CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-444

Chemistry Review(s)

Table of Contents
NDA 21-444
Risperdal (risperidone)
Orally Disintegrating Tablets

Volume 1

Volume 2

NDA 21-444

Risperdal® (risperidone) Orally Disintegrating Tablets

Janssen Research Foundation

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-444 Risperdal® (risperidone) Orally Disintegrating Tablets**

2. **CHEMISTRY REVIEW #2**

3. **REVIEW DATE:** March 30, 2003

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** CMC Review #1 dated September 16, 2002

6. **SUBMISSION BEING REVIEWED:**

Submission Reviewed	Document Date
EDR-Response (AZ)	31-JAN-2003
CMC Information Request	10-MAR-2003
CMC Information Request	13-MAR-2003
EDR-Response (BL)	13-MAR-2003
EDR-Response (BC)	26-MAR-2003

7. **NAME AND ADDRESS OF APPLICANT:** Janssen Research Foundation
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

8. **DRUG PRODUCT NAME:**

Proprietary:	Risperdal® Orally Disintegrating Tablets
Nonproprietary/USAN[1989]:	risperidone
Code Name/Number:	not applicable
Chem. Type/Ther. Class:	3S

9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Schizophrenia

11. **DOSAGE FORM:** Disintegrating Tablet

12 **STRENGTHS:** 0.5mg (light coral, round, biconvex, etched **R0.5**)
1.0mg (light coral, square, biconvex etched **R1**)
2.0mg (light coral, round, biconvex, etched **R2**)

13. **ROUTE OF ADMINISTRATION:** Oral

14. **DISPENSED:** x RX ___OTC

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___ Yes x NO

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**
3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one

Molecular formula: $C_{23}H_{27}FN_4O_2$

Molecular Weight:
CAS Registry # 106266-06-2

17. **RELATED/ SUPPORTING DOCUMENTS:**

A. DMF's:

—	II	J&J Pharma API Support, Division of Janssen Pharmaceutica	Risperidone	1	Adequate	28-SEP-01	drug substance
—	II	—	— (Amberlite —)	1, 7	Inadequate Inadequate Adequate Memo to DMF File	22-OCT-01 20-AUG-02 24-OCT-02 24-MAR-03	(7: The applicant has set specifications for
—	III	—	—	1	Adequate	26-MAR-02	blister packaging
—	III	—	—	1	Adequate	09-AUG-02	blister packaging

[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

B. Other Documents:

20-272	Janssen Research Foundation	Risperdal® Tablets	12-DEC-92
20-588	Janssen Research Foundation	Risperdal® Oral Solution	19-JUN-96
21-330	Glaxo-SmithKline	Commit® (Nicotine Polacrilex)	31-OCT-02

18. **STATUS:**

EES	OC Overall recommendation is Acceptable	16-SEP-02	Office of Compliance
Methods Validation	Requested Methods and validation data Revised Method Validation packaged received from applicant	13-MAR-03 28-MAR-03	Donald Klein, Ph.D.
DDMAC/DMETS ODS	Not Acceptable Acceptable Presently still negotiating with the agency	29-MAR-02 09-SEP-02 28-MAR-03	Hye-Joo Kim, Pharm.D. Alina Mahmud, RPh. DDMAC/DMETS and HFD-120
Microbiology	Approval	04-MAR-02	James McVey, Ph.D.
OCPB	Approvable Approval	26-JUL-02 03-MAR-03	Brian Booth, Ph.D. Vaneeta Tandon, Ph.D.
EA	Acceptable	16-SEP-02	Donald Klein, Ph.D.
Clinical	Approval	07-JUL-02	Andy Mosholder, M.D.
Pharm/Tox	N/A	N/A	N/A

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-444

I. Recommendations:

A. Recommendations and Conclusions on Approvability:

NDA 21-444 for Risperdal® (risperidone) Orally Disintegrating Tablets is recommended Approval from the CMC standpoint.

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

Individual Specified — the reduction from NMT —% to NMT —% will be reevaluated by the applicant in two years from approval of this NDA.

