Feedback from:
SAPRAA/MCC Mini-Workshop held to discuss MRF1 to ZACTD Conversions & Amendments

SALMA ISMAIL 19/11/2009

WORKSHOP

- **DATE: 10 NOVEMBER 2010**
- **TIME: 09:00 – 13:00**
- **VENUE: CIVITAS BUILDING - PRETORIA**

SAPRAA:	MCC SECRETARIAT:
1. Hilde Rodseth 2. Elizabeth Filby 3. Marti Bredenham 4. Salma Ismail	1. Estelle Taute 2. Frank Hlangwane 3. Silverani Padayachee 4. Anita Smal 5. Joy van Oudsthoorn

AGENDA FOR THE SAPRAA/MCC WORKSHOP ON CTD CONVERSIONS

- Introduction from Industry/SAPRAA perspective – Hilde Rodseth
- Introduction to challenges faced by MCC – Estelle Taute/Frank Hlangwane
- Discussion regarding the technical aspects of conversion (document “Format CTD vs MRF1 vs MBR1”)
- Discussion regarding questions and comments from SAPRAA members
- Discussion of timelines/roadmap for the roll-out of CTD conversions and how these relate to post-registration amendments Types A, B or C

AIM/OBJECTIVE OF WORKSHOP

- Iron out the complex issues faced when practically compiling a paper ZA CTD dossier
- SAPRAA & MRA- develop “Best Practices Document” for conversions
- Establish way forward for MRF1/MBR1 ZA CTD conversions.

TERMINOLOGY

- Conversion of a dossier?
- Update of a dossier?
- Amendment to a dossier?
- Transfer?
- Re-format of a dossier?

Post-registration unit:

TRANSFER/CONVERSION:

- **A FORMAT CHANGE ONLY**
- **NO CHANGE TO CONTENT**

UPDATE:

- **CHANGE TO AND ADDITION TO CONTENT OR INFORMATION**

GRANULARITY

- **Granularity**: extent to which a system is broken down into small parts, either the system itself or its description or observation. It is the "extent to which a larger entity is subdivided.
- **Coarse-grained** systems: fewer, larger components than **fine-grained** systems; a **coarse-grained** description of a system regards large subcomponents while a **fine-grained** description regards smaller components of which the larger ones are composed.

From Wikipedia

- This will be updated in the MCC guidelines
- Refer to ICH M4

GRANULARITY ctd.

- **Data granularity**
- The *granularity* of data:fineness with which data fields are sub-divided.

For example, a postal address can be recorded, with *low granularity*, as a single field:
address = 200 MCC Ave., Pretoria, South Africa

or with *high granularity*, as multiple fields:
street address = 200 2nd Ave. South #358
city = St. Petersburg
postal code = FL 33701-4313
country = USA

or even higher granularity:
street = 2nd Ave. South
address number = 200
suite/apartment number = #358
city = St. Petersburg
state = FL
postal-code = 33701
postal-code-add-on = 4313
country = USA

- ICH M4 GRANULARITY.pdf

Comment or suggestion from SAPRAA members & Outcome of discussion from MCC workshop

E-mail sent out by SAPRAA 09/2010-request for comment

Comment or suggestion from SAPRAA members & Outcome of discussion from MCC workshop

Conversion: All approved information from one format to another – no changes = reformat = transfer = transcribe = move

Inclusion of additional information as required by format = update
Amendment or variation to approved information = update

Comment or suggestion from SAPRAA members &Outcome of discussion from MCC workshop

QUESTION 1: **The CTD guidelines allow applicants to submit more than one strength of the same dosage form in one dossier.** **It should be allowed that applicants convert previously separate MFR1 or MBR1 dossiers into a combined dossier at the time of conversion. This will avoid unnecessary repetition of effort and reduce the overall volume of paper that MCC (and applicants) need to handle in the long run.** ***(Applicable to full MBR1/MRF1 → CTD conversions)***	**Module 1.2.1 per strength to be submitted** **Numbers are to be directly sequential** **A gap of even one is not allowed e.g. 42 001/2 + 42 004/5 not acceptable**

