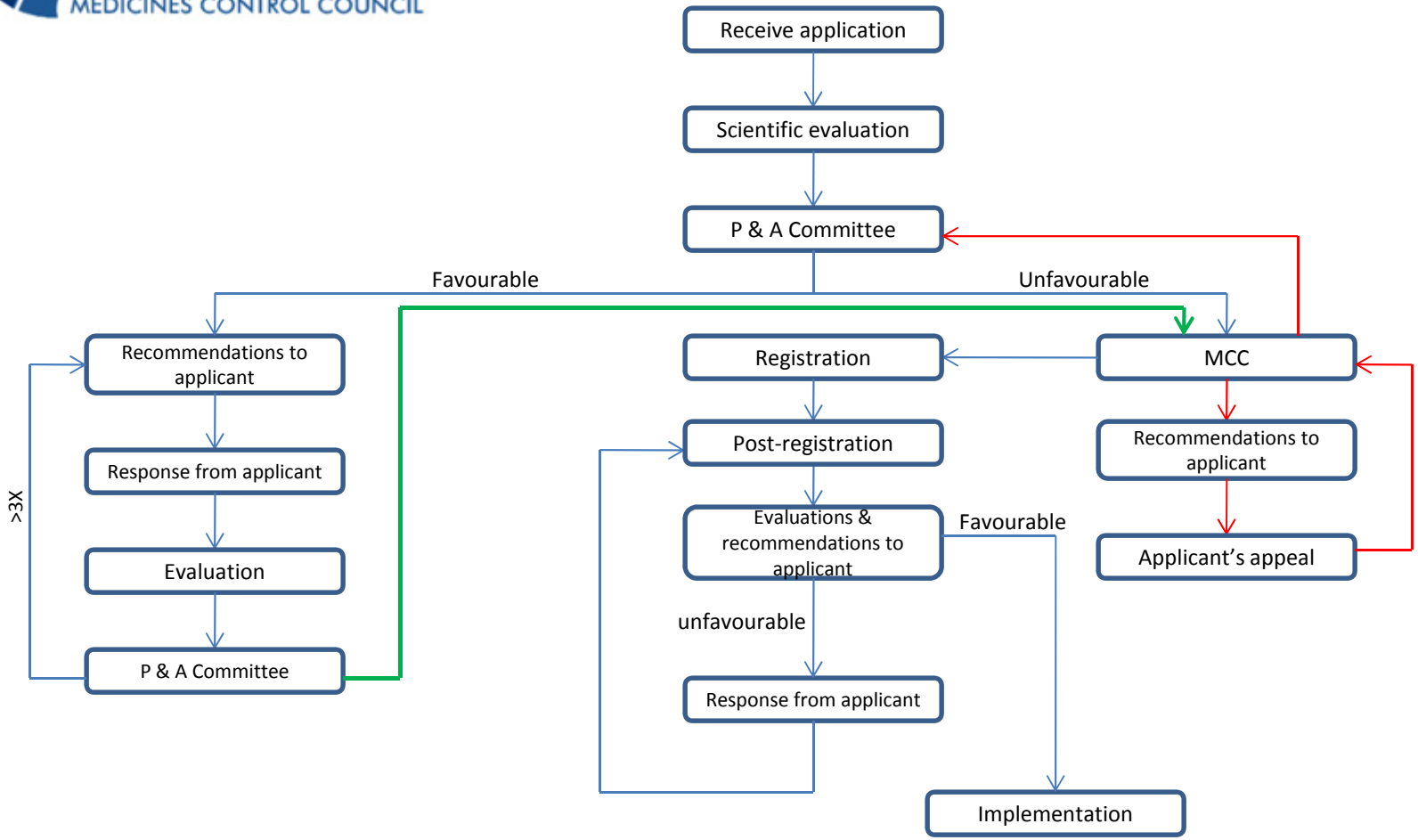
MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

Pharmaceutical Industry: Challenging Issues Experienced

Centralised procedure



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The Dossier

Responses

- Responses should only address requests as per the MCC communication
- Correct working code
- Correct Amendment Schedule format facilitates evaluation – limits cross checks
- Completed PART 1A/Module 1.2.1 + relevant front pages of PARTs/Sub PARTs / CTD Module 1.1 / Amendment history
- Copy P&A recommendation + previous correspondence if relevant
- P&A recommendation may not- be paraphrased, be omitted, be inserted above the response in merged columns
- The ‘before’ and ‘after’ must be clearly stated, do not refer to detail elsewhere
- Clearly indicate which PARTs/Modules or sections thereof should be replaced

