	Title: Guideline for Management of Safety Variations	
Rev No: 00	**Doc No: PBSL/GL/056**	Version no. 01
Issue date: 25 Nov 2025	**Effective date: 28 Nov 2025**	Approved by: Registrar

Adopted By PBSL	
Start of public Consultation	
End of public Consultation	
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Approved by Board	

PHARMACY BOARD OF SIERRA LEONE
PMB 322
CENTRAL MEDICAL STORES COMPOUND
NEW ENGLAND VILLE
FREETOWN

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Abbreviations

ADR	Adverse Drug Reaction
DHPC	Direct Healthcare Professional Communications
EMA	European Medicines Agency
HCP	Health Care Professional
MAH	Marketing Authorisation Holder
NRA	National Regulatory Authority
PASS/PAES	Post-Authorisation Safety Study/ Post-Authorisation Efficacy Study
PBSL	Pharmacy Board of Sierra Leone

RMP	Risk Management Plan
RMM	Risk Minimisation Measure
PSUR/PBRER	Periodic Safety Update Reports/ Periodic Benefit-Risk Evaluation Report
SmPC	Summary of Product Characteristics
WHO	World Health Organisation

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Executive summary

This guideline provides specific considerations for variation from a pharmacovigilance perspective.

1. Introduction

In pursuance to the Pharmacy and Drugs Act this guideline is developed by the Pharmacy Board of Sierra Leone (PBSL), to define the regulatory framework for handling safety variations of medicinal products authorised for human use in Sierra Leone to ensure that the safety profile of products remains current and accurately reflects known risks. This guideline is for information, guidance and strict compliance by marketing authorisation holders (MAHs). Penalties for non-compliance with these guidelines will be enforced according to the relevant provisions of the Act.

This guideline solely focuses on safety variations within the context of pharmacovigilance and it should be read in conjunction with other applicable PBSL guidelines.

This guideline on safety variations was primarily developed in alignment with EU Guideline 2013/C 223/01 as well as Guideline on Variation for the National Medicines Regulatory Authorities of Ghana, Liberia, Sierra Leone, and The Gambia Version 1.0, 3rd July, 2024.

Others include:

EU Guideline (2013/C 223/01)
EU Commission Regulation 1234/2008
GVP Module V – Risk Management systems (Rev 2)
GVP Module II – Pharmacovigilance system master file (Rev 2)
Guideline on Withdrawal, Suspension, Revocation or Cancellation of Marketing Authorization, Version 1, Updated December 2, 2022, Joint Technical Working Group for Development of Guidelines in Marketing Authorization (TWG-MAG)

2. Objective

The objectives of this guideline are

- provide guidance on the timely implementation of safety variations by MAHs through establishing a clear and efficient process for the submission, evaluation, and approval of safety variations in the context of pharmacovigilance related to medicinal products;
- to foster transparency in the internal and external communication of safety information to all stakeholders, including healthcare professionals (HCPs), patients, the public, and other national regulatory authorities (NRAs), ensuring that any safety variations are well understood and implemented accordingly.

3. Scope

The guideline applies to all pharmacovigilance stakeholders operating in Sierra Leone and focuses on the submission, evaluation, and implementation of safety variations related to medicinal products including vaccines and medical devices in humans and animals which are approved for marketing.

4. Requirements and procedural guidance on the handling of variations

4.1. Variation categories

This guideline covers the following categories of variations:

- Minor variations of Type IA
- Minor variations of Type IB
- Major variations of Type II
- Urgent safety restrictions

For classification of the variation categories, see **Annex 1**.

4.2. Triggers of safety variations

Safety variations are critical updates made to the safety profile of a medicinal product. These variations may be triggered by new safety information coming from different sources, including but not limited to:

4.2.1. Periodic Reporting

Periodic Safety Update Reports/ Periodic Benefit-Risk Evaluation Reports (PSURs/PBRERs) and Development Safety Update Reports (DSURs) are a mandatory requirement for MAHs and provide a comprehensive evaluation of the benefit-risk balance of a medicinal product at regular intervals (see PBSL guidelines of PBRER and DSUR). A PSUR/PBRER or DSUR may trigger a safety variation if it reveals:

- New adverse reactions or increased frequency of known adverse reactions;
- Evidence of reduced effectiveness in certain populations;
- Emerging safety issues or trends that indicate a need for new warnings, precautions, or contraindications.

4.2.2. Signal Detection

Signal detection involves identifying a potential new risk related to a medicinal product based on data from various sources, including adverse event reports, scientific literature, and clinical studies (see PBSL guideline on signal management). Significant safety signals may trigger safety variations.