Sponsor already agreed. Do not want to raise this to level of phase IV commitment per Tom Oliver

BA 4/1/03

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

As stated in CMC Review #1, the orally disintegrating tablet formulation of risperidone, ——Quicklet™, has been developed by the Janssen Research Foundation (JRF). Janssen intends to market the 0.5 mg (round, light coral, **R0.5**), 1.0 mg (square, light coral, **R1**), and 2.0 mg (round, light coral, **R2**) Risperdal® Orally Disintegrating Tablets. Janssen has assigned the following formula code designations to each strength: 0.5 mg is **F554**; 1.0 mg is **F555**; and 2.0 mg is **F556**. These tablets are manufactured from a common formulation of 2 mg/g suspension of risperidone. It should be noted that during the clinical investigation and development, Janssen utilized a 4.0 mg Orally Disintegrating Tablet, but the applicant does not plan to marketing the 4.0 mg dosage strength.

Added drug expiry statement to letter

BA 4/1/03

Below is a summary of the function of the non-active components.

1. — Gelatin, NF; Mannitol, USP; Glycine, USP.
2. Carbomer Simethicone, USP; Purified Water, USP.
3. Sodium Hydroxide, NF.
4. Aspartame, NF; Peppermint Oil, NF.
5. Red Ferric Oxide, NF.
6. — resin AMBERLITE —

The applicant submitted 7 separate lots of primary stability data (25°C/60%RH, 30°C/70%RH, and 40°C/75%RH) consisting of 0.5 mg (3 lots) and 2.0 mg (3 lots) and 1.0 mg (1 lot) in the proposed marketing blister packaging —

The Overall Compliance recommendation was acceptable.

As a result of Review #2, the following CMC issues were resolved:

1. Janssen's acceptance specifications for the Amberlite Resin — submitted in NDA 21-444 were found satisfactory. This conclusion is supported by the following:
   a. DMF — was found adequate on 10/24/02 by M.Theodorakis, Ph.D., HFD-170.
   b. Memo to the DMF File dated 3/24/03, D.Klein, HFD-120.

2. Based upon the analytical data submitted (summarized in Table 9), the applicant has established acceptable manufacturing parameters.

3. The applicant has tightened the specification limits as follows:

   a. Individual Specified — from NMT —% to NMT — %.

   b. Individual Specified — the reduction from NMT — % to NMT — % will be reevaluated by the applicant in two years from approval of this NDA.

   c. Individual Unspecified from NMT — % to NMT— %.

   These NDA 21-444 specifications are tighter than those of the currently approved Risperdal® Immediate Release Tablets (NDA 20-272).

4. Adequate analytical method validation information was provided in order for the critical methods to be evaluated by the FDA laboratory.

Drug Substance

As stated in CMC Review #1, risperidone is a pychotropic agent belonging to the chemical class of benzisoxazole derivatives. Risperidone blocks both the serotonin 5-HT_{2A} and dopamine D_2 receptors.

The applicant references DMF —, Type II, for the drug substance and the DMF — Holder is the Janssen Research Foundation. DMF — was found adequate on September 29, 2001 by R.Lostritto (HFD-120).

The drug substance has two distinct polymorphs, Polymorph I and Polymorph II. Polymorph I is the thermodynamically stable polymorph and is used in the manufacture of the Risperdal® Orally Disintegrating Tablets (0.5 mg, 1.0 mg, and

2.0 mg).

Janssen used three different drug substance lots to manufacture the primary drug product stability batches, 0.5 mg (3x), 1.0 mg (1x), and 2.0 mg (3x). Each of these drug substance lots were manufactured using the same synthetic approach.

The drug substance manufacturing site was found Acceptable by Compliance.

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

Dosing recommendations for Risperdal® (risperidone) Orally Disintegrating Tablets (0.5 mg, 1.0 mg, and 2.0 mg) are the same as those for commercially available Risperdal (risperidone) Tablets. The maximum dose is 16 mg per day. The Risperdal® Orally Disintegrating Tablet formulation disintegrates in saliva within seconds and releases risperidone bound to a resin (Amberlite ..., before swallowing. Since the risperidone is bound to the ion exchange resin, the drug risperidone's unpleasant taste is masked. After ingestion, the risperidone is released from the resin in the gastrointestinal tract for absorption.

The applicant proposed to market the drug product in 2 x 2 ——
blister packaging in Climate Zones I, II, III as proposed by the applicant.

