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Explanatory note on fees payable for technical amendments related to quality

UPDATE HISTORY

Version	Publication date
First Publication **V1**	Dec 2020
Second Publication **V2** Update includes defining explanatory note for technical amendments related to quality, inclusion of details on capping and grouping	For implementation 01 Apr 2021

Note: This section on fees for quality variations of medicinal products for human use should be read in conjunction with the SAHPRA new fees published on the Government Gazette dated 22 December 2020 (http://www.gpwonline.co.za/Gazettes/Gazettes/44026_22-12_Health.pdf) and Guidance on the payment of fees, version 5 dated November 2020 (https://www.sahpra.org.za/wp-content/uploads/2020/11/SAHPRA-Payment-Guideline-Nov-2020.pdf)

Introduction

The SAHPRA fees that have been gazetted are implementable from 22 December 2020. The fees outlined in most cases are self-explanatory, however in the case of fees payable for technical amendments related to quality, there are several options listed which require clarity and hence the focus of this explanatory note is for clarification on quality variations defined in 2(b) v-ix of the SAHPRA fees gazette. (https://www.sahpra.org.za/wp-content/uploads/2021/01/Published-SAHPRA-Fees.pdf)

This explanatory note provides clarity on capping in the case of Type IA (including IAin) and Type IB, as well as provide information on grouping of technical amendments related to quality. These clarifications are applicable technical variations related to quality for both orthodox small molecules and biological medicines. Please note that when payments are made that the respective references made should be aligned with that of the SAHPRA guidance on payments of fees.

1.1 Definitions

Type IA variation (inclusive of Type IA_{IN})

'Minor variation of type IA' means a variation or amendment which has only a minimal impact, or no impact at all, on the quality,safety or efficacy of the medicinal product concerned;

Type IB variation

'Minor variation of type IB' means a variation or amendment, which is neither a minor variation of type IA nor a major variation of type II, nor an extension;

Type II variation

'Major variation of type II' means a variation or amendment which is not an extension, and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned;

1.2 Fees

1.2.1 Type IA variation (inclusive of Type IA_{IN})

R3 300.00 (Basic fee)

For a minor variation to a registered medicine, as defined in the current Variations Addendum for Human and Veterinary Medicines and the Biological medicines Amendment guideline

1.2.2 Type IB variation

R5 400.00 (Basic fee)

For a minor variation to a registered medicine, as defined in the current Variations Addendum for Human and Veterinary Medicines and the Biological medicines Amendment guideline

1.2.3 Type II variations

R28 500.00 Level 1 (Basic fee)

For a major variation/amendment supported by new quality and pre-clinical and/or clinical data to a registered medicine, as defined in the current Variations Addendum for Human and Veterinary Medicines and Biological medicines Amendment guideline (note that Bioequivalence data qualify as clinical data)

Some examples of Type II, Level 1 quality variations include:

- reformulation of the product introducing a novel excipient that has previously not been included in a medicinal product
- flu vaccine – new manufacturer or manufacturing process or annual strain update
- inclusion of a bioequivalence study as part of a data package
- reformulation of the product that is supported by a bioavailability study or clinical data for biological medicines
- change in excipients which significantly affects the pharmaceutical or therapeutic properties

R13 300.00 Level 2 (Basic fee)

For a quality variation/amendment for which no clinical or non-clinical data are submitted or no cross-references to previously submitted clinical or non-clinical data are made by the applicant (HCR). (Note: Bioequivalence data qualify as clinical data. Biowaiver dossiers are not considered as clinical data.)

Some examples of changes which may have a significant impact on the quality include:

- a new route of synthesis for an active ingredient that has not previously been assessed by SAHPRA and a Ph Eur Certificate of Suitability and WHO CPQ (WHO Confirmation of Active Pharmaceutical Ingredient Prequalification) is not available*
- new method of sterilisation of the product*
- new immediate contact container materials for a sterile product
- new active ingredient manufacturer not previously approved to manufacture the active ingredient concerned and who does not hold a Ph Eur Certificate of Suitability/WHO CPQ for the substance concerned*
- deletion or the widening of a significant specification parameter/limit
- change to a complex manufacturing process/synthesis (terminal sterilisation process)
- reformulation supported by comparative dissolution data
- change in product preservative system
- a change requiring a product or site inspection
- change in the product's preservative system
- change which may affect the delivery of a metered dose for an inhaler

* Specific to the active ingredient

R4 400.00 Level 3 (Basic fee)

For each of the third and subsequent type II variations that are grouped in a single application. For example, if 2 Type II variations are included in one application/submission, and the next each subsequent type II variation on the same application/submission will be charged as level 3.

1.3 Grouping procedures for variations

Fees defined in section 1.2 are interpreted as follows

1.3.1 Type IA variation (inclusive of Type IA_{IN}) for R3 300.00 as described in 1.2.1 above refers

1.3.1.1 A capping of a maximum of three type IA variations for a fee of R3 300 is applicable for a product submitted at the same time i.e within the same submission. Application for a product containing multiple type IA variations may be grouped into multiples of three type IA's and each grouping of three type IA variations is charged at R3 300 per group of three.