4.2.3. Risk Management Plans

Risk Management Plans outline identified risks, potential risks, and plans for minimizing them. Regular updates or reviews of the RMP may trigger a safety variation (see PBSL guideline on RMP

4.2.4. Clinical Trials and post-authorization safety and efficacy studies (PASS/PAES)

Clinical trials and PASS/PAES (see PBSL guideline on PASS/PAES) may trigger safety variations if:

- New safety or efficacy issues are identified through clinical trials, PASS/PAES or the analysis of observed real-world use in broad patient populations (observational non-clinical post-authorisation study).
- The results indicate a need to update the product's labelling or restrict its use in certain populations.

4.2.5. Pharmacovigilance inspection

Pharmacovigilance inspection findings may trigger safety variations through corrective and/or preventive actions in response to safety concerns of medicinal products or quality management systems.

4.2.6. Scientific Literature and Databases

Scientific research and published studies as well as database findings may identify new risks or expand the understanding of existing ones. Peer-reviewed articles, meta-analyses, and independent research can provide evidence of:

- New adverse reactions or contraindications.

- Subpopulations at higher risk (e.g., elderly, pregnant women).

Such findings can prompt updates to the product's safety information and trigger a safety variation.

4.2.7. Safety variations in recognised national or international organisations

Updates from international organisations like the European Medicines Agency (EMA), WLAs, WHO ML3 and above NRAs, African Medicines Agency (AMA) or the World Health Organization (WHO) may lead to changes in safety-related recommendations. Also, safety variations implemented by other NRAs may be considered by PBSL, through the PBSL reliance mechanism (see <PBSL Reliance Policy>). Likewise, if a product is withdrawn or suspended in another jurisdiction due to safety concerns, this may trigger safety variations in Sierra Leone.

4.2.8. Changes in life cycle management of the product

Safety variation could be triggered by changes in GMP including acceptance limits, test procedures, expiry dates and shelf life, adjustment of product characteristics to the different climate zones, new manufacturing site.

4.2.9. Changes due to the public emergency, local or global public health threats

If any of this applies and lead to safety variation of the registered product, the respective procedures should be followed.

4.3. Submission and approval process for a safety variation

PBSL is available to address any questions which MAHs may have regarding a particular upcoming safety variation. Where appropriate, a pre-submission discussion may be organised with PBSL in order to obtain further regulatory and procedural advice.

It must be noticed that where a group of variations consists of different types of variations, the group must be submitted and will be handled according to the 'highest' variation type included in the group. For instance, a group consisting of minor variations of Type IB and Type IA will be handled as a Type IB notification.

The application form for variations to a marketing authorisation for medicinal products is available on PBSL website.

The guidance for implementation of the safety variation is not discussed in this guideline, please see Guideline on Variations For the National Medicines Regulatory Authorities of Ghana, Liberia, Sierra Leone, and The Gambia Version 1.0, 3rd July, 2024 for further guidance.

4.3.1. Minor variations of Type IA

Minor variations of Type IA do not require prior examination by PBSL before they can be implemented by the MAH. However, at the latest within 12 months from the date of the implementation, the MAH must submit a notification of the relevant variation(s) to PBSL. The MAH may group several minor variations of Type IA regarding the terms of one single marketing authorisation provided that they are notified at the same time to PBSL. The MAH may group one or more minor variations of Type IA to the terms of several marketing authorisations under a single notification provided that the variations are the same for all marketing authorisations concerned and they are notified at the same time to PBSL.

The 12 months deadline to notify minor variations of Type IA allows MAHs to collect Type IA variations for their medicinal products during a year. However, the notification of these variations in a single submission is only possible where the conditions for grouping apply (same variations for all medicinal products concerned). Therefore, it may be the case that the submission of variations implemented over a period of 12 months (so called 'annual report') requires several submissions; e.g. one referring to a single minor variation of Type IA, another referring to group of minor variations of Type IA to the terms of one marketing authorisation, and another referring to group of the minor variations of Type IA to the terms of several marketing authorisations.

The notification must contain the following elements:

- Cover letter
- The completed PBSL variation application form, including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation as applicable. Where a variation is the consequence of, or related to, another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.
- All necessary documentation to support the finding of minor variation of Type IA, please see Guideline on Variations For the National Medicines Regulatory Authorities of Ghana, Liberia, Sierra Leone, and The Gambia Version 1.0, 3rd July, 2024 for further guidance.
- In case that the variations affect the summary of product characteristics (SmPC), labelling or package leaflet: the revised product information presented in the appropriate format in English. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IA, mock-ups or specimens should be provided to PBSL
- Confirmation that the relevant fees have been paid as required by PBSL. The fees for minor variation(s) of Type IA are laid down in the fee schedule.