PRODUCT NAME AND APPLICATION NUMBER				
Module PART	**Current Annexure / PART**	**Amended Annexure / PART**	**Reason for amendment**	**Comment of reviewer (for office use only)**
P&A Com recommendation quoted completely and not paraphrased e.g ***2.7 Include the outer carton in the description of the final presentation pack of vial and ampoule to facilitate identification. It is noted that the package insert and patient information leaflet do not concur.***				
	Presentation: **Vial and ampoule**	**Presentation:** **Vial and ampoule in an outer carton** **Refer to pages &** **Replace pages.....**	**Outer carton now reflected** **The package insert and patient information leaflet concur**	☺
2.7 Include outer carton in description of final presentation pack of vial and ampoule.				
	----	***One vial and one ampoule are presented in an outer carton, for single use only***	***The updated package insert and patient leaflet are provided in PART 1C attached.***	☹
3.2.S.2.1	***ABC approved supplier.***	***XYZ included as alternative supplier.***	***Routine update***	☹
3.2.S.2.1	**ABC approved manufacturer.**	**XYZ included as alternative manufacturer.** ***List the information that has been included in support of the new manufacturer.** ***Confirm that the information for the approved manufacturer remains the same.**	**ABC cannot keep up with the demand, and an alternative source has to be available.**	☺
	Replaced entire Annexure 3 with the amended Annexure submitted ***or*** **Replaced pages 3.1 and 3.2 with the amended pages submitted, and included pages 3.20 to 3.30**			

PRODUCT NAME AND APPLICATION NUMBER				
Module / PART	**Current PART / Module**	**PART / Module**	**Reason for amendment**	**Comment of reviewer (for office use only)**
PART 2A ***4.1 The change of manufacturer from xyz France to xyz Peru is not approved as equivalence between the final product manufactured at these two sites has not been addressed. Instead the comparison is between Anotherset USA and Anotherset Peru. Confirm and clarify the current final product manufacturer or correct.*** **Please note that equivalence could not be demonstrated between Anotherset France and Anotherset Peru as manufacturing activities at the xyz site in France had ceased and there are no test samples available to conduct the comparative dissolution studies.** **In order to demonstrate equivalence between Anotherset from xys France and Antotherset from xyz Peru we conducted comparative dissolution between Anotherset from xyz USA and Anotherset Peru. Equivalence between anotherset USA and Anotherset France was demonstrated in our original submission therefore Anotherset France is equivalent to Anotherset Peru.**				
	Previously not included	**Please note that equivalence could not be demonstrated between Anotherset France and Anotherset Peru as manufacturing activities at the xyz site in France had ceased and there are no test samples available to conduct the comparative dissolution studies.** **In order to demonstrate equivalence between Anotherset from xyz France and Anotherset from xyz Peru we conducted comparative dissolution between Anotherset from xyz USA and Anotherset Peru. Equivalence between Anotherset USA and Anotherset France was demonstrated in our original submission therefore Anotherset France is equivalent to Anotherset Peru.**	**As per P&A Recommendations**	

Comments Request/Recommendations

- **General:**
  - Consistent compliance with metrication requirements
  - Deviations in final submissions and screening files.
  - Photocopies for each page - legibility .
  - Dossiers-
    - incompleteness
    - legibility of copies
    - Nonpagination
- **Module 1**:
  - Specify the dosage form accurately.
  - Authorised persons - permanent employees
  - Responsible pharmacist (SAPC)
  - Comprehensive Table of contents.
  - Include Conditions of Registration as conditions in the EU countries.
  - English translations – MCC aligned authorities.

Comments Request/Recommendations

- **LABELLING (PI/PIL/LABEL)**
  - Regulations 8,9,10 .
    - Where applicable, the statement ‘for external use only’
    - do not use for more than 30 days after opening
    - keep out of reach of children
    - shake bottle before use
    - name of antioxidant/s
    - Bacteriostatic/bactericide(name and % age)
    - Ethyl alcohols (% age of total volume)- if > 2%
    - Tartrazine
    - Expand on storage instructions e.g. “Protect from moisture, light, store at or below....”.
    - Composition (PI, PIL)
      - Delete “purified water”
      - List all the excipients in final product

Comments Requests/Recommendations

- **Module 3.2.S:**
  - APIF documentation (P & A guideline).
    - Current
    - Unique version and date
  - Specify solubility temperature
  - Two API manufacturers are applied for, comparative data:
    - routes of synthesis,
    - impurity profiles and
    - residual solvents
    - isomerism, polymorphism and superimposed IR spectra.
  - Provide a description and flow chart of the manufacturing process.
  - Limit for residual solvents e.g. benzene in toluene.
  - Re-test period
    - Data on stability on all batches, specific conditions (ambient and accelerated)
      - Follow up with full data to enable evaluation

Comments Requests/Recommendations

- **Module 3.2.P**:
  - Excipients grades e.g. of microcrystalline cellulose, HPMC, colloidal silicon dioxide etc.
  - Colour index number e.g. titanium dioxide.
  - Include the additional specification(s) for the specific grade of microcrystalline cellulose.
  - Absence of BSE/Asbestos – confirm/declare.
  - Holding time – stability data.
  - In-process control specification/frequency
  - Content uniformity.
  - Provisional shelf-life - stability data for at least 9 months – submit update to avoid in full shelf life

