CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022377Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-377

(b) (4)

Sumatriptan Injection

Review #2

King Pharma

David J. Claffey, PhD
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-377

2. REVIEW #: 2

3. REVIEW DATE: 7 MAY 2009.

4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application	17 JUL 2008
N-000(BC)	13 AUG 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	19 FEB 2009
Amendment	26 MAR 2009
Amendment	21 APR 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	King Pharmaceuticals
Address:	501 Fifth St, Bristol, TN
Representative:	Greg Carrier, VP, Regulatory Affairs

Telephone: 423 989 8166

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Sumatriptan succinate
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: selective 5-hydroxytryptamine receptor subtype 1 agonist for the acute treatment of migraine attacks with or without aura and for the acute treatment of cluster headache episodes.

11. DOSAGE FORM: Injection (subcutaneous)

12. STRENGTH/POTENCY: 6 mg / 0.5 ml (free base)

13. ROUTE OF ADMINISTRATION: subcutaneous

14. Rx/OTC DISPENSED: __x_Rx ___OTC

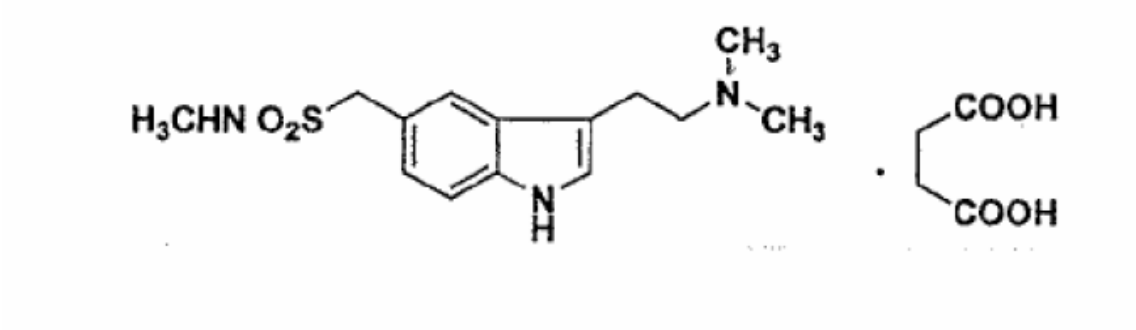
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x____Not a SPOTS product

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

[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-Nmethylmethanesulphonamide hydrogen butanedioate



Molecular formula: $C_{18}H_{27}N_3O_6S$

Molecular weight: 413.40

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			(b) (4)	4			
				4			
				3	Adequate	7 FEB 2008	Drug substance manufacturing

[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:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Sumatriptan Succinate

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	26 AUG 2008	S Ferguson
Pharm/Tox			
Biopharm			
CDRH			
Microbiology	Not yet available		Stephen Langille

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
____ Yes ____ No If no, explain reason(s) below: N/A

The Chemistry Review for NDA 22-239

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend that this Application be approved from a CMC perspective should the microbiological reviewer find it acceptable.

The biopharmaceutics reviewer (Patrick Marroum, PhD) granted a biowaiver for this application (refer to Attachment 2 of this review).

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

N/A

II. Summary of Chemistry Assessments

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

Regulatory background (from IQA): This is a 505(b)(2) application as the applicant determined that the design and operating principles of the proposed device is sufficiently different to that of the approved STATdose® system. They determined that a clinical study would be required to evaluate the usability of this product due to the differences in patient use instructions between it and the approved product.

Drug Product: The proposed drug product ("(b) (4) is composed of a pre-filled, disposable, single-use 'autoinjector' which delivers a 8.4 mg subcutaneous dose of sumatriptan succinate (*via* needle) in a sterile isotonic aqueous solution. The device differs from the approved Imitrex® product with respect to design and operation. The STATdose® system requires assembly of a prefilled cartridge with the non-disposable STATdose® injector, and disassembly after use. The proposed product is a single-use device that is completely disposable. Administration of the proposed product requires the user (or caregiver) to remove the device from its storage case, remove the safety pin, place the needle end of the device against the injection site and to apply pressure until the device actuates. The device is then held in place for 5 seconds while the drug is delivered.

