Example of a Completed Application for a New Version of an Active Pharmaceutical Ingredient Master File (APIMF)

This example of a completed application form is for the submission of a new version of an existing APIMF.

In this submission the applicant has submitted a new version of the APIMF referring to amendment #1c, meaning that there are substantive differences between the original and new versions.

In this scenario, the applicant has lodged two amendments after the original acceptance of the APIMF (version AP/01 and RP/01). These were given the WHO Prequalification Team: medicines (PQTm) codes AAME-2014-0098 and AAME- 2014-0134.

In accordance with the amendment procedure the applicant is required to collate these changes within two years and submit a revised APIMF incorporating these changes. Therefore a revised version of the APIMF is now being submitted.

In order to comply with the amendment procedure, the revisions in the new APIMF version include only changes that have been accepted previously; with the exception of the noted annual notification amendment (AAN) and editorial changes. The editorial changes are listed in section 4.1 and the AAN changes in section 4.2.

In section 5, a Summary of Changes table has been completed, noting all differences between the original and the new APIMF versions. This includes changes made in the two previous amendments and the changes made as part of this submission (editorial and AAN changes).
In support of this application the applicant has provided:

1. Completed application form (in Word and text-selectable PDF).
2. A revised APIMF divided into the open part and restricted part sections, correctly formatted and bookmarked.
3. A tracked change API Quality Information Summary (QIS).[1]

Note: The API QIS is issued as part of an APIMF or amendment acceptance letter. It should not be confused with the Quality Information Summary: Product Dossier (QOS-PD), which is a key element of an application seeking prequalification of a finished pharmaceutical product.

Application for New Version of an Active Pharmaceutical Ingredient Master File (APIMF)

Please complete each section of this application form electronically as a Word document and as a scanned signed PDF file. Please ensure that the electronic and the printed versions of the completed form accompany your submission.

1. APPLICATION DETAILS

WHO APIMF Number	APIMF330
API name (International Nonproprietary Name)	Ritonavir
Therapeutic area	HIV/AIDs
Applicant company	The Chemical Corporation
Original APIMF open part version number	CC/Ritonavir/AP-01/June-2013
Original APIMF restricted part version number	CC/Ritonavir/RP-01/June-2013
Proposed APIMF open part version number	CC/Ritonavir/AP-02/March-2015
Proposed APIMF restricted part version number	CC/Ritonavir/RP-02/ March-2015
Amendment application number	*For WHO use only*

2. AMENDMENT TYPE: PLEASE TICK ONE

Amendment 1a	No changes to currently accepted APIMF version	☐
Amendment 1b	New APIMF version (editorial changes only)	☐
Amendment 1c	New APIMF version	☒

3. APPLICANT DETAILS

Please note that the contact listed in this form will be the primary contact for email and mail communication for this specific application.

Contact person responsible for this application	**Title: Ms** **First name: Lucy** **Family name: Grant**
Contact person's position	Regulatory Affairs Manager
Contact person's postal address	
Unit	
Building/PO Box Number	The Chemical Corporation API Towers
Road/Street	
Plant/Zone	
Village/Suburb	
Town/City	
District/Mandal	
Province/State	
Postal code	1292
Country	Switzerland
Contact person's email address	lucyg@chemcorp.com
Contact person's phone number	+41 22 567 890

4. SUMMARY OF EDITORIAL CHANGES ANNOUNCED IN THIS APPLICATION ONLY

If editorial changes have been made please complete this section, otherwise delete.

Summary of proposed changes:

Affected CTD subsection	Pre-change details	Post-change details	Justification for Change
3.2.S.1	CAS number not included	CAS number now included	Previous omission
3.2.S.2.2	Ethanol is misspelt several times in this section	The spelling of ethanol has been corrected throughout section 3.2.S.2.2	Editorial change
3.2.S.3.1	pXRD diffractograms from three pilot scale batches	pXRD diffractograms now added for three commercial scale batches	Update in data

Note:

1. **For APIMFs that have an agreed upon API Quality Information Summary (QIS), the API-QIS should be revised and submitted with any revised sections highlighted.**

4.1 Amendment summary – for new annual notification (AAN) changes announced in this application only

If the revised version of the APIMF includes any AAN changes please complete this section, otherwise delete.

Summary of proposed changes:

Amendment category	Affected Common Technical Document (CTD) subsection	Pre-change details	Post-change details	Justification for change	Date of implementation
3a	3.2.S.2.3	Current suppliers of starting material (SM) – Compound D Starting Materials Inc. Plant 2, Economic Zone Taizhou China And Fine Chemicals Corp 12 East Road Mumbai India	Proposed suppliers of starting material - Compound D Fine Chemicals Corp 12 East Road Mumbai India	SM supplier has ceased production	1 Feb 2015
14b	3.2.S.6	HDPE packaging material is tested for ID (IR) and thickness	HDPE packaging material is tested for ID (IR) and thickness Plus a skip test for light emission	Better quality control	25 January 2014

Note:

1. For APIMFs that have an agreed upon API-QIS, the API-QIS should be revised and submitted with any revised sections highlighted.

5. SUMMARY OF CHANGES DOCUMENT

Please record in the table below all differences between the proposed version of the APIMF and the last complete APIMF version accepted. i.e. APIMF/RP04 compared to APIMF/RP/05. For such changes please list the WHO amendment application number associated with the change in the applicable section of the table.