As a result of Review #2, the primary stability data supports a 24 month expiration date.

As a result of Review #2, the following statement was added to the labeling:

> *Phenylketonurics: Phenylalanine is a component of aspartame Each 2 mg Risperdal Orally Disintegrating Tablet contains 0.56 mg phenylalanine; each 1 mg Orally Disintegrating Tablet contains 0.28 mg phenylalanine and each 0.5 mg Orally Disintegrating Tablet contains 0.14 mg phenylalanine.*

C. Basis for Approvable or Not-Approval Recommendation:

NDA 21-444 is approved from the chemistry standpoint. There are no outstanding CMC issues related to this application.

D. Administrative:
Reviewer: Donald N. Klein, Ph.D.
Team Leader: Thomas F. Oliver, Ph.D.
Project Manager: Steve Hardeman, R.Ph.

Redacted 51

pages of trade

secret and/or

confidential

commercial

information

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

/s/

Donald Klein
3/31/03 10:41:59 AM
CHEMIST

minor revisions made as requested on 3/31/03

Thomas Oliver
3/31/03 10:49:27 AM
CHEMIST

CHEMISTRY REVIEW

NDA 21-444

Risperdal — (risperidone) Orally Disintegrating Tablets

Janssen Research Foundation

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-444 Risperdal ——— (risperidone) Orally Disintegrating Tablets**
2. **CHEMISTRY REVIEW #1**
3. **REVIEW DATE:** September 16, 2002
4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** None

6. **SUBMISSION BEING REVIEWED:**

Submission Reviewed	Document Date
ORIGINAL	16-NOV-01
Amendment- (BL)	04-APR-02
Amendment- (BC)	23-AUG-02

7. **NAME AND ADDRESS OF APPLICANT:** Janssen Research Foundation
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

8. **DRUG PRODUCT NAME:**

Proprietary:	Risperdal ———
Nonproprietary/USAN[1989]:	risperidone
Code Name/Number:	not applicable
Chem. Type/Ther. Class:	3S

9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Schizophrenia

11. **DOSAGE FORM:** Disintegrating Tablet

12. **STRENGTHS:** 0.5mg (light coral, round, biconvex, etched **R0.5**)
1.0mg (light coral, square, biconvex etched **R1**)
2.0mg (light coral, round, biconvex, etched **R2**)

13. **ROUTE OF ADMINISTRATION:** Oral

14. **DISPENSED:** XXX RX ___OTC

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Yes XXX NO

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**
3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one

Molecular formula: $C_{23}H_{27}FN_4O_2$
Molecular Weight:
CAS Registry # 106266-06-2

17. **RELATED/ SUPPORTING DOCUMENTS:**

A. DMF's:

DMF #	Type	Holder	Item Referenced	Code	Status	Date Review Completed	Comments
	II	J&J Pharma API Support, Division of Janssen Pharmaceutica	Risperidone	1	Adequate	28-SEP-01	drug substance
	II		(Amberlite	1	Inadequate Inadequate	22-OCT-01 20-AUG-02	
	III			1	Adequate	26-MAR-02	blister packaging
	III			1	Adequate	09-AUG-02	blister packaging

[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

B. Other Documents:

Drug	Applicant	Trade Name	Date Applied
20-272	Janssen Research Foundation	RISPERDAL Tablets	12-DEC-92
20-588	Janssen Research Foundation	Risperdal Oral solution	19-JUN-96

18. STATUS:

EES	OC Overall recommendation is Acceptable	16-SEP-02	Office of Compliance
Methods Validation	Not submitted to FDA lab for validation because of CMC deficiencies		Donald Klein, Ph.D.
DMETS	Not Acceptable Acceptable	29-MAR-02 09-SEP-02	Hye-Joo Kim, Pharm.D. Alina Mahmud, RPh.
Microbiology	Approval	04-MAR-02	James McVey, Ph.D.
OCPB	Approvable	26-JUL-02	Brian Booth, Ph.D.
EA	Acceptable	16-SEP-02	Donald Klein, Ph.D.
Clinical	Approval	07-JUL-02	Andy Mosholder, M.D.
Pharm/Tox	not assigned		

APPEARS THIS WAY
ON ORIGINAL

Executive Summary Section

The Chemistry Review for NDA 21-444

I. Recommendations:

A. Recommendations and Conclusions on Approvability.
NDA 21-444 for Risperdal —— (risperidone) Orally Disintegrating Tablets is recommended Approvable from the CMC standpoint. The approval from the CMC standpoint is contingent on adequate responses to the CMC deficiencies related to the drug product as outlined in this review.

