MCC PERSPECTIVE:
PROCESS FOR IMPLEMENTATION OF AMENDED REGULATIONS 9 & 10

Cluster: Food Control and Pharmaceutical Products Regulation and Management

Directorate: Clinical Evaluations and Trials

Ms Hellen Moropyane

Deputy-Director: Clinical Post-registration Evaluations

09 July 2015

OVERVIEW OF THE PROCESS FOR IMPLEMENTATION OF AMENDED REGULATIONS 9 & 10

Objectives of this presentation:

- To give an overview of the process for implementation of amended regulations 9 and 10
- To clarify/explain the process and what is expected of the applicants
- To address concerns of applicants with regard to this process

INTRODUCTION

Purpose of this communication

The purpose of this communication is to outline the process for the implementation of the amended Regulations 9 and 10 to Act 101 of 1965 as well as the revised package insert(PI) and patient information leaflet (PIL) guidelines.

The amended regulations were published in Government gazette No. 37032 of 15 November 2013. The PIs and PILs guidelines were revised in January 2014 to be in line with the amended regulations.

INTRODUCTION *cont…*

The guidelines required that the PIs and PILs of all registered medicines and “Old Medicines” should be compliant by 02 February 2015.

One of the general conditions of registration is that the applicant must comply with all legal requirements

The package insert (PI) is a document with information that ensures the safe and effective use of medicine under most circumstances. It presents a scientific objective account of the medicine’s use and limitation as established by the supporting evidence

INTRODUCTION *cont…*

Patient information leaflet (PIL) is a version of the package insert written in a language that is understood by the patients and caregivers to ensure that the medicine is properly used. The PIL is based on the information contained in the PI.

The headings of the PI should be as stipulated in regulation 9 of Act 101 of 1965.

The headings of the PIL should be in line with the heading in the PIL guidelines but written in a language that is understood by the patients and caregivers.

WHAT ARE THESE AMENDMENTS TO REGULATIONS 9 AND 10/PIL ?

Regulation 9 amendment:

-The Warnings and Special Precautions should be under one heading

Regulation 10 amendments:

-"If you are taking medicines on a regular basis, using the medicine at the same time with another medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice".

NB: These amendments will be handled as notifications as no new information will be added, or previously approved information be omitted.

WHAT ARE THESE AMENDMENTS TO REGULATIONS 9 AND 10/PIL? Cont…

replaced by “Always tell your healthcare professional if you are taking any other medicine (This includes complementary or traditional medicines)”

-"If you are pregnant or breast feeding your baby while taking this medicine please consult your doctor, pharmacist or other health care professional for advice. “ **replaced by** "If you are pregnant or breast feeding your baby, please consult your doctor, pharmacist or other health care professional for advice before taking this medicine. "

WHAT ARE THESE AMENDMENTS TO REGULATIONS 9 AND 10/PIL?…

-Not all side-effects reported for this medicine are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice"

GENERAL REQUIREMENTS

- All applicants should submit the proposed amendments to PIs and PILs to comply with the amended regulations and the revised guidelines (PI and PIL guidelines)
- Ensure that only information approved by the Medicines Control Council (MCC) is reflected on the PIs and PILs. Do not omit or add information. However, information under "**Warnings and Special Precautions**" should be integrated such that it flows and makes scientific sense, that is,

GENERAL REQUIREMENTS cont….

-Subheadings: Warnings and Special Precautions fall off

-Information about the same condition should be integrated and grouped together and should not be duplicated or omitted.

-The applications should be in CTD format and contain the following:

- **Module 1.0**: Letter of application

  -The submission should be coded CPA-Reg 9 and CIA-Reg 10

GENERAL REQUIREMENTS cont….

-Declaration that the information submitted has been approved by the MCC and that no information has been added or omitted.

-The cover letter should be signed by the responsible pharmacist and the person responsible for the overall management and control of the business of the company.

- **Module1.2.1**

GENERAL REQUIREMENTS cont….

- **Modules 1.3 and 1.5**: The clean PI and PIL (as per the amended regulations) should be included in module 1.3 (***NB: this is for the purpose of this communication***) and the annotated PI and PIL should be in module 1.5. The clean PI and PIL should reflect the date of the most recently revised package insert as approved by MCC, and the date of this submission (compliant with Regulations 9 & 10)

GENERAL REQUIREMENTS cont….

Example:

Approved PI (last approved in 1974) → PI in compliance with regs 9 & 10 **with annotations**

Two dates: 1.Last approval (1974)

2 Date compliant with regs 9 & 10

(submission date e.g. 15 Jan 2015)

Clean PI (in compliance with regs 9 & 10)

Two dates: 1.Last approval (1974)

2. Date compliant with regs 9 & 10

(submission date e.g. 15 Jan 2015)

Module 1.3 should also include current approved PI and PIL by the MCC (If these were not submitted, the applicant will be requested to submit and this will be verified against the ones on the product file or the ones sourced from the market)

GENERAL REQUIREMENTS cont….

- The application should be submitted as follows:

  -One hard copy

  -One CD containing the application in a PD format (v1.4, 1.5 or 1.7) should be as prescribed in section 2.4.2 of the communication together with a hard copy of the letter of application

NB: The hard copy is filed in the product file. The CD and cover letter are downloaded in the Clinical Unit

GENERAL REQUIREMENTS cont….