The labeled strength (6 mg) is expressed in terms of the free base. Few details of the pharmaceutical development were provided, however the drug product solution was designed to be identical to that of the approved Imitrex (sumatriptan) Injection, i.e. same qualitative and quantitative composition. The actual device is the same as that used for

another marketed product by the applicant. (b) (4) The drug product specifications contain tests and acceptance criteria typical of a parenteral product in addition to several tests specific to the device (activation force, volume dispensed, dispensing time and extended needle length). Issues concerning the drug product specification detailed in the previous review have been resolved. Stability data through six months was provided in the initial submission and up to 18 months at 25°C±2°C/60%±5%RH in the 20 FEB 2009 amendment. These data support the proposed 24 month expiry period. Data were provided during this review cycle that demonstrated the comparability of the performance of the proposed drug product with that of the reference listed drug (Imitrex STATdose).

Drug substance: The drug substance, sumatriptan succinate is a well characterized water soluble small molecule with a molecular formula $C_{18}H_{27}N_3O_6S$ and a molecular weight of 413.40. The bulk of the drug substance information is cross referenced to the manufacturer's DMF (b) (4). This was most recently found to be adequate by Susan Rosencrance, PhD on 7 FEB 2008. The 20 FEB 2009 amendment contains revised drug substance specification so that it conforms with the USP monograph for sumatriptan succinate which became official after submission of this application.

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

The drug product is intended for 1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes. The maximum single recommended adult dose is 6 mg injected subcutaneously. The maximum recommended dose that may be given in 24 hours is two 6 mg injections separated by at least 1 hour.

Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery will need to be avoided. Patients will be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

C. Basis for Approvability or Not-Approval Recommendation

An approval recommendation will be made for this application from a CMC perspective pending an acceptable recommendation from the microbiological reviewer. This approval will be based on:

- the acceptable responses on 20 FEB 2009 to the 12 JAN 2009 information request and on 26 MAR 2009 to 18 MAR 2009 information request.
- the acceptable recommendation from the Office of Compliance.
- the final recommendation of the biopharmaceutics reviewer (biowaiver granted).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

David Claffey
5/7/2009 04:30:01 PM
CHEMIST

Ramesh Sood
5/7/2009 04:33:31 PM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To:	NDA 22-377
From:	Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date:	28-Apr-2009
Drug:	(b) (4) (sumatriptan) Injection
Route of administration:	Subcutaneous Injection
Strength:	6 mg/0.5 ml.
Subject:	**Approval** recommendation for NDA 22-377

Introduction (b) (4)N (sumatriptan) injection is indicated for the treatment of acute migraine attacks with or without aura and for the acute treatment of cluster headache episodes. Sumatriptan succinate and sumatriptan are marketed by the innovator firm, GlaxoSmithKline, as Imitrex® under three approved applications, NDA 20-080 (Imitrex Injection, 4 mg/0.5 mL and 6 mg/0.5 mL), NDA 20-132 (Imitrex Tablets, 25 mg, 50 mg and 100 mg) and NDA 20-626 (Imitrex Nasal Spray, 5 mg and 20 mg). King Pharmaceuticals has submitted this application as a 505(b)(2) application based on their determination that the design and operating principles of the proposed device are sufficiently different than those of the approved STATdose® system. The proposed "autoinjector" system is a sterile, pre-filled, disposable, single use delivery system, designed to deliver 6 mg/0.5 ml aqueous dose of sumatriptan (as the succinate salt) into the patient's subcutaneous tissue. The administration of the proposed product requires the user (or caregiver) to remove the device from its storage case, remove the safety pin, place the needle end of the device against the injection site and to apply pressure until the device actuates. The device is then held in place for 5 seconds while the drug is delivered. It is the same dose and concentration as the existing marketed injectable formulation (IMITREX® Injection 6 mg).

Drug Substance: The active ingredient, sumatriptan succinate [[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-N-methylmethanesulphonamide butanedioate (1:1)], is a well characterized small molecule with molecular formula $C_{18}H_{27}N_3O_6S$ and molecular weight 413.40. The drug substance is freely soluble in water. The drug substance is manufactured and supplied by (b) (4) The CMC information for the bulk drug substance is incorporated by cross-reference to DMF (b) (4). The proposed drug substance specification updated through a recent amendment to the DMF conforms to the current USP monograph. The DMF has been previously reviewed and found to be adequate to support other products.