For grouped minor variations of Type IA a common cover letter and application form should be submitted together with separate supportive documentation and revised product information (if applicable) for each medicinal product concerned. This will allow PBSL to update the dossier of each marketing authorisation included in the group with the relevant amended or new information

PBSL will review the Type IA notification within 30 days following receipt. By day 30, PBSL will inform the MAH of the outcome of its review. In case the marketing authorisation requires any amendment to the decision granting the marketing authorisation, PBSL will update the decision granting the marketing authorisation within 6 months following the date of information to the MAH of the outcome of the review, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to PBSL.

Where one or several minor variations of Type IA are submitted as part of one notification, PBSL will inform the MAH which variation(s) have been accepted or rejected following its review.

While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the MAH provides any missing documentation immediately on request of PBSL, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the MAH must immediately cease to apply already implemented variations concerned.

4.3.2. Minor variations of Type IB

Minor variations of Type IB must be notified before implementation. The MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ('Tell, Wait and Do' procedure).

The MAH may group under a single notification the submission of several minor variations of Type IB regarding the same marketing authorisation, or group the submission of one or more minor variation(s) of Type IB with other minor variations regarding the same marketing authorisation when this has been agreed previously with PBSL.

In addition, the MAH may also group several minor variations of Type IB affecting several marketing authorisations, or one or more minor variation(s) of Type IB with other minor variations affecting several marketing authorisations provided that

(i) the variations are the same for all the marketing authorisations concerned,
(ii) the variations are submitted at the same time to PBSL, and
(iii) PBSL has previously agreed to the grouping.

The notification must contain the following elements:

- Cover letter
- The completed PBSL variation application form, including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation as applicable. Where a variation is the consequence of, or related to, another variation, a description of the relation between these variations should be provided in the appropriate section of the application form
- All necessary documentation to support the finding of minor variation of Type IB, please see Guideline on Variations For the National Medicines Regulatory Authorities of Ghana, Liberia, Sierra Leone, and The Gambia Version 1.0, 3rd July, 2024 for further guidance.
- For variations requested by PBSL resulting from new data submitted, e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the request should be annexed to the cover letter.
- In case that the variations affect the SmPC, labelling or package leaflet: the revised product information presented in the appropriate format in English. Where the overall

design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IB, mock-ups or specimens should be provided to PBSL

- Confirmation that the relevant fees have been paid as required by PBSL. The fees for minor variation(s) of Type IB are laid down in <See fee schedule>.

PBSL will check within 7 calendar days whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete ('validation') before the start of the evaluation procedure.

When the proposed variation is not considered a minor variation of Type IB and PBSL is of the opinion that it may have a significant impact on the quality, safety, or efficacy of the medicinal product, the MAH will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated (see section 4.3.3).

When PBSL is of the opinion that the proposed variation can be considered a minor variation of Type IB, the MAH will be informed of the outcome of the validation and of the start date of the procedure.

Within 30 days following the acknowledgement of receipt of a valid notification, PBSL will notify the MAH of the outcome of the procedure. If PBSL has not sent the MAH its opinion on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification will be deemed acceptable.

In case of an unfavourable outcome, the MAH may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the MAH does not

amend the notification within 30 days as requested, the variation will be deemed rejected by PBSL.

Within 30 days of receipt of the amended notification, PBSL will inform the MAH of its final acceptance or rejection of the variation(s), including the grounds for the unfavourable outcome.

Where a group of minor variations were submitted as part of one notification, PBSL will inform the MAH which variation(s) have been accepted or rejected following its review.

Where necessary, PBSL will update the marketing authorisation within 6 months following closure of the procedure, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to PBSL. However, the accepted minor variations of Type IB may be implemented without awaiting the update of the marketing authorisation.

4.3.3. Major variations of Type II

MAHs may group under a single notification the submission of several major variations of Type II regarding the same marketing authorisation, or group the submission of one or more major variation(s) of Type II with other minor variations regarding the same marketing authorisation, provided that this has been agreed previously with PBSL.

In addition, the MAH may also group several major variations of Type II affecting several marketing authorisations, or one or more major variation(s) of Type II with other minor variations affecting several marketing authorisations, provided that

1. the variations are the same for all the marketing authorisations concerned,
2. the variations are submitted at the same time to PBSL, and
3. PBSL has previously agreed to the grouping.

