to ensure antimicrobial integrity in the multidose vial presentations. It is formulated in a concenetration of 100ug/ml (0.1mg/ml) and stored in presentations of 4ml and 10ml vials. The drug product is indicated for sedation of non-intubated patients prior to and/or during surgical.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Manufacturing facilities are listed at the end of the Review.
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Manufacturing facilities are listed at the end of the Review.

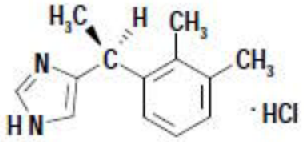
	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12	Does the section contain a description of the DS manufacturing process?	X		And Referenced to DMF (b) (4)
13	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	And Referenced to DMF (b) (4)
14	Does the section contain information regarding the characterization of the DS?	X		And Referenced to DMF (b) (4)
15	Does the section contain controls for the DS?	x		
16	Has stability data and analysis been provided for the drug substance?		X	Referenced to DMF (b) (4)
17	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

Drug Substance General Properties

Table 1: General Properties

International Non-Proprietary Name (INN)	Dexmedetomidine hydrochloride
United States Adopted Name (USAN)	Dexmedetomidine hydrochloride
Chemical Name(s)	(1) 1*H*-Imidazole, 4-[1-(2,3-dimethyl-phenyl)ethyl]-, monohydrochloride (S) (2) (+)-4-[(S)-α,2,3-trimethylbenzyl]-imidazole monohydrochloride
Product Code	(b) (4)
CAS Number(s)	CAS-145108-58-3 (hydrochloride salt) CAS-113775-47-6 (base)
Structural Formula	
Molecular Formula	$C_{13}H_{16}N_2$ * HCl
Molecular Weight	236.74
Isomerism	(S)-enantiomer
Appearance	Almost white or white, (b) (4) powder
pH of solution (1 %, aqueous solution)	About (b) (4)
Optical rotation	(b) (4) °
Actual density	1.17 g/cm^3
pKa	7.1
Melting point	About 153.8 °C (purity 99.5 %)
Partition coefficient – log(P)	(b) (4)

Dexmedetomidine Hydrochloride **API Specifications**

Table 12: Specifications

Test	Limits	Analytical Procedure
Appearance	Almost white or white	Visual
Identification A: IR	Positive	USP <197K>
Identification B: HPLC	Positive	USP
Identification C: (b) (4)	Positive	USP <191>
Assay: (b) (4)	(b) (4) %	USP
Heavy Metals	NMT (b) (4) ppm	USP <231> Method II
(b) (4)	NMT (b) (4) %	PhEur 2.4.14 (harmonized procedure with USP <281>)
Organic Impurities Any unspecified Total unspecified	(b) (4) NMT % NMT %	USP
Optical Purity (b) (4)	(b) (4) NMT %	USP
Loss on drying	NMT %	USP <731>
Residual Solvents (b) (4)	NMT % NMT %	GC (In-house)
Microbiological impurities - Total Aerobic Microbial Count - Total combined yeasts/moulds count	(b) (4) CFU/g CFU/g	USP <61>
Bacterial Endotoxin	(b) (4)	USP <85>

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?	x		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

Drug Product Composition:

Table 1: Batch formula 4 mL

Name of Ingredients	Amount per Batch (L)	
	Exhibit Batch Size (Pilot Scale) (b) (4)	Proposed Commercial Batch Size
(b) (4)		(b) (4)
Dexmedetomidine hydrochloride		
Methylparaben		
Propylparaben		
Sodium Chloride		
WFI		
Total		
Theoretical Number of Containers		

Table 2: Batch formula 10 mL

Amount per Batch (L)	
Exhibit Batch Size (Pilot Scale)	Proposed Commercial Batch Size
(b) (4)	

Drug Product Release and Stability Specifications

Table 1: Specifications

Test	Specification
Clarity of solution / Color of solution	Clear / Colorless
Particulate matter – particles (b) (4) or larger in container – particles or larger in container	Nmt (b) (4) Nmt
Extractable volume 4mL 10mL	(b) (4)
pH	
Identification of dexmedetomidine – by HPLC – by UV / DAD	Positive Positive
Assay of dexmedetomidine	(b) (4)
Identification of methyl parahydroxybenzoate (methylparaben) – by HPLC – by UV / DAD	Positive Positive
Assay of methyl parahydroxybenzoate (methylparaben)	(b) (4)
Identification of propyl parahydroxybenzoate (propylparaben) – by HPLC – by UV / DAD	Positive Positive
Assay of propyl parahydroxybenzoate (propylparaben)	(b) (4)
Optical purity (b) (4)	(b) (4) Nmt %
Degradation products – Any unspecified – Total unspecified	Nmt % Nmt %
Degradation product (b) (4)	Nmt %
Residual solvents	Comply with USP <467>
Bacterial endotoxins	Nmt (b) (4)
Test for sterility	Sterile

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		x	

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**

30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	x		.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		LOAs for all pertinent DMFs are provided.