Drug product: The qualitative and quantitative formulation of the drug product solution was designed to be identical to the approved Imitrex (sumatriptan) injection. The formulation contains sumatriptan succinate, sodium chloride, water for injection, (b) (4) . All excipients are USP/NF grade. The manufacturing steps include (b) (4) (b) (4); The proposed device to be used in this case has been previously used by King Pharmaceuticals for another approved product. The drug product quality is ensured through appropriate in-process controls and final drug product specification. The drug product specification includes tests and acceptance limits for visual clarity and color of the solution, bacterial endotoxin, sterility, two methods for identification, assay (HPLC), pH,

impurities (HPLC), activation force, volume dispensed, dispending time, and extended needle lengths.

The provided stability data support a 24-month expiration period for the product when stored at controlled room temperature.

The office of Compliance has provided a final overall acceptable recommendation for all manufacturing facilities as of 26-Aug-2008. The microbiology reviewer has found the sterility related information to be acceptable.

Recommendation: All CMC related issues had been resolved for this application. The application is recommended for **"Approval"** from the CMC perspective.

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/s/

Ramesh Sood
5/12/2009 03:04:38 PM
CHEMIST

NDA 22-377

(b) (4)

Sumatriptan Injection

King Pharma

David J. Claffey, PhD
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-377

2. REVIEW #: 1

3. REVIEW DATE: 12 DEC 2008.

4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Application	17 JUL 2008
N-000(BC)	13 AUG 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	King Pharmaceuticals
Address:	501 Fifth St, Bristol, TN
Representative:	Greg Carrier, VP, Regulatory Affairs
Telephone:	423 989 8166

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Sumatriptan succinate
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: selective 5-hydroxytryptamine receptor subtype 1 agonist for the acute treatment of migraine attacks with or without aura and for the acute treatment of cluster headache episodes.

11. DOSAGE FORM: Injection (subcutaneous)

12. STRENGTH/POTENCY: 6 mg / 0.5 ml (free base)

13. ROUTE OF ADMINISTRATION: subcutaneous

14. Rx/OTC DISPENSED: __x_Rx ___OTC

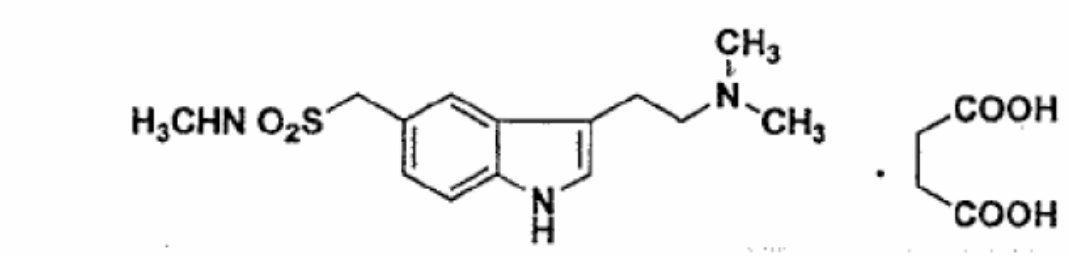
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x____Not a SPOTS product

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

[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-Nmethylmethanesulphonamide hydrogen butanedioate



Molecular formula: $C_{18}H_{27}N_3O_6S$

Molecular weight: 413.40

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			(b) (4)	4			
				4			
				3	Adequate	7 FEB 2008	Drug substance manufacturing

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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
IND	(b) (4)	Sumatriptan Succinate

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	26 AUG 2008	S Ferguson
Pharm/Tox			
Biopharm			
CDRH			
Microbiology			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
____ Yes ____ No If no, explain reason(s) below: N/A

The Chemistry Review for NDA 22-239

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation will be subject to the applicants response to the deficiencies forwarded to them in January 2009 and to the final recommendation of the microbiology reviewer.