The notification must contain the following elements:

- Cover letter
- The completed PBSL variation application form, including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation as applicable. Where a variation is the consequence of, or related to, another variation, a description of the relation between these variations should be provided in the appropriate section of the application form
- Supporting data relating to the proposed variation(s).
- For variations requested by PBSL resulting from new data submitted, e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the request should be annexed to the cover letter.
- In case that the variations affect the SmPC, labelling or package leaflet: the revised product information presented in the appropriate format in English. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IB, mock-ups or specimens should be provided to PBSL
- Confirmation that the relevant fees have been paid as required by PBSL. The fees Type II variations are laid down in <See fee schedule>.

The procedure starts from the date of acknowledgement of the receipt of a valid application by PBSL. As a general rule, for major variations of Type II, a 60 day evaluation period will apply. This period may be reduced by PBSL having regard to the urgency of the matter, particularly for safety issues, or may be extended by PBSL to 90 days.

Within the evaluation period, PBSL may request the MAH to provide supplementary information. The request for supplementary information will be sent to the MAH together with a timetable stating the date by when the MAH should submit the requested data and where appropriate the extended evaluation period.

The procedure will be suspended until the receipt of the supplementary information. As a general rule, a suspension of 1 month will apply. For longer suspension the MAH should send a justified request to PBSL for agreement.

The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the MAH.

4.3.4. Urgent Safety Restrictions

In the event of a risk to public health the MAH may take provisional urgent safety restrictions. Urgent safety restrictions concern interim change(s) in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product. These urgent changes must be subsequently introduced via a corresponding variation in the marketing authorisation.

The MAH must immediately notify PBSL of the restrictions to be introduced. If no objections have been raised by PBSL within 24 hours following receipt of that information, the urgent safety restrictions are deemed accepted. They must be implemented within a time frame agreed between PBSL and the MAH.

Urgent safety restrictions may also be imposed by PBSL in the event of a risk to public health in the case of medicinal products for human use or in the event of a risk to human or animal health in the case of veterinary medicinal products.

The corresponding variation application reflecting the urgent safety restrictions (whether requested by the MAH or imposed by PBSL) must be submitted by the MAH as soon as possible within 15 days.

4.4. Safety and pharmacovigilance changes

Safety and pharmacovigilance changes resulting from variations may include but are not limited to:

- Change(s) in the SmPC, labelling or package leaflet*
    - of the medicinal product(s) in question;
    - of a generic/hybrid/biosimilar medicinal product following assessment of the same change for the reference product;
    - intended to implement the outcome of a procedure concerning PSUR/PBRER/DSUR, clinical trials, or post-authorisation studies (PASS/PAES), or the outcome of the assessment done PBSL;
    - due to new preclinical, clinical or pharmacovigilance data.
- Change in the legal status of a medicinal product for authorities PBSL practices reliance or recognition to.
- Change(s) to therapeutic indication(s).
- Introduction of, or changes to, a summary of pharmacovigilance system.
- Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system.
- Change in the frequency and/or date of submission of PSUR/PBRER.
- Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan.
- Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring.

*In case of change(s) to the SmPC, labelling or package leaflet, the updated information should be submitted to PBSL for review before public release.

4.5. Post-approval obligations for MAHs

4.5.1. Implementing safety and pharmacovigilance changes

MAHs are required to adhere to the obligations concerning the implementation of safety variations imposed by PBSL in the timelines outlined above or as stipulated by PBSL.

4.5.2. Communication of Safety Variations

Once approved, MAHs must implement the safety variation in the timelines outlined above or as agreed with PBSL. This includes updating all relevant product documentation and ensuring that the information is disseminated to HCPs and the public via the appropriate channels and as agreed with PBSL.

In cases where major safety variations significantly impact patient care, MAHs are required to issue a direct healthcare professional communication (DHPC). This ensures that doctors, pharmacists, and other relevant professionals are informed about the change and can adjust their treatment practices accordingly.

4.5.3. Documentation of the management of safety variations

- MAHs are required to include in the PSMF the implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets (PIL) as well as the procedures for both internal and external communications of safety variations.
- MAHs are required to provide in the PSMF an overview of the methods used to ensure timeliness of safety variation submissions compared to internal and PBSL deadlines, including the tracking of required safety variations that have been identified but not yet been submitted.
- MAHs are required to provide a clear overview of the companies involved in the management of safety variations in the PSMF section covering the organisational structure of the marketing authorisation.