Do not compare the proposed version to the most recently amended APIMF version, e.g. APIMF/RP04/Amendment06 compared to APIMF/RP/05.

Please also include all AAN amendments and editorial changes announced in this application

Affected CTD subsection	Details in original APIMF version See note above	Details in proposed APIMF version	WHO amendment reference number (if applicable)
3.2.S.1	CAS number not included	CAS number now included	Current submission - editorial
3.2.S.2.1	All intermediates produced in-house	New external intermediate manufacturer added (compound 34-t) Pharmaceutical Supply Ltd 123 West Rd Shanghai China	5c.2 (Amaj) – AAME-2014-0098 October 2014
3.2.S.2.2	In-house method of preparation of intermediate	Preparation of intermediate 34-t added to section	5c.2 (Amaj) – AAME-2014-0098 October 2014
3.2.S.2.2	Ethanol is misspelt several times in this section	The spelling of ethanol has been corrected throughout section 3.2.S.2.2	Current submission - editorial
3.2.S.2.2	Current text specifies the application of two crystal washes with ethanol. Current text does not specify washing solvent temperature.	Revised text includes ethanol temperature and reduction in the number of washing steps to 1. The mother liquor recovery process is included	7c.1 (Amin) – AAME-2014-0134 November 2014
3.2.S.2.3	Current suppliers of starting material - Compound D Starting materials Inc Plant 2, Economic Zone Taizhou China	Proposed supplier of starting material - Compound D Fine Chemicals Corp 12 East Road Mumbai India	5b.1 (AIN) – AAME-2014-0134 November 2014 And Current submission - AAN
3.2.S.2.3	Materials used for internal manufacturer of intermediate	New solvent (DMF) added to control of materials section due to introduction of new intermediate supplier	5c.2 (Amaj) – AAME-2014-0098 October 2014
3.2.S.4.1	Total impurity content is listed as 2.5%	Total impurity content is listed as 2.0%	11e (AAN) – AAME-2014-0134 November 2014
3.2.S.6	HDPE packaging material is tested for ID (IR) and thickness	HDPE packaging material is tested for ID (IR) and Thickness. Plus a skip test for light emission	Current submission - AAN
3.2.S.7.1	Current storage condition is stated as 24 months, do not store above 30°C	Storage conditions are stated to be 36 months, do not store above 30°C	16b (Amin) - AAME-2014-0134 November 2014

3.2.S.7.1	Summary of data for primary batches	Information on stability studies commenced for API produced using new intermediate supplier.	5c.2 (Amaj) – AAME-2014-0098 October 2014
3.2.S.7.3	Data is provided for long-term storage to 24 months	Stability data has been extended to include data up to the 36-month time point	16b (Amin) - AAME-2014-0134 November 2014
3.2.S.7.3	Primary batches stability study data	6 months stability data for API produced using new intermediate supplier added to section	5c.2 (Amaj) – AAME-2014-0098 October 2014

Note:

1. **For APIMFs that have an agreed upon API-QIS, the API-QIS should be revised and submitted with any revised sections highlighted.**

5.1 Documentation checklist

The following documents have been submitted together with this application form:

Note: All documents must be provided for this application to be valid.	
A completed revised APIMF application form (Word) and A signed and completed revised APIMF application form (PDF)	☒ *Yes* ☒ *Yes*
An amendment summary document introducing, explaining, discussing the proposed changes in (Word or text-selectable PDF).	☒ *Yes* ☐ *not applicable*
If annual amendment notifications are included in the submitted application the documents as specified in the *WHO Guidance on Amendments to an APIMF submitted in support of a prequalified product (FPP) or prequalified active pharmaceutical ingredient (API)* are available on request or at the time of inspection	☒ *Yes* ☐ *not applicable*
Open and restricted sections of the APIMF revised in fulfillment of the requirements under section 3.2.S of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.* (Refer to APIMF documentation requirements on website of the Prequalification Team: medicines website.)	☒ *Yes* ☐ *not applicable*
API-Quality Information Summary (API-QIS) For APIMFs that have an agreed upon API-QIS, the QIS should be revised and submitted. All revised details should be highlighted. To assist with rapid identification of changes, all revisions should be made in red font and obsolete information struck through. If there are no alterations required to the API-QIS then it does not need to be provided. If there is no agreed API-QIS then this document can be omitted.	☒ *Yes* ☐ *No agreed QIS* ☐ *No change to QIS*

6. DECLARATIONS

6.1 Declaration (*Please check all declarations that apply*)

I declare that:

☒ For each change all conditions as stipulated in the *Guidance on Amendments to an APIMF submitted in support of a prequalified product (FPP) or prequalified active pharmaceutical ingredient (API)* for the change requested are fulfilled.

☒ There are no changes to the revised APIMF subsections other than those stated in the summary of changes document, or

☐ not applicable, there are no changes to APIMF subsections.

☒ The API-QIS has been updated to reflect each change notified in this application, or

☐ There are no changes to the currently agreed upon API-QIS and therefore a copy of the currently agreed API-QIS has not been included in this submission.

☒ The information submitted is true and correct.

Name: _____Lucy Grant_____

Signature: _____ Date:_21 May 2015___