Comments Requests/Recommendations

- **Module 3.2.R:**
  - Provide
    - the dates of manufacture/age of the batches used in the determination of essential similarity.
  - Overview in accordance with the Pharmaceutical and Analytical guideline 2.1.2 with:
    - A tabulated summary of the biostudy test and reference products in the Overview stating
    - confirmation whether of not the final product manufacturer, final product formulation, manufacture of the API used in the biostudy test batch, are the same as those being applied for.
  - A comparison of the final product characteristics including the formulation and physical characteristics, in support of essential similarity of the test product and the corresponding innovator reference product should be addressed in Module 3.2.R. Pharmaceutical and Analytical guideline 2.1.1 iii)

Improvements Noted: Post Reg (since March 2012)

- Granularity of the ZA CTD
- Coding of submissions
- The amendment submission
  - Cover page of submission
  - Cover letter (module 1.0)
  - Comprehensive table of contents (module 1.1)
  - Application form (1.2.1)
  - Classification of amendments
  - Amendment schedule (1.5.2.1)
  - Managing the format/hybrid dossier formation

Screening

- Ensure appropriate identification of volumes submitted e.g - x of y volumes
- Include the proprietary name, application/reg no
- Type A only amendments (<10) are returned at screening
- Code your responses as VRR only and not the initial amendment code or a combination of these codes.

➢ Remember wrong code results in delayed responses

- Absence of 1.5.2.1 (amendment schedule); cover letter letterhead) and 1.2.1 (application)–rejected at screening

Upliftments

- Upliftments : Time frame - 30 days
- Arrange beforehand for collection of document
- Absence of 1.5.2.1 (amendment schedule); cover letter (letterhead)
- Do not submit a response to an uplifted document. Submit a new request.
- Multiple submissions in one application: sequential and non-sequential numbers (uplift)

Evaluations

- Section 1.2.1 (f)- Amendment history:

✓ List all amendments approved and pending, except current.

✓ Indicate approved/not approved or pending additional information.

✓ Should include with the date the relevant status comment e.g. 05/09/2013 (approved) or 04/09/2013 (pending data)

- Tabs used in submissions
- Hybrid Submissions vs Hybrid formation (at MCC)
- Do not include additional amendments to a Post Reg response – they will not be evaluated.
- Include all the amendments requested on the cover page- these affect screening and routing
- Amendment schedule - indicate why change is made in the reason column.

Evaluations cont...

- Technical Type B &C amendments follow queue system (Currently Type C : Sept-Oct 2012 submissions allocated)

- Administrative Type C without technical evaluations are processed on screening (±2weeks from entry), acknowledgement /partial update letter generated and submission transferred to Inspectorate for evaluation and then transfer to Ops and Admin for certificate generation

- Combination of Administrative Type C with Technical amendments follow queue as for technical evaluation and then transferred to Inspectorate for further processing

Once-Offs

- A once-off is a one time only request, i.e: it is not a permanent change. Refer to 5.8 of Amendments guideline & Type C cat 20 Amendment. In most cases these changes are actually deviations that are not planned.

- If the change is a permanent change such as change in API source, then an amendment request must be submitted as per the amendment guideline requirements.

- **Challenge:** Once-off requests especially for API source changes are being requested.

➢ Does not qualify as a once-off
➢ Requires full evaluation-not done by Inspectorate
➢ Requests are made without submission of an amendment request/sometimes submitted at the same time
➢ Referred to Post Reg: i.e follow the technical amendment route

Re-submissions

- Do not re-submit any document without contacting the unit to obtain a re-submission reference number.

- Disadvantage of not obtaining a re-submission number is that document is rejected at screening and if passes through then the document enters the normal queuing system

- What is the benefit of a re-submission ref number
  - Enables priority allocation
  - Prevents duplication (verification done apriori)

HOW CAN A FOLLOW UP BE DONE?

- All follow ups should be done by hard copy request using the VGC code
- Call at least 6-8 weeks after submission (only if necessary)
- Call Post Reg Unit for all P&A Amendments only
- Contact details are:

  Sylvester Johnson 012 395 9527

  Mogale Modiane 012 395 9344

  Silverani Padayachee on 012 395 9316 (technical)

What you need to have handy

If submission enquired on is older than 3 months then have the following information at hand to enable tracking of your document

- Proprietary name
- Registration/Application number
- Date of cover letter
- Variation code: e.g VAC, VPC,VLC
- Proof of submission
- Provide your contact details

There has been a noticeable improvement in the amendment submissions

Your co-operation is appreciated

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THANK YOU!!!!!