1.3.1.2 Where there are type IA variations that are not in multiples of three, such as if only one or two type IA's are submitted this will attract the basic fee of R3 300. Therefore if for example an applicant submits four type IA variations then a maximum of three of these are grouped to a basic fee of R3 300 and the remaining one would also attract the basic fee of R3 300 hence the total fee payable for the four type IA variations is therefore R6 600.

Note: This capping of three type IA's for the basic fee of R3 300 per group of three is only applicable for type IA (inclusive of type IA_{IN}) variations and does not include any other variation types. This is further only applicable to applications for the same product within the same submission.

1.3.2 Type IB variation R5 400.00 as described in 1.2.2 above refers

1.3.2.1 A capping of a maximum of two type IB variations for one fee of R5 400 is applicable for a product if submitted at the same time i.e within the same submission. Applications for a product containing multiple type IB variations may be grouped into multiples of two type IB's and each grouping of two type IB variations is charged at R5 400.

1.3.2.2 Where there are type IB variations that are not in multiples of two such as when only one Type IB is submitted this will also attract the same fee for R5 400.

- If 8 type IB's are made in a submission they can be grouped in twos then 4x2's=4x R5 400=R21 600. Hence a fee of R21 600 will be payable for the eight type IB's that have been grouped into four groups of two's
- If an applicant submits five type IB's in the same submission then the type IB's can be grouped into two sets of two attracting a fee of R5 400 per set and the remaining one will also attract a basic fee of R5 400. Thus the total fee payable for five type IB's is 2x R 5400+R5 400=R16 200.

Note: This is only applicable for type IB variations and does not include any other variation types. This is only applicable for applications for the same product in the same submission

1.3.3 **Type II variation as described in 1.2.3 above refers**

1.3.3.1 The applicable level 1 and level 2 basic fees specified in sub-section 1.2.3 above are payable for the first and second type II variation respectively when both levels of fees are applicable to variations in the same grouping. Consequential variations in a grouping shall be similarly charged the applicable fees as specified 1.2.3 above.

1.3.3.2 In the case where submission of changes in the composition (introducing new/novel excipients) of the finished product (B.II.a.3.b.5, Type II) whereby the change is supported by a bioequivalence study, then this technical variation would be classified as a Type II level 1 and would be requiring that a fee of R28 500 be paid

1.3.3.3 In the case where for instance a submission of a change in the specification parameters (B.I.b.1.e, Type II) and change in immediate container (B.I.c.1.b, Type II) is made in the same submission then the fee payable will be: 2 Type II, level 2 fee, i.e 2 x R13 300.00 = R26 600.00

1.3.3.4 In the case where a submission of a change in the specification parameters (B.I.b.1.e, Type II), Change in coating weight of oral dosage forms or change in weight of capsule shells (B.II.a.4.b, Type II) and change in immediate container (B.I.c.1.b, Type II) is submitted, although all of these are type II level 2 changes, the first two fees paid will be for Type II level 2 and the third type II is then charged at the rate of level 3 as

per 1.2.3 “For each of the third and subsequent type II variations that are grouped in a single application, will be charged as level 3, therefore the fee payable will be 2 Type II, level 2 fees + 1 Type II, level 3, i.e 2 x R13 300.00 + 1 x R4 400.00 = R31 000.00

1.3.3.5 In the case where submission of changes in the composition (introducing new/novel excipients) of the finished product (B.II.a.3.b.5, Type II), introduction of a manufacturer of the active substance supported by an ASMF (B.I.a.1b, Type II) and change in immediate container (B.I.c.1.b, Type II). In this case we have 1x type II level1; and two type II level 2, the charges would be the level 1 +1x level 2 and the third level 2 will attract the fee of the third and subsequent fee of R4 400; i.e total fee payable is (R28 500 +R13 300+ R4 400) = R46 200.

Note: That when there is a type II level 1 fee included in a group of type II amendments this automatically becomes the first type II to be charged as it involves extensive review with major quality impact on both safety and efficacy.

1.3.4 Grouping Considerations

1.3.4.1 It must be noted that Grouping of Amendments may be done as per EMA post-authorisation procedural advice for users of the centralised procedure https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf

1.3.4.2 This grouping does not in any way change the applicability of the fees as described in this document (Explanatory notes for Technical Variations related to Quality)

1.3.4.3 The grouping of line extensions, clones, replicas and duplicates where the review is done and is applicable to other strengths, clones, replicas and duplicates of same dosage form and submitted at the same time will be charged per individual application number (i.e per product)

1.3.4.4 Where grouping involves a number of amendment types eg. type IA’s; IB’s and Type II’s, the fees levied will be based on the provisions for capping of type IA and IB. The type II fees are calculated as outlined for type II. These amendment fees are additive.

Note : The a grouping will adopt the highest amendment time line for review eg. In this case of 1.3.4.4 above, the type II amendment is the highest classification of the amendments, hence the other type IA’s, and IB’s would not be implementable until the entire group of variations has been reviewed and outcome provided.

For example: An amendment is submitted with two type IA’s two type IB’s and 5 type II (level II) changes then:

2xtype IA=R3 300

2xtype IB=R5 400

5x type II =R39 800 [Calculation: (level II) =first two level II=2x R13 300 (R26 600) and the remaining three adds on R4 400 each (3xR4 400) = R13 200

Total cost=R48 500