Example of a Completed Application for an Amendment to an Active Pharmaceutical Ingredient Master File (APIMF)

The following example application form is for a single amendment application covering four changes.

The grouping of all four changes together is permitted in this instance since the changes all relate to the same APIMF.

As a result of the grouping of several changes, the overall change type of the amendment defaults to the highest category, namely a minor amendment (Amin) and the application will follow the Amin procedure.

1. In support of this application the applicant provided on a single CD to Geneva the following information.
2. The application form (in both Word and PDF)
3. A covering letter with four attachments in which the changes were discussed and justified
4. Replacement sections of the APIMF
5. A tracked change API Quality Information Summary (QIS).[1]

[1] The API QIS is issued as part of an APIMF or amendment acceptance letter. It should not be confused with the QIS-PD, which is a key element of an application seeking finished product prequalification.

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	APIMF630
API name (INN)	Ritonavir
Therapeutic Area	HIV/AIDS
Applicant Company	The Chemical Corporation
Applicant's document number	Amendment 03 – November 2014
Amendment application number	For WHO use only

2. AMENDMENT TYPE:

Amendment #	Title	Change category
11e	Change to the test parameters or acceptance criteria of the API specifications involving: tightening of an acceptance criterion	AAN
5b.1	Replacement or addition of a new manufacturing site or manufacturer of an API involving: production of API starting material	AIN
16b	Change in the retest period/shelf-life of the API involving: Extension	Amin
7c	Change in the manufacturing process of the API	Amin

2.1 Amendment application overall change category: Amin

(being the most severe categories of the amendments applied for).

3. APPLICANT DETAILS

Contact person responsible for this application	Title: Ms First name: Lucy Family name: Grant
Contact person's job title	Regulatory Affairs Manager
Contact person's postal address	
Unit	The Chemical Corporation
Building/PO Box number	API Towers
Road/Street	
Plant/Zone	
Village/suburb	
Town/City	Geneva
District and Mandal	
Province/State	
Postal code	1292
Country	Switzerland
Contact person's email address	Lucyg@chemcorp.com
Contact person's phone number	+41 22 567 89

4. SUMMARY OF AMENDMENT CHANGE

4.1 For amendment types AIN, Amin and Amaj only

- Reproduce section 4 and provide separate summaries for each proposed change.
- The specifics of the change should be described in the table below, but a separate document should be provided discussing and justifying the change in depth.
- If there are no AIN, Amin or Amaj changes please delete this section.

4.1.1 Amendment title and number

5b.1 (AIN) Replacement or addition of a new manufacturing site or manufacturer of an API involving: production of API starting material

4.1.2 Conditions and documents

All conditions specified for this category in the amendment guidance has been met ☒ YES

All documents as specified for this category in the amendment guidance has been provided ☒ YES

4.1.3 Summary of current and proposed details:

Current details	Proposed details
Current supplier of starting material - Compound D Starting materials Inc Plant 2 Economic Zone Taizhou China	Proposed suppliers of starting material - Compound D Starting materials Inc Plant 2 Economic Zone Taizhou China And Fine Chemicals Corp 12 East Road Mumbai India

4.1.4 Justification for change:

An additional suppler has been sought to ensure sufficient supply of material. See attachment 1 for: • Information on the API SM preparation • API starting material specifications justification • Certificates of Analysis for a batch of SM test upon receipt in compliance with specifications • Comparative batch analysis of API produced using starting material from both suppliers.

4.1.5 Date of implementation (*for Immediate Notifications only*):

Following acceptance

5.1 For amendment types AIN, Amin and Amaj only

- Reproduce section 4 and provide separate summaries for each proposed change.
- The specifics of the change should be described in the table below, but a separate document should be provided discussing and justifying the change in depth.
- If there are no AIN, Amin or Amaj changes please delete this section.

5.1.1 Amendment title and number

16b (Amin) Change in the retest period/shelf-life of the API involving: Extension

5.1.2 Conditions and documents

All conditions specified for this category in the amendment guidance has been met ☒ YES

All documents as specified for this category in the amendment guidance has been provided ☒ YES

5.1.3 Summary of current and proposed details:

Current details	Proposed details
Current retest period is: 24 months, do not store above 30℃	Proposed re-test period is: 36 months, do not store above 30℃

5.1.4 Justification for change:

Additional long-term stability data is now available on the primary batches RIT123-2, RIT123-3, and RIT123-4. An extension is requested. See attachment 2 for summary and analysis of the available stability data.