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

N/A

II. Summary of Chemistry Assessments

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

Regulatory background (from IQA): This is a 505(b)(2) application as the applicant determined that the design and operating principles of the proposed device is sufficiently different to that of the approved STATdose® system. They determined that a clinical study would be required to evaluate the usability of this product due to the differences in patient use instruction between it and the approved product.

Drug Product: The proposed drug product ("(b) (4) is composed of a pre-filled, disposable, single-use 'autoinjector' which delivers a 8.4 mg subcutaneous dose of sumatriptan succinate (*via* needle) in an sterile isotonic aqueous solution. The device differs from the approved Imitrex® product with respect to design and operation. The STATdose® system requires assembly of a prefilled cartridge with the non-disposable STATdose® injector, and disassembly after use. The proposed product is a single-use device that is completely disposable. Administration of the proposed product requires the user (or caregiver) to remove the device from its storage case, remove the safety pin, place the needle end of the device against the injection site and to apply pressure until the device actuates. The device is then held in place for 5 seconds while the drug is delivered.

The labeled strength (6 mg) is expressed in terms of the free base. Few details of the pharmaceutical development were provided, however the drug product solution was designed to be identical to that of the approved Imitrex (sumatriptan) Injection, i.e. same qualitative and quantitative composition. The actual device is the same as that used for another marketed product by the applicant. The manufacturing process consists of (b) (4)

(b) (4) The drug product specifications contain tests and acceptance criteria typical of a parenteral product in addition to several tests specific to the device (activation force, volume dispensed, dispensing time and extended needle length). Inadequate justification was provided for the acceptance criteria for the four drug product impurities whose limits exceed those recommended by the ICH Q3B guidance – the applicant was informed of this fact in the 74-day letter and provided recommendations on how this may be remedied. Further, separate drug product acceptance criteria were proposed for release and for the stability analyses. The applicant was asked to provide a single regulatory drug product specification. Batch analysis data was provided for the three registration drug product lots. No data on the equivalent clinical lots was provided, therefore assurance that the commercial lots would be sufficiently equivalent to the clinical lots was not provided (the applicant was asked to provide these data.) Stability data through six months was provided to support the proposed 24 month expiry period. The applicant stated that they would provide a stability update during this review cycle – a determination of the commercial expiry period will be made on receipt of these data.

Drug substance: The drug substance, sumatriptan succinate is a well characterized water soluble small molecule with a molecular formula $C_{18}H_{27}N_3O_6S$ and a molecular weight of 413.40. The bulk of the drug substance information is cross referenced to the manufacturer's DMF (b) (4). This was most recently found to be adequate by Susan Rosencrance, PhD on 7 FEB 2008. In the 74-day letter the applicant was advised to revise the drug substance specification so that it conforms with the USP monograph for sumatriptan succinate which became official after submission of this application.

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

The drug product is intended for 1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes.
The maximum single recommended adult dose is 6 mg injected subcutaneously.

The maximum recommended dose that may be given in 24 hours is two 6 mg injections separated by at least 1 hour.

Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery will need to be avoided. Patients will be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

C. Basis for Approvability or Not-Approval Recommendation
The final recommendation will be subject to the applicants response to the deficiencies forwarded to them on DEC 2008 and to the final recommendation of the microbiology reviewer.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

David Claffey
1/9/2009 04:02:22 PM
CHEMIST

Ramesh Sood
1/12/2009 09:01:41 AM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-377
Applicant:	King Pharmaceuticals, Inc.
Stamp Date:	17-Jul-2008
PDUFA Date:	17-May-2008
Trademark:	(b) (4)™
Established Name:	sumatriptan (succinate)
Dosage Form:	Injection
Route of Administration:	Subcutaneous
Indication:	Migraine
PAL:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

Summary

Sumatriptan succinate and sumatriptan are marketed by the innovator firm, GlaxoSmithKline, as Imitrex® under three approved applications, NDA 20-080 (Imitrex® Injection, 4 mg/0.5 mL and 6 mg/0.5 mL), NDA 20-132 (Imitrex® Tablets, 25 mg, 50 mg and 100 mg) and NDA 20-626 (Imitrex® Nasal Spray, 5 mg and 20 mg). Imitrex® Injection is marketed in two presentations, a prefilled cartridge containing either 4 mg/0.5 mL or 6 mg/0.5 mL sumatriptan (Imitrex® STATdose®), and a 6 mg/0.5 mL vial. The approved route of administration is by subcutaneous injection. King Pharmaceuticals has submitted a 505(b)(2) application that provides for marketing of sumatriptan injection, 6 mg/0.5 mL, in a prefilled, single-use, auto-injector.