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

Manufacturing Facilities for Drug Substance and Drug Product:

The Manufacturer for the API is:

Function	Name and Address	Facility Information	Contact Information
Manufacturing Address Finished Drug Substance:	(b) (4)	Registration Number: (b) (4) DUNS Number: (b) (4	(b) (4)
US AGENT			

Drug Product Manufacturing Sites

Table 1: Manufacture

Address	(b) (4)
FEI Number	
DUNS Number	

Table 2: Alternate Testing Site

Address	(b) (4)
FEI Number	
DUNS Number	

See appended electronic signature page}
NAME : *Julia Pinto, Ph.D.*
CMC-Lead
Division III
Office of New Drug Quality Assessment

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

Biopharmaceutics Filing Review

NDA Number	206628
Submission Date:	05/12/14
Product name/generic name of the API and dosage form and strength	Dexmedetomidine HCL
Applicant Name	HQ Specialty Pharma Corp.
Clinical Division	DAAP
Type of Submission	505(b)(2)
Biopharmaceutics Reviewer	Tien-Mien Chen, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.

BIOPHARMACEUTICS FILING CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes No v
Biopharmaceutics Filing Issues:

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes No v
Biopharmaceutics Comments for 74-Day Letter:

Additional information:

Initial Quality-Biopharmaceutics Assessment

Biopharmaceutics Synopsis, Critical Issues or Complexities
Submission: HQ Specialty Pharma Corp. submitted NDA206628, a 505(b)(2) submission, for Dexmedetomidine HCl Injectable; injection.
Introduction: It is referenced to the Hospira's Precedex (200µg/2 mL vial) the RLD (reference listed drug) approved on 12/17/99 under NDA 21038. Precedex is indicated for 1. Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Precedex by continuous infusion not to exceed 24 hours. 2. Sedation of non-intubated patients prior to and/or during surgical and other procedures. (1.2)
Product Description: Dexmedetomidine HCl Injectable; injection for infusion (after dilution and prior to injection), 400µg/4 mL vial and 1000µg/10 mL vial.
Review Objectives: The biopharmaceutics review will focus on the acceptability of the differences in composition and formulation between the RLD and the proposed injectable sterile solution for infusion.
Issues Identified: Upon Agency's request in the meeting response (dated 09/24/13) to Question No. 7 under Pre-IND 119008, the Applicant provided a side-to-side summary table comparing their proposed product to the reference product. The proposed composition and the formulation of the proposed Dexmedetomidine HCl Injectable; injection for infusion is the same as the RLD except for the addition of the inactive ingredients; i.e., preservatives of methylparaben (1.6mg/mL) and propylparaben (0.2 mg/mL) as shown below.

Product:	Proposed Drug Product	Reference Listed Drug
Product Proprietary Name:	None	Precedex®
Product Established name	Dexmedetomidine HCl	Dexmedetomidine HCl
Conditions of Use:	(b) (4) - sedation of non-intubated patients prior to and/or during surgical and other procedures.	- sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting - sedation of non-intubated patients prior to and/or during surgical and other procedures.
Active Ingredient(s):	Dexmedetomidine HCl	Dexmedetomidine HCl
Inactive Ingredients:	methylparaben, propylparaben sodium chloride WFI.	Sodium Chloride WFI
Route of Administration:	Injectable	Injectable
Dosage Form:	IV (Infusion)	IV (Infusion)
Strength:	100 µg/mL in 4 mL vial 100 µg/mL in 10 mL vial	100 µg/mL in 2mL vial

Filing Recommendation:

This NDA is fileable from the Biopharmaceutics perspective.

Biopharmaceutics Filing Review Checklist

Depending on the drug product and type of submission, some of the following parameters are necessary to initiate the Biopharmaceutics review (e.g., The NDA submission should be complete enough to review but may have minor deficiencies that can be addressed during the review cycle).

J. BIOPHARMACEUTICS FILING PARAMETERS				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?		X	IV Injectable injection
2.	Is the dissolution test part of the drug product specifications?		X	
3.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		X	
4.	Is there a validation package for the analytical method and dissolution methodology?		X	
5.	Does the application include a biowaiver request?	X		
6.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development?	X		
7.	Are there any formulation and/or manufacturing changes implemented to the clinical formulation? If yes. Are data supporting the bridging between the clinical and commercial drug products and/or manufacturing sites?		X	
8.	Is the proposed drug product a modified release dosage form (e.g., controlled release, delayed release).		X	
9.	Does the application include an IVIVC model?		X	
10.	Does the application include information/data on the in vitro alcohol dose-dumping potential of the proposed drug product?		X	
11.	Is there enough information to assess the extended release designation claim?		X	

12.	Is there any in *vivo* BA or BE study in the submission?		X	
13.	Is the Biopharmaceutics team responsible of reviewing the *in vivo* BA or BE studies? If yes. • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies)?		NA	
14.	Is there any design space proposed using in vitro release as a response variable?		X	
15.	Is the control strategy related to in vitro drug release?		X	

K. BIOPHARMACEUTICS FILING CONCLUSION AND COMMENTS

	Parameter	Yes	No	Comment
16.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
17.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	
18.	Are there any potential review issues identified?		X	
19.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?		X	
20.	Are there any internal comments for the other disciplines?		X	

{See appended electronic signature page *06/30/14*

Tien-Mien Chen, Ph.D. Date
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{See appended electronic signature page} *06/30/14*

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