Comment or suggestion from SAPRAA members & Outcome of discussion from MCC workshop

QUESTION 2: **The current ZA CTD roadmap Jun 10 v1 states that post-registration amendments Type A will not be accepted after 30 November 2010.** **It is assumed that this refers to all new Type A changes only. (There could be a number of previously done Type A amendments, which were done in the MRF1 (or MBR1 format), which have just not been submitted to MCC yet, and which still need to be provided to MCC.** **It is suggested that these guidelines be reconsidered once the amendment process has been agreed, since the nature of Type A & B amendments is to permit expeditious implementation of non-major changes. These cannot be delayed for administrative issues around dossier formats.**	**Refers to all type A at the time of submission of B or C in CTD format. The type A's are to be consolidated into CTD format.** **Reconsidered. See new timelines.**

Comment or suggestion from SAPRAA members &Outcome of discussion from MCC workshop

QUESTION 3: **Is MCC sticking to the current roadmap dates?:**	**No**
•Post reg amendments Type C mandatory to be in CTD format from 1 Jan 2011? (voluntary from 1 Oct 2010) **•Post-reg amendments Type B mandatory to be in CTD format from 1 Jan 2011? (voluntary from 1 Oct 2010)**	**All amendments (irrespective of type) to be submitted in ZA CTD format from 1 April 2011**
•The last date of acceptance of Type B and C amendments; 30 Nov 2010 seems to contradict the above-mentioned dates.	**31 March 2011**
•It is suggested that these guidelines be reconsidered once the amendment & dossier conversion processes have been agreed.	

Comment or suggestion from SAPRAA members & Outcome of discussion from MCC workshop

QUESTION 4: **According to the MCC's "post-registration amendments guideline Jun10 v4_2", page 14 of 42, applicants are required to provide MCC with pagination instructions in the amendment schedule table.** • **This would presuppose that an update of the table of contents of the dossier will be done.** • **However, at the CTD workshop it was mentioned by one MCC speaker that it would be possible to have a "hybrid dossier" (partly in CTD format and partly in MFR1 format, but not confirmed by another MCC official. It is unclear how applicants should handle the pagination instructions in the amendment schedule in these circumstances).** • **Can the Amendments Section deal with/accept a hybrid dossier?** • **We need clarification of MCC's document management requirements in order to plan an acceptable procedure for all future amendments.**	**The Post Registration Amendments guideline (now Amendments guideline) as well as the General information guideline will be updated to include relevant guidance (and removal obsolete information) with respect to ZA CTD.** **PART 1B will change to Module 1.1** **Indicate here what is in which format – i.e. MRF1 or CTD** **Yes, only if the transition process in terms of (modular/sectional) partial updates are followed**

Comment or suggestion from SAPRAA members & Outcome of discussion from MCC workshop

Question 5: **MCC should provide industry with a guideline describing the standard way to proceed when converting from the MFR1 (or MBR1) format to the CTD format.** **Industry should adopt a common approach on how to manage post-reg. amendments moving forward.**	**Separate document as discussed** **Agreed**

Comment or suggestion from SAPRAA members & Outcome of discussion from MCC workshop

Question 6: **When the conversions were done from MBR1 to MRF1 format, some applicants were asked to resubmit some of the preclinical and clinical information, whereas others were not.** **MCC should provide clear guidance on this issue and apply it uniformly across the board.**	**Not required**

Comment or suggestion from SAPRAA members & Outcome of discussion from MCC workshop