The (b) (4)™ auto-injector was developed by the firm under IND (b) (4). In September 2006, prior to submission of the IND, the firm sought concurrence from the clinical division that:

- The application could be submitted via the 505(b)(2) route, rather than as a generic application under 505(j).
- A bioequivalency study would not be required for the proposed delivery system.
- Use of aseptic processes for manufacture of the sumatriptan succinate auto-injector is acceptable.
- Submission of 6 months long-term and accelerated data in the original NDA, with update to 9 months long term data during the review cycle, would support a two year shelf life.

The firm's rationale for submission of the application under 505(b)(2) is based the differences in design and operating principles between the approved STATdose® system and the (b) (4)™ injector. The firm argued that, due to the differences between the delivery systems and the resulting differences in patient use instruction, a clinical trial to evaluate usability of the (b) (4)™ device would be needed. On 23-Oct-2006, the division forwarded its agreement to the first three items as preliminary responses for a pre-IND meeting scheduled on 24-Oct-2006. The sponsor was also advised that the proposed registration stability would not support a two year shelf life for the product. The sponsor subsequently cancelled the pre-IND meeting.

It is noted that, at the time firm proposed use of the 505(b)(2) route, a number of generic application for sumatriptan auto-injectors were already under review in the Office of Generic Drugs. It is also noted that the firm subsequently submitted a Citizens Petition (2007P-0361l) asking FDA to only approve ANDAs and 505(b)(2) applications that reference drug products containing auto-injectors that meet the following standards:

1. Operation and delivery of an auto-injector product must be identical to the RLD; specifically a product must:
   a. Contain the same active ingredients to achieve identical delivery
   b. Have a dosage form identical to the RLD
   c. Have the same route of administration (including needle length, etc.) as the RLD.
   d. Have the identical strength, quality, and purity as the RLD.

2. The "sameness" requirement means there must be no difference in operating instructions or graphic illustrations between a product and the RLD.

The Agency has not formally responded to Firm's petition; however it is noted that the above criteria, if accepted by the Agency, might preclude approval of the current 505(b)(2) application. The applicant has requested a waiver of *in vivo* bioequivalence requirements. The firm has not, however, provided a comparison of the physical properties (e.g., needle length, etc.) of the proposed (b) (4)™ auto-injector to those of the Imitrex® STATdose® system.

Drug Substance

The active ingredient, sumatriptan succinate [[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-N-methylmethanesulphonamide butanedioate (1:1)], is a well characterized small molecule with molecular formula $C_{18}H_{27}N_3O_6S$ and molecular weight 413.40. The drug substance is freely soluble in water. The bulk drug substance will be supplied by (b) (4) (b) (4) and CMC information for the bulk drug substance is incorporated by cross-reference to DMF (b) (4) The DMF has been reviewed and found adequate. [The most recent review was done by S. Rosencrance (final 07-Feb-2008).] The applicant's proposed acceptance specification for sumatriptan succinate is based on the test methods and acceptance criteria given in the USP monograph for sumatriptan (base) and the test methods described in the European Pharmacopeia (EP). A copy of the EP monograph is provided [Vol. 5, p. 105]. The sponsor states that there is no USP monograph for Sumatriptan Succinate. The USP Sumatriptan Succinate monograph was officially adopted as of USP 31/NF 26 Supplement No. 1 (official August 1, 2008). The EP and USP analytical procedures are similar but there are some differences in acceptance criteria. As an example, the USP Assay limit is 98.0-102.0% versus 97.5-102.0% for the EP monograph.