5.1.5 Date of implementation (*for Immediate Notifications only*):

Following acceptance

5.2 For amendment types AIN, Amin and Amaj only

- Reproduce section 4 and provide separate summaries for each proposed change.
- The specifics of the change should be described in the table below, but a separate document should be provided discussing and justifying the change in depth.
- If there are no AIN, Amin or Amaj changes please delete this section.

5.2.1 Amendment title and number

7c.1 (Amin) Change in the manufacturing process of the API

5.2.2 Conditions and documents

All conditions specified for this category in the amendment guidance has been met ☒ YES

All documents as specified for this category in the amendment guidance has been provided ☒ YES

5.2.3 Summary of current and proposed details:

Current details	Proposed details
The final purification of the API by crystallisation included two crystal washing steps using ethanol at room temperature. No recovery of mother liquors.	Washing of the recrystallized material will only occur once. The ethanol used will be warmed to 30℃. It is proposed to introduce a single mother liquor recovery cycle

5.2.4 Justification for change:

To increase the yield of the final API without adversely affecting quality, it is proposed to: 1. Reduce the number of washing cycles, but increase the temperature of the washing solvent. 2. Introduce a single cycle of mother liquor recovery. See attachment 3 for a complete discussion and justification for the change in washing process See attachment 4 for a complete discussion and justification for the introduction of a mother liquor recovery.

5.2.5 Date of implementation (*for Immediate Notifications only*):

Following acceptance

6. SUMMARY OF AMENDMENT CHANGE

6.1 Amendment summary — for annual amendments only (AANs)

If there are no AAN changes please delete this section 4.2

Amendment category	Pre-change details	Post-change details	Justification for change	Date of implementation
11e	API specifications AA-API-0001A The limit for total impurity content is currently NMT 2.5%	API specifications AA-API-0002A The proposed limit for Total impurities content has been tightened to NMT 2.0%	Process improvements have reduced overall impurity content	1 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.**
2. **When an Annual notification involves a change in specifications, the signed and dated version of the revised specification should be submitted. In other cases the documentation indicated for AAN's should be available on request or at the time of inspection, but do not need to be submitted.**

7. SUMMARY OF CHANGES DOCUMENT – (FOR REPLACEMENT CTD SUBSECTIONS PROVIDED WITH APPLICATION, IF APPLICABLE)

Please list the revised sections provided with the amendment.

Affected CTD subsection	Details in current CTD subsection version	Details in proposed CTD subsection	Justification for change
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	To improve yield
3.2.S.2.3	Current supplier of starting material - Compound D Starting materials Inc Plant 2, Economic Zone Taizhou China	Proposed suppliers of starting material - Compound D Starting materials Inc Plant 2, Economic Zone Taizhou China And Fine Chemicals Corp 12 East Road Mumbai India Revised text includes information on the preparation of the SM by Fine Chemicals Corp and representative batch analysis.	Material costs
3.2.S.4.1	Total impurity content is listed as 2.5%	Total impurity content is listed as 2.0%	Improved process capability
3.2.S.7.1	Current storage condition is stated as 24 months, do not store above 30℃	Storage conditions are stated to be 36 months, do not store above 30℃	Improved retest period

Note:

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

8. 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 APIMF amendment form (Word) and A signed and completed APIMF amendment form (PDF)	☒ Yes ☒ Yes
An amendment summary document introducing, explaining, discussing the proposed changes in (Word or text selectable PDF). See attachments 1 – 4	☒ Yes
All supporting conditions and documents as specified in the *Guidance on Amendments to an APIMF submitted in support of a prequalified product (FPP) or prequalified active pharmaceutical ingredient (API)*. (Word or text selectable PDF). These documents should be presented in a folder entitled "supporting documents". For Annual amendment notifications documents discussing and supporting the implemented changes should not be provided, but should be available on request or at the time of inspection,	☒ Yes
Replacement subsections for the APIMF resulting from the change in fulfillment of 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 PQT - Medicines website). When an Annual notification involves a change in specifications, the signed and dated version of the revised specification should be submitted. In other cases updated sub-sections do not need to be submitted.	☒ Yes
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

9. DECLARATION (PLEASE CHECK ALL DECLARATIONS THAT APPLY)

I declare that:

☒ For each change all conditions and documents 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 being made other than those applied for in this submission.

☒ 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:__3 March 2016___