Question 7: **The CTD format has additional headings in the table of contents for information which was not required to be included in the MBR1 or MRF1 format.** **•Will MCC require that this additional information be provided when converting to the CTD format, or would it be acceptable to simply leave these sections blank with a comment "NA – CTD conversion"?** **•It may be the case that some additional information needs to be obtained whereas other information can be left blank – MCC should provide guidance in this regard.**	**To convert from MRF1 to CTD you have to transcribe the approved info into the new format.** **This converted document is not submitted.** **Then update according to current requirements.**
•It may be the case that amendments cannot be compiled/submitted should MCC require fully completed CTD sections to be supplied, since additional information will have to sourced, that could significantly delay the ability of the Applicant to complete such amendments, with implementation ramifications at the manufacturing sites in the case of Type A & B amendments.	**If urgent don't do full conversion but only relevant parts (i.e partial update).**

Comment or suggestion from SAPRAA members & Outcome of discussion from MCC workshop

Question 8: **Could the post-registration unit provide a submission code for CTD conversions.**	**Amendment codes as currently for amendments submitted, however if it includes a partial update a code VPU (Variation with Partial Update) should be included.** **This is necessary as previously, partial updates were not permitted and hence no code for partial updates.**

FORMAT CTD vs MBR1 vs MRF1

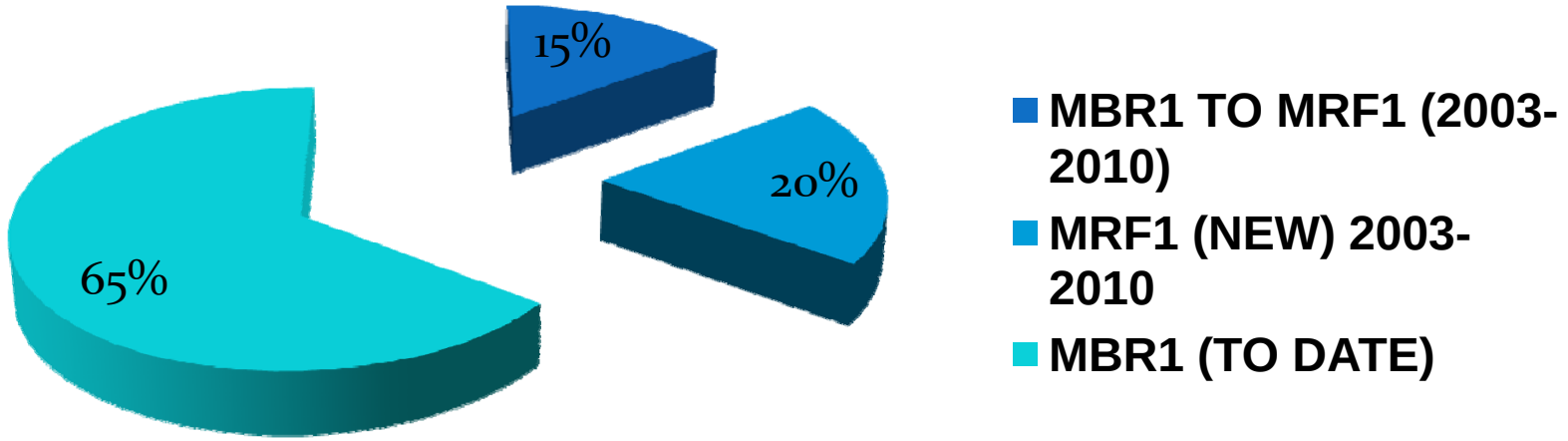
- CTD vs MRF1 vs MBR1_5_Hilde.doc

Post Registration Unit's Approach to ZA CTD (presented by Ms. S. Padayachee)

- Current status
- Previous Experiences
- Ways forward

Current Status-facts

% DOSSIERS IN SPECIFIED FORMAT



- Historically: Post Reg unit –not allow partial updates/conversions
- Dossier integrity was maintained by Post Reg unit

Previous Approach & Experiences of Conversions

- Previous Full update & Conversions
  - MBR1 - Completely replaced by MRF1 format

"The applicant is advised that the **MRF1 should be complete** as it replaces the MBR1 on the MCC records. Whilst the process of updating the format of MBR 1 to MRF1 is not an evaluation for registration purposes, it is a process of ensuring that the data submitted at the time of registration or updated data are reflected in the MRF1 and that the MRF1 is complete."