Drug Product

The (b) (4)™ system is a pre-filled, disposable, single use, needle-free injector device designed for subcutaneous delivery of 0.5 mL of a sterile aqueous solution containing sumatriptan succinate (8.4 mg) equivalent to 6 mg sumatriptan base.

The unit formulation for the drug product is shown in the applicant's Table 3. [It is presumed that the reference to (b) (4) in the footnote is an oversight since the firm has an approved (b) (4) auto-injector.]

Table 3. Sumatriptan Succinate Formulation

Ingredient	8.4 mg/0.5 mL[1] (Equivalent to 6 mg/0.5 mL as Sumatriptan Base)	
	Amount per mL	Amount per 0.5 mL
[4]Sumatriptan Succinate	16.8 mg (equivalent to 12 mg as sumatriptan base)	8.4 mg (equivalent to 6 mg as sumatriptan base)
Sodium Chloride USP	7.0 mg	3.5 mg
Water for Injection USP (b) (4)	(b) (4)	(b) (4)
		(b) (4)

The (b) (4)™ system is designed for patient self-administration or caregiver administration. The device differs from the approved Imitrex® (sumatriptan succinate injection) STATdose® system with respect to design and operation. The STATdose® system requires assembly of a prefilled cartridge with the non-disposable STATdose® injector, and disassembly after use. The (b) (4)™ system is a single use device that is completely disposable.

An exploded view of the (b) (4)™ auto-injector injector assembly is shown on the following page. It consists of a pre-filled glass cartridge contained within the external auto-injector system. The design of the device component of the (b) (4)™ system is similar to that of the EpiPen® and EpiPen Jr® (epinephrine injection) auto-injectors marketed by Meridian Medical Technologies (a King Pharmaceuticals subsidiary) under NDA 19-430. Similar auto-injector systems are used for other King/Meridian products. The primary difference between the proposed product ((b) (4)™) and the EpiPen injectors is the route of administration, which is by subcutaneous injection for sumatriptan and intramuscular injection for epinephrine.

In order to administer the dose, the user removes the device from its storage case, removes the safety pin, places the needle end against the injection site, pushes down until the injector is actuated, and holds the injector in place for 5 seconds to deliver the drug.

(b) (4) (b) (4) (b) (4)

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The proposed product specification includes appropriate test parameters for a parenteral product and device functionality tests. It is noted that the proposed shelf-life acceptance criteria for related substances includes limits for four specified (b) (4)

The NDA contains limited stability data for the proposed product. Accelerated stability data through 6 months are provided for three registration batches. Long-term stability data are limited to 9 months for two batches and 6 months for the third batch.

Critical issues for review

Drug Substance

No critical issues specific to the drug substance are identified. The applicant should be advised to adopt the current USP requirements for Sumatriptan Succinate as the regulatory specification. It is recommended that the reviewer verify that the drug substance DMF is current and that the supplier has adopted the USP monograph requirements.

Drug Product

The drug product is a drug/device combination designed for subcutaneous injection. It contains an aqueous solution that is compounded and filled into the device under aseptic conditions. The drug formulation is quantitatively identical to that of the marketed product, Imitrex® (sumatriptan succinate) Injection, 6 mg/0.5 mL. The primary critical issues for the product are related to assurance of sterility and to the design, control, and performance of the delivery device. The issue of sterility assurance will be addressed by the Microbiology reviewer. Evaluation of the device design, performance and manufacturing controls would normally be done in consultation with CDRH. In this case, the Agency has extensive experience with the design and operation of the applicant's EpiPen-type auto-injectors. CDRH review of the application is therefore not needed.

The proposed regulatory specification for the (b) (4)™ auto-injector includes acceptance criteria for impurities/degradants that exceed the ICH qualification threshold. The proposed limits should be evaluated in consultation with the pharmacology reviewer. It is noted that the sponsor refers to the USP Sumatriptan Nasal Spray to support the proposed impurity limits. The pharmacology review team has previously advised another applicant that reference to the nasal spray monograph is not acceptable since the route of administration is different. Use of comparative accelerated stability for the (b) (4)™ vs. Imitrex® STATdose® is not appropriate. Reliance on the accelerated stability results may result in overestimation of the levels of individual impurities present in the approved product.