For more guidance on the documentation requirements for safety variations, see the <PBSL Guideline for Pharmacovigilance System, Pharmacovigilance System Master File and Qualified Person Responsible for Pharmacovigilance>.

Penalties

Non-adherence to the requirements of these guidelines by manufacturer representatives and MAH will result in PBSL imposing sanctions as stipulated by the Act.

5. Glossary

Adverse drug reaction (ADR)	A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding for example), symptom or disease temporarily associated with the use of the medicine.
Marketing Authorisation	Approval to market a medicinal product in the NMRA's country. Marketing authorisation is issued by PBSL with a legal document for the purpose of marketing or distribution of a product within the country after evaluation for safety, efficacy and quality in the marketing authorization assessment process.

Marketing Authorisation Holder (MAH)	A person or entity whose product has been authorized by PBSL to be on the market.
Medicinal Product	Any substance or combination of substances prepared, sold or presented for use in the diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal physical state or the symptoms of it or restoring, correcting or modifying organic functions in human beings. The term Medicinal products in the context of these guidelines include finished pharmaceutical products, biotherapeutics, and vaccines. Not included are medical devices, in-vitro diagnostics, blood products and animal products, if not indicated otherwise.
Periodic safety update report (PSUR) used interchangeably with Periodic benefit-risk evaluation report (PBRER)	A regular update of the world-wide safety experience of a medicinal product at defined times during post-registration period.
Risk management plan (RMP)	A systematic approach and set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, and the assessment of effectiveness of those intervention and how these risks will be communicated to PBSL and the general population.
Safety concern	An important identified risk, important potential risk, or important missing information.
Signal	Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known

	association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.
Variation	A variation is a change in the dossier of an authorised product. There are four different types of variations: Type IA, Type IB, Type II and extension.

6. References

6.1. This guideline on safety variations was primarily developed in alignment with EU Guideline 2013/C 223/01 as well as Guideline on Variation for the National Medicines Regulatory Authorities of Ghana, Liberia, Sierra Leone, and The Gambia Version 1.0, 3rd July, 2024.

6.2. EU Guideline (2013/C 223/01)

6.3. EU Commission Regulation 1234/2008

6.4. GVP Module V – Risk Management systems (Rev 2)

6.5. GVP Module II – Pharmacovigilance system master file (Rev 2)

6.6. Guideline on Withdrawal, Suspension, Revocation or Cancellation of Marketing Authorization, Version 1, Updated December 2, 2022, Joint Technical Working Group for Development of Guidelines in Marketing Authorization (TWG-MAG)

8. Annexes

Annex 1: Classification of variations

1) The following variations shall be classified as minor variations of type IA:
   a) variations of purely administrative nature that are related to the identity and contact details of:
      i) the MAH;
      ii) the manufacturer or supplier of any starting material, reagent, intermediate, active substance used in the manufacturing process or finished product;
   b) variations related to the deletion of any manufacturing site, including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place;
   c) variations related to minor changes to an approved physico-chemical test procedure, where the updated procedure is demonstrated to be at least equivalent to the former test procedure, appropriate validation studies have been performed and the results show that the updated test procedure is at least equivalent to the former;
   d) variations related to changes made to the specifications of the active substance or of an excipient in order to comply with an update of the relevant monograph of the European Pharmacopoeia or of the national pharmacopoeia of a Sierra Leone, where the change is made exclusively to comply with the pharmacopoeia and the specifications for product specific properties are unchanged;
   e) variations related to changes in the packaging material not in contact with the finished product, which do not affect the delivery, use, safety or stability of the medicinal product;
   f) variations related to the tightening of specification limits, where the change is not a consequence of any commitment from previous assessment to review specification limits and does not result from unexpected events arising during manufacture.

2) The following variations shall be classified as **major variations of type II:**

a) variations related to the addition of a new therapeutic indication or to the modification of an existing one;

b) variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or **pharmacovigilance findings;**

c) variations related to changes outside the range of approved specifications, limits or acceptance criteria;

d) variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;

e) variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product;

f) variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines;

g) variations concerning a change to or addition of a non-food producing target species;

h) variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;

i) variations concerning the replacement of a strain for a veterinary vaccine against equine influenza;

j) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

k) variations related to changes to the withdrawal period for a veterinary medicinal product.

3) Minor variation of type IB means a variation which is neither a minor variation of type IA nor a major variation of type II nor an extension.

Annex II: fee schedule

Type of variation	**Fee**
Type IA	Le 500
Type 1B	Le 500
Type II	Le 1000