- **Package insert with no information under certain headings**

  -Regulation 9 should always be followed.

  -Medicines with package inserts which do not have some of the headings as per regulation 9 e.g. **Pregnancy and lactation** or **Interactions** should follow the usual process for amendments if there are data available.

  -If there are **definitely** no data available they should write that “Safety in pregnancy and lactation has not been established” or “interaction studies have not been performed or no interactions have been experienced”. The package insert can be submitted as a notification. This will be treated as a regulation 9 & 10 compliant amendment

GENERAL REQUIREMENTS cont….

- **Medicines without approved PILs**

-The applicant should submit the PI in compliance with regulation 9

-The applicant should immediately submit the proposed PIL based on the PI with proposed amendments capturing the latest safety information under the usual process of amendments

GENERAL REQUIREMENTS cont….

For amendments currently in the evaluation process -Applicants should within 30 calendar days upon receipt of finalised PIs and PILs in the old format, submit the amended PI and PIL and PIL as required by the communication

This is specifically for responses that are 100 % compliant. The applicants with responses which still need committee intervention will be requested to comply with regulations 9 & 10.

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GENERAL REQUIREMENTS cont….

- **Submission of amendments after 2 February 2015**

  The proposed amendments should be made on the annotated PI & PIL submitted for compliance with regulations 9 & 10, clearly marked to indicate changes in compliance with regulations 9 and 10 and the new proposed amendments. This will enable the office to review both amendments at the same time.

The last PI approved PI and PIL should be included

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

CONCLUSION

- Most applicants have submitted as requested
- The challenges experienced are that:

  -some of the discs do not open

  -some applicants regard the PIs submitted in compliance with regulations 9 & 10 as approved PIs

  (***These applicants will be requested to resubmit the CDs and also the currently approved PIs***)

This was a fruitful exercise as most applicants have realised that they have not updated their PIs for quite some time

LIMITATIONS EXPERIENCED DURING AMENDMENTS REVIEW

Submissions following MCC requests for class updates

-Applicants only make changes detailed in the request even if their PI is outdated. This results in further requests to the applicants to update their PIs to the latest safety information. Therefore implementation of the originally requested class update is delayed

Submissions are often not in CTD format

-All submissions should be in CTD format by June 2016. It is noted that some applicants still submit their Pis in the old format

LIMITATIONS EXPERIENCED DURING AMENDMENTS REVIEW Cont…

Duplicate ('clone') dossiers

-Dossiers are not always submitted simultaneously

-Cover letters not clearly stating that the PIs are identical

Approved PI

-Some applicants do not include approved PI & PIL

Not all amendments clearly indicated

-This prolongs the review time as the proposed PI is compared to the approved PI to identify additions

Approved PI and proposed PI not labelled as such

LIMITATIONS EXPERIENCED DURING AMENDMENTS REVIEW Cont…

Incomplete information

-Some applicants do not update their PI and PILs after registration and submit amendment with “approved” PI with neither registration number nor registration date

Text not numbered

-The guideline requires that the text line should be numbered. The numbers help during discussions by the Committees

Set of 3 copies bound in one document

-Three separate copies of amendment submissions make it easier for allocations as the document does not have to be dismantled to separate the copies.

FREQUENTLY ASKED QUESTIONS

-Only a few questions will be answered. The questions received showed that there is a need for workshop to train applicants and clarify most of the issues raised.

-Some of the questions are P&A issues or are related to complementary medicines

-Questions pertaining the process of amended regulations 9 & 10 have been answered in the presentation

FREQUENTLY ASKED QUESTIONS Cont..

- **Questions relating to the SR-PIN guideline**

-The need for re-evaluation of the guideline is acknowledged. The Unit is looking into the matter and will engage the industry.

-Suggestion on the improvement of the guideline will be appreciated.

-Ways of acknowledging receipt of SR-PIN application are being looked into.

- **Deletion of already approved indication**

The reasons for deletions depend on various issues. A case-by-case discussion/clarification with the secretariat is recommended

FREQUENTLY ASKED QUESTIONS Cont..

- **USRN guideline**

There are no changes to the current guideline but the Clinical Unit is busy updating the guideline

- **Questions pertaining to 'Possible side effects' ,'Side effects' and 'Warnings and Special Precautions' sections**

The guideline should be read very carefully as it provides very clear guidance. It is acknowledged that these sections **need to be workshopped** as they sometimes delay the finalisation of the amendments reviews.

FREQUENTLY ASKED QUESTIONS Cont..

- **Product ranges**

-There should be a separate PI and PIL for different schedules

-There should be a separate PIL for different routes e.g. the should be a PIL for oral preparations and for injections

- **Line numbering**

-Line numbering is only for annotated PI and PIL

- **Is the MRF form still applicable for post-registration amendments?**

-Yes

FREQUENTLY ASKED QUESTIONS Cont..

- **Inclusion of '*all*' excipients under 'Composition'**

-Only excipients present in the final product should be listed. This will be taken into consideration when revising the guideline