Additional issues

Format: The NDA was submitted as a non-CTD paper submission. As a non-CTD submission, the application does not include a Pharmaceutical Development section. The proposed product is essentially a combination of the approved Imitrex® formulation with a proprietary auto-injector system that is currently used for approved products manufactured by the applicant. Except for the initial compounding process, the manufacturing procedures for the (b) (4)™ are similar to the procedures used for filling and assembly of the applicant's other approved auto-injector products. Thus, there does not appear to have been significant formulation, device, or manufacturing process development studies specific to this product.

Administrative: A claim for categorical exclusion from environmental assessment is included in the application.

Microbiology: The product is required to be sterile, thus a microbiology review is required. It is requested that the ONDQA Project Manager arrange for a microbiology consult.

Establishment Evaluation: Drug substance and drug product manufacturing sites are listed in the application; however, the applicant has not provided facility contact information or the registration number for the drug substance manufacturer. The EER will be submitted when the information is provided by the firm.

Labeling/Established Name: The product is labeled based on the content of the active moiety, sumatriptan, not the salt form. In order to ensure consistency between the established name and labeled potency, the applicant should be advised to use the established name 'sumatriptan injection' in labeling. Correction of the innovator labeling is a separate issue that should be addressed in the future.

The applicant submitted an annotated copy of the draft physician and patient labeling package in the NDA, but did not submit carton and container labels. The applicant states that draft labeling (container, carton, prescribing information) will be submitted separately in electronic format, including SPL. The electronic submission had not been received as of 8/11/08.

Comments for 74-Day Letter

The drug substance specification should be revised to comply with the requirements of the USP Sumatriptan Succinate monograph, which became official on August 1, 2008.

We are unable to locate the regulatory specification for the proposed product in the submission. A table titled "Proposed Finished Product Specifications" is included in the application (Table 6, Vol. 1, p. 101 or Table 4-4 Vol. 5, p. 10). This, however, appears to be an (b) (4) release specification rather than a regulatory (shelf-life) specification for the product, as you include justification for (b) (4) in the submission (Vol. 5, pp. 80-85). The regulatory specification should be submitted for review. This specification should include all tests, analytical procedures, and acceptance criteria applicable throughout the product shelf-life.

The proposed acceptance criteria for several specified impurities, and individual unknown impurities, in the (b) (4)™ auto-injector exceed the ICH qualification threshold, which is 0.5% w/w for the maximum daily dose of 12 mg. The justification provided for the proposed limits is based, in part, on the limits given in the USP monograph for Sumatriptan Nasal Spray and, in part, on comparison of accelerated stability data for the proposed (b) (4)™ auto-injector to accelerated data obtained by testing the approved innovator product, Imitrex® Injection.

- The impurity limits given in the USP Sumatriptan Nasal Spray monograph are only applicable to a product intended for delivery by the intranasal route. As there is no compendial monograph for Sumatriptan Succinate Injection, no public standard for acceptable levels of exposure sumatriptan related substances via the parenteral route exists.
- (b) (4)
-

With respect to product labeling, we recommend that the established name for the product be consistent with the expression of potency. Please revise the established name to "sumatriptan injection" and revise product labeling to indicate the relationship between the active ingredient (sumatriptan succinate) and the active moiety (sumatriptan).

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is a well-characterized small molecule and the active formulation is relatively simple. The device design is not novel and the manufacturing processes related to assembly of the device are not complex. The OPS Microbiology Staff will be consulted regarding sterile process validation. The submission does not appear to require a review by the Manufacturing Sciences Branch. Assignment the NDA to a single CMC reviewer is recommended. The ONDQA Biopharmaceutics Staff should be consulted regarding the applicant's request for a waiver of *in vivo* BE studies.

Martha R. Heimann, Ph.D. _____
Pharmaceutical Assessment Lead Date

Ramesh Sood, Ph.D. _____
Branch Chief Date

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

/s/

Martha Heimann
8/13/2008 04:09:14 PM
CHEMIST

Added 'three or more batches' the the 74-day letter comment on impurities comparison.

Ramesh Sood
8/14/2008 10:25:57 AM
CHEMIST