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

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

The orally disintegrating tablet formulation of risperidone, —— /Quicklet™, has been developed by the Janssen Research Foundation (JRF). Janssen intends to market the 0.5mg (round, light coral, **R0.5**), 1.0mg (square, light coral, **R1**), and 2.0mg (round, light coral, **R2**) Risperdal® Orally Disintegrating Tablets. Janssen has assigned the following formula code designations to each strength: 0.5mg is **F554**; 1.0mg is **F555**; and 2.0mg is **F556**. These tablets are manufactured from a common formulation of 2mg/g suspension of risperidone. It should be noted that during the clinical investigation and development, Janssen utilized a 4.0mg Orally Disintegrating Tablet, but the applicant does not plan to marketing the 4.0mg dosage strength.

Below is a summary of the function of the non-active components.

1. Gelatin, NF; Mannitol, USP; Glycine, USP.
2. Carbomer
   Simrthicone, USP; Purified Water, USP.
3. Sodium Hydroxide, NF.
4. Aspartame, NF; Peppermint Oil, NF.
5. Red Ferric Oxide, NF.
6. resin AMBERLITE

The applicant submitted 7 separate lots of primary stability data (25°C/ 30°C/ and 40°C/) consisting of 0.5mg (3 lots) and 2.0mg (3 lots)

and 1.0mg (1 lot) in the proposed marketing blister packaging —— However, these seven lots were all manufactured in 1998.

Drug Substance

Risperidone is a pychotropic agent belonging to the chemical class of benzisoxazole derivatives. Risperidone blocks both the serotonin 5-HT_{2A} and dopamine D_2 receptors.

The applicant references DMF —— Type II, for the drug substance and the DMF Holder is the Janssen Research Foundation. DMF —— was found adequate on September 29, 2001 by R.Lostritto (HFD-120).

The drug substance has two distinct polymorphs, Polymorph I and Polymorph II. Polymorph I is the thermodynamically stable polymorph and is used in the manufacture of the Risperdal® Orally Disintegrating Tablets (0.5mg, 1.0mg, and 2.0mg).

Janssen used three different drug substance lots to manufacture the primary drug product stability batches, 0.5mg (3x), 1.0mg (1x), and 2.0mg (3x). Each of these drug substance lots were manufactured using the same synthetic approach.

The drug substance manufacturing site was found Acceptable by Compliance.

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

Dosing recommendations for Risperdal® —— (risperidone) Orally Disintegrating Tablets (0.5mg, 1.0mg, and 2.0mg) are the same as those for commercially available Risperdal (risperidone)Tablets. The maximum dose is 16mg per day. The Risperdal® —— formulation disintegrates in saliva within seconds and releases risperidone bound to a resin (Amberlite) before it is swallowed. Since the risperidone is bound to the ion exchange resin, the drug risperidone's unpleasant taste is masked. After ingestion, the risperidone is released from the resin in the gastrointestinal tract for absorption.

The applicant proposes to market the drug product in 2 x 2 —— blister packaging.

At this time, an expiration date cannot be determined due to the outstanding stability and specification deficiencies.

C. Basis for Approvable or Not-Approval Recommendation

NDA 21-444 (Risperdal —— Tablets, Janssen Research Foundation) is recommended for approvable based on the following:

a. CMC concerns relate to the drug product. The deficiencies are detailed in the draft deficiency letter at the end of this review.

D. Administrative:

Reviewer: Donald N. Klein, Ph.D.
Team Leader: Thomas F. Oliver, Ph.D.
Project Manager: Steve Hardeman, R.Ph.

59 pages redacted from this section of the approval package consisted of draft labeling

---

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

/s/

Donald Klein
9/16/02 01:58:47 PM
CHEMIST

revisions made as discussed this morning

Thomas Oliver
9/16/02 02:21:02 PM
CHEMIST