CONSUMER INC.
McNeil Consumer Healthcare Division

JUSTIFICATION OF PROPOSED SPECIFICATIONS

Formula Number: C-1376-1

Product Specification Justification Document Number:
PSJ-1376 US

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1. INTRODUCTION

The justification of the specifications for active ingredients, related substances, physical tests, and performance attributes for formula C-1376-1 are described in this document. C-1376-1 is a chewable tablet containing Calcium Carbonate (CALCIUM_CARBONATE) (800mg/tablet), Famotidine (FAM) (10mg/tablet), and Magnesium Hydroxide (MGOH) (165mg/tablet).

C-1111-1 is a product with the same active ingredients as C-1376-1. The C-1111-1 and C-1376-1 formulations are similar with the only exception being a change in colorant. D&C Yellow No. 10 Aluminum Lake has been removed and Iron Oxide Yellow has been added to C-1376-1.

2. U.S. HEALTH AGENCY FILING STATUS

C-1111-1 is filed with the regulatory health agency in the U.S. (NDA 20-958)[1]. The C-1376-1 specifications will align to the C-1111-1 specifications within NDA 20-958. Historical data for the C-1111-1 formulation supports the specifications.

3. COMPENDIAL STATUS

This product does not have a United States Pharmacopeia (USP) drug product monograph.

4. SENSORY TESTS

The sensory attributes to be examined during R&D Stability testing include: Appearance, Color, and Odor. The specification lists an action limit of NMT 3 for each of these attributes. This is equivalent to a change that is barely noticeable to the consumer. Appearance, Color and Odor are not NDA submitted specifications.

5. DETAILED DESCRIPTION OF PRODUCT

The appearance description for C-1376-1 per the Master Formula Record (MFR)[2] and the NDA[1] is: Green, mottled round tablet with concave center debossed with “P” on one side with a characteristic mint odor.

6. IDENTIFICATION

6.1. Identification of FAM by High Performance Liquid Chromatography (HPLC)

The identification test passes when the HPLC retention time of the FAM peak of the assay sample preparation corresponds to the retention time of the FAM peak of the standard preparation when concomitantly measured. This test is only performed at release and is aligned with the NDA.

6.2. Identification of FAM by Thin Layer Chromatography (TLC)

The identification by Thin Layer Chromatography (TLC) passes when the sample exhibits a principal spot of approximately the same intensity and of approximately the same R_f value as the principal spot of the standard solution. This test is only performed at release and is aligned with the NDA.

6.3. Identification for Calcium and Magnesium by Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES)

The identification test by ICP-OES passes when the emission lines for Calcium and Magnesium are the same in the sample solutions as in the standard solutions when concomitantly measured. This test is performed only at release.

6.4. Identification of Calcium by Wet Method

The identification test for Calcium passes when a test solution responds to the chemical test for Calcium, when performing the test method listed in the specification document. This test is performed only at release.

6.5. Identification of Magnesium by Wet Method

The identification test for Magnesium passes when a test solution responds to the chemical test for Magnesium, when performing the test method listed in the specification document. This test is performed only at release.

7. PHYSICAL ANALYSES

7.1. Specifications for Acid Neutralizing Capacity

Release: The limits are set to 20.0 – 23.4 mEq/tablet per the NDA[1].

Stability: The limits are set to NLT 18.9 mEq/tablet per the NDA[1].

7.2. Color

Data will be collected at release and on stability using a data collection testing code, per SOPs 17-QA-QA-010 and 99-RD-AN-064, until sufficient data has been collected to set appropriate specifications. A review of the data collected will take place as per product specification lifecycle requirements as described in SOP 99-QA-DC-1002.

8. ASSAY

Analyte	Label Claim	Release Limit	Stability Limit
CALCIUM_CARBONATE	800mg/tablet	92.0% - 108.0%	90.0% - 110.0%*
FAM	10mg/tablet	93.0% - 107.0%	90.0% - 110.0%
MGOH	165mg/tablet	92.0% - 108.0%	90.0% - 110.0%*
Sodium (NA)	N/A	LT 5mg/tablet	N/A

*Performed at Initial Time-Point only. Stability testing other than the Initial Time-Point Testing is not required as the test for Acid Neutralizing Capacity is an acceptable indicator of the strength of the base metals.

8.1. Active Ingredient(s)

8.1.1. CALCIUM_CARBONATE (800mg/tablet)

Release: The limits are set to allow for acceptable analytical variation and are aligned with the NDA[1].

Stability: The limits are aligned with NDA[1,3].

8.1.2. FAM (10mg/tablet)

Release: The limits are set to allow for acceptable analytical variation and to ensure product remains within the stability limits through expiry and are aligned with the NDA[1.]

Stability: The limits are aligned with NDA[1].

8.1.3. MGOH (165mg/tablet)

Release: The limits are set to allow for acceptable analytical variation and are aligned with the NDA[1].

Stability: The limits are aligned with NDA[1,3].

8.2. Preservative(s)

There are no preservatives in this product.

8.3. Sodium

Release: The limits ensure that Sodium levels for a single dosage unit are less than 5 mg and is aligned with 21 CFR 201.64 Sodium Labeling[4]. The limits are aligned with NDA[1].

Stability: Not required per the NDA[1].

9. RELATED SUBSTANCES/DEGRADATION PRODUCTS

Table 1: Specified Degradation Products and Acronyms

FAM	
Famotidine Impurity A1	FAM-A1
Famotidine Impurity A2	FAM-A2
Famotidine Impurity A3	FAM-A3
Famotidine Impurity A6	FAM-A6
Famotidine Impurity C1	FAM-C1

NOTE: No degradation products are generated from the inorganic actives, calcium carbonate and magnesium hydroxide.