&

"The conversion or full update in MRF1 format is treated as the entire and complete file. No back references to the MBR1 would be permitted as the MBR1 *then* becomes obsolete. Hence it does not involve re-evaluating data but rather a process of ensuring that all data in the MBR1 is included in the MRF1 format."

Previous Approach & Experiences of Conversions cont…

- Challenges faced by P & A unit: MBR1 previously submitted did not always contain full complement of data as required by MRF1 format
- This resulted in

  “ Requests for exemption from certain parts”
- This gave rise to responses such as

  “In view of the proposed re registration of all medicines, exemption cannot be granted from certain sections of the MRF1 form, however, the status quo may be retained until the re registration may commence.” &

  “ The request for exemption of the following parts cannot be granted however the status quo will be retained”

Previous Approach & Experiences of Conversions cont…

- 2008: Some Applicants were granted permission to not re submit parts 4 & 5 in conversion and full updates which resulted in the following responses such as

  “The conversion/ full update in MRF1 format is treated as the entire and complete file. No back references to the MBR1 would be permitted as the MBR1 *then* becomes obsolete. Hence it does not involve re-evaluating data but rather a process of ensuring that all data in the MBR1 is included in the MRF1 format.”

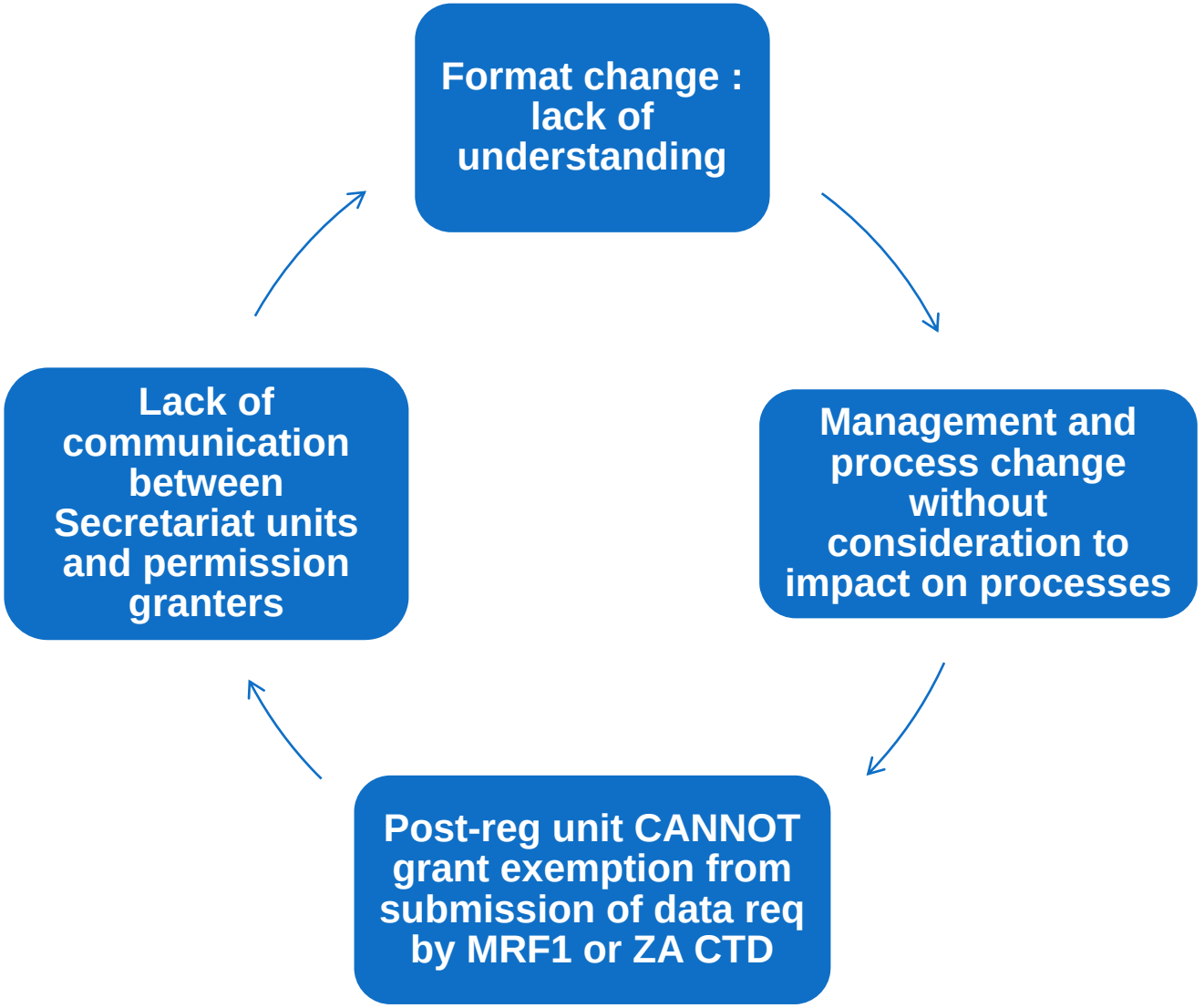
Previous Approach & Experiences of Conversions cont…