Table 2: Degradation Product Specifications

Degradation Product	**ICH ID Threshold[5]**	**ICH Qualification Threshold**	**ICH Reporting Threshold**	**Release Limit**	**Stability Limit**
Degradation Products Related to FAM					
FAM-A1	0.2%	0.5%	0.1%	< 0.3%	< 0.5%
FAM-A2	0.2%	0.5%	0.1%	< 0.3%	< 0.5%
FAM-A3	0.2%	0.5%	0.1%	< 0.3%	< 0.5%
FAM-A6	0.2%	0.5%	0.1%	< 0.6%	< 1.0%
FAM-C1	0.2%	0.5%	0.1%	< 0.2%	< 0.5%
Individual Unspecified Degradation Products quantitated relative to FAM	0.2%	0.5%	0.1%	NMT 0.2%	NMT 0.2%
Total Degradation Products quantitated relative to FAM	N/A	N/A	N/A	NMT 1.0%	NMT 1.5%

9.1. FAM Related Substances

The maximum daily dose of FAM is 40 mg.[6]

The potential degradation products of FAM were the subject of research report, RR-2922[7]. Any degradation products, other than FAM-A1, FAM-A2, FAM-A3, FAM-A6 and FAM-C1, observed will be monitored as an Unspecified Degradation Product Quantitated Relative to FAM for Release and Stability. Statistical analysis was not performed because the minimum data requirements were not met per SOP 17-QA-QA-1003.

9.1.1. FAM-A1

Release: The limit is set to the NDA[1].

Stability: The limit is set to the NDA[1].

9.1.2. FAM-A2

Release: The limit is set to the NDA[1].

Stability: The limit is set to the NDA[1].

9.1.3. FAM-A3

Release: The limit is set to the NDA[1].

Stability: The limit is set to the NDA[1].

9.1.4. FAM-A6

Release: The limit is set to the NDA[1] and supported by the toxicity assessment study[8].

Stability: The limit is set to the NDA[1] and supported by the toxicity assessment study[8].

9.1.5. FAM-C1

Release: The limit is set to the NDA[1].

Stability: The limit is set to the NDA[1].

9.1.6. Unspecified Degradation Products Quantitated Relative to FAM

The method has been validated to monitor FAM related substances and unspecified degradation products relative to FAM[9].

Release: The limit is set to the NDA[1].

Stability: The limit is set to the NDA[1].

9.1.7. Total Degradation Products Quantitated Relative to FAM

Release: The limit is set to the NDA[1].

Stability: The limit is set to the NDA[1].

10. UNIFORMITY OF DOSAGE UNITS

The limits for Uniformity of Dosage Units apply to FAM, CALCIUM_CARBONATE, and MGOH and reflect the requirements of USP <905>. This test is only performed at release and is aligned with the NDA[1].

11. DISSOLUTION

The limit is set to the approved NDA[1] stability and release limit of 75% (Q) at 30 minutes for FAM. Staged evaluation is in accordance with USP <711> Dissolution.

12. RESIDUAL SOLVENTS

Methanol and Acetone are used in the manufacture of the coated famotidine and are controlled through the in process testing of the coated famotidine. No other solvents are used during the manufacture of this product and therefore further testing is not required. Compliance with USP <467> will be demonstrated per 99-RD-AN-051.

13. MICROBIOLOGICAL REQUIREMENTS

Release:

Total Aerobic Microbial Count (TAMC)	NMT 1000 CFU/g
Total Yeast Mold Count (TYMC)	NMT 100 CFU/g
Escherichia coli	Absent/g
Objectionable organisms	Absent

Stability: Water Activity is set to an alert level of ≥ 0.75.

The microbiological requirements are compliant with SOP 99-QA-ML-020, *Establishing Microbiological Specifications and Waiver for Reduced Testing of Finished Products*, and SOP 99-QA-ML-029, *Microbiological Stability Requirements*. Microbiological specifications are aligned with the USP and comply with NDA[1].

14. VERSION HISTORY

Document Version	Date Approved	Version Description
PSJ-1376 US Version 1.0		Initial Issuance

15. REFERENCES

1. NDA 20-958. 3.2.P.5.1. SPECIFICATIONS [PEPCID® COMPLETE®, CHEWABLE TABLET]. CONNECT Doc ID: J0081743.
2. MFR-C-1376-1. CONNECT Doc ID: J0178343.
3. 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment [10mg famotidine, 800mg calcium carbonate, 165mg magnesium hydroxide chewable tablet]. CONNECT – supporting document to PSJ-1376-US, Doc ID: J0178921.
4. 21 CFR 201.64 Sodium Labeling. CONNECT – supporting document to PSJ-1376 US, CONNECT Doc ID: J0178921.
5. Impurities in New Drug Products. Q3B(R2). ICH Harmonized Tripartite Guideline. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2 June 2006. CONNECT – supporting document to PSJ-1376-US, Doc ID: J0178921.
6. Minimum Therapeutic Dose and Maximum OTC Daily Dose: Reference Information. CONNECT Doc ID: J0181277.
7. RR-2922. Known Impurities of Famotidine. CONNECT Doc ID: J0122260.
8. Qualification of Famotidine Degradant A6 (26-April 2012). CONNECT Doc ID: J0051049.
9. MVR/AMTR-2095-ASY,ID,DEGS-JJCILN. Test Method Validation and Transfer Report for Identification/Assay /Degradation Products of Famotidine in Calcium Carbonate 800mg, Magnesium Hydroxide 165mg, and Famotidine 10mg Tablets by HPLC. CONNECT Doc ID: J0177815.