- When applications were received involving a mixed format, responses like these were communicated

"The applicant has further made use of an MRF1 front page when the rest of the application is still in the MBR1 format. Applicants are required to maintain consistency in the relevant format of the applications."

" The applicant is advised to maintain the format of the dossier in its entirety, i.e either submit a full update or conversion to change the dossier format from MBR1 to MRF1 , partial updates are not permitted"

Previous Approach & Experiences of Conversions cont…



Consideration points that determine future

- Understand the implications of format changes
  - Guidelines need update
  - MBR1 format did not require as extensive data as is required MRF1 and ZA CTD…is simple conversions possible?
  - Newer formats require additional information-?? full updates more practical option than simple conversions
  - How are records going to be filed… are older formats obsolete? Does newer formats replace older ones or are they all filed together and hence cross referencing to previous formats are permissible

Consideration points that determine future ctd.

- Factors:
  - Urgency of implementation of format change
  - Capacity to handle dossier update within implementation time frame
  - How to achieve the implementation/harmonization of format without compromising availability, quality, safety & efficacy of registered products on market
  - Consider what other regulatory authorities have done with CTD implementation
  - Does our current status (including having more than one format to convert from) permit us to follow the same approach without compromising the objectives of availability, quality, safety, efficacy of medicines required by public

Consideration points that determine future ctd.

- Consider “transitional” format from existing format to proposed ZA CTD

  - Accept roadmap implication of hybrid dossiers arising from amendments submitted in ZA CTD without prior conversion

  Or

  - Consideration of partial updates i.e whole sections of ZA CTD modules updated together with applicable amendment submissions (more structured hybrid dossier formation & monitoring of transition)

Consideration points that determine future ctd.

- Transitional (Hybrid) route is the route of choice

- This implies-implementation date for all amendments would be 1 April 2011 and
- the last date for updates/conversions to be completed by 31 March 2016 or is it 01 April 2016?

Consideration points that determine future ctd.

- **Filing system: State of the Art-ZIPPEL SYSTEM**
- **Emphasis: 4 cm limit to files including binders**

Maintain A POSITIVE way forward

- Much work has already been done to facilitate implementation of ZA CTD & there is no turning back!!
- Consider revised implementation time frames to accommodate process
- Be practical and realistic –MRA + APPLICANT
- Consultative & collaborative process
- Communication (effective & transparent)
- Commitment (from all parties)

THANK YOU TO THE MRA FOR AVAILING THEMSELVES TO CONDUCT A PRACTICAL & CONSTRUCTIVE WORKSHOP

Perseverance is the hard work you do after you get tired of doing the hard work you already did. ~Newt Gingrich