Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority

Guidance note

Version History

Version Number	Effective date	Comments
1	24 September 2019	First version published
2	21 December 2020	Updated to reflect the current status of the UK's withdrawal from the EU and to make the necessary updates to implement the Protocol on Ireland/Northern Ireland

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Introduction

The United Kingdom (UK) left the European Union (EU) on 31 January 2020 and entered into a transition period immediately thereafter, which will end on 31 December 2020. During the transition period the provisions of Union law (acquis communautaire) concerning medicines regulation continue to apply in the UK. Following the end of the transition period, the Human Medicines Regulations 2012 (HMR) (statutory instrument (SI) 2012 No. 1916, as amended) will be further amended by:

- The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (SI 2019 No. 775);
- The Human Medicines and Medical Devices (Amendment etc.) (EU Exit) Regulations 2019 (SI 2019 No. 1385), and;
- The Human Medicines (Amendment etc.) (EU Exit) Regulations 2020 (SI 2020 No. 1488),

which were made in exercise of the powers conferred by section 8(1) of, and paragraph 21(b) of Schedule 7 to, the European Union (Withdrawal) Act 2018.

Regulation 205B (Guidance in respect of good pharmacovigilance practice and post authorisation efficacy studies) of the HMR, as inserted by regulation 169 of SI 2019 No. 775, states that the guidance issued by the Commission[1] under Article 108a of the 2001 Directive on good pharmacovigilance practices (GVP) continues to apply to both the Medicines and Healthcare products Regulatory Agency ("the licensing authority") and UK marketing authorisation holders (MAH) until the date on which the licensing authority publishes guidance on GVP. It also states that whilst the Commission guidance on GVP continues to apply in the UK, the licensing authority may determine that specific provisions of it no longer apply in the UK or are to be read subject to modification.

GVP are a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU. GVP applies to MAHs, the European Medicines Agency ("the Agency"), the licensing authority and medicines regulatory authorities in EU Member States. They cover medicines authorised centrally via the Agency as well as medicines authorised at national level.

This guidance note sets out the licensing authority's determination as to the provisions of the Commission's GVP guidance that no longer apply to the licensing authority and UK MAHs or are to be read subject to modification. The modifications set out in this document apply from 1 January 2021.

This document is intended to be read in conjunction with the GVP modules, product- or population-specific chapters and annexes. This document references the version of the Commission's GVP guidance that applied at the end of the transition period and future revisions and development of the GVP shall be duly considered by the licensing authority.

[1] www.ema.europa.eu

Legislative framework for authorising medicinal products for sale or supply in the United Kingdom

The Protocol on Ireland/Northern Ireland (hereafter termed “the Protocol”) in the EU Withdrawal Agreement was designed as a practical solution to avoid a hard border within the island of Ireland, whilst ensuring that the UK, including Northern Ireland, could leave the EU. The Protocol introduces new arrangements whereby Northern Ireland remains aligned with the EU on goods. Under the terms of the Protocol, which will apply as of 1 January 2021 to the UK in respect of Northern Ireland, medicinal products licensed for sale or supply on the Northern Ireland market must continue to conform to applicable European Union law.

Throughout this document, where reference is made to ‘products authorised in respect of Northern Ireland’, this includes **UK-wide marketing authorisations as well as products authorised for sale or supply in Northern Ireland only**, which must be granted and maintained in accordance with the EU acquis.

Union law referenced throughout this document is outlined below:

- Regulation (EC) No. 726/2004 as amended, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (REG).

- Directive 2001/83/EC as amended, on the Community code relating to medicinal products for human use (DIR).

- Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council (IR).

Consequently, and in respect of pharmacovigilance, the following legal provisions will apply to UK marketing authorisations (MA):

- Those in Part 11 (Pharmacovigilance) of the HMR will apply to all UK MAs, unless expressly stated otherwise;

- those in Schedule 12A (further provision as to the performance of pharmacovigilance activities) of the HMR will apply to products authorised for sale or supply in Great Britain only;

- those in the IR will apply to products authorised for sale or supply in the UK and Northern Ireland only.

Overview of the modifications to the EU GVP

It is important that the regulatory framework for the conduct of pharmacovigilance by the licensing authority and UK MAHs is clearly set out following the departure of the UK from the EU’s regulatory and scientific pharmacovigilance network. The Commission’s statutory guidance on GVP is an important instrument in setting common standards for the conduct of

pharmacovigilance in the EU and, both during and from the end of the transition period, it will continue to apply in the UK.

In exercise of the power conferred by regulation 205B(3) of the HMR, the licensing authority has determined that specific provisions of the GVP no longer apply in the UK (or in specific regions of the UK) or are to be read subject to modification. In practice, this means the following:

- This guidance note applies to UK MAHs and the licensing authority; therefore, its scope is national UK marketing authorisations. Medicines which are granted a centralised marketing authorisation by the European Commission are generally not within its scope, unless expressly stated otherwise.

- The EU guidance on GVP continues to broadly apply to medicinal products authorised nationally in the UK. Additional or modified guidance in relation to UK authorised products, including those authorised for sale or supply in Northern Ireland or Great Britain only, has been highlighted in the respective section(s) of the applicable Modules (described below).

- Guidance that applies to “competent authorities” will generally apply to the licensing authority, except where the guidance is describing the operation of the EU’s regulatory and scientific pharmacovigilance network, in which case this will no longer apply to products authorised for sale or supply in Great Britain only.

- Sections of the guidance that no longer apply to the licensing authority and UK MAHs are specified. These are typically the sections that describe the operation of the EU network, including the role of European agencies and committees such as the European Medicines Agency and the Pharmacovigilance Risk Assessment Committee (PRAC), which will no longer apply to products authorised for sale or supply in Great Britain only.

- Where specific text is modified to ensure that it adequately describes the practical functioning of pharmacovigilance in the UK, including communication between the licensing authority, UK MAHs, patients, healthcare professionals and other concerned parties, this has been specified. Text enclosed in inverted commas (“ ”) can be read as a complete substitution of the existing cited paragraph or section.

- Where paragraphs of text or whole sections of the GVP are not mentioned in this guidance note, they can be considered to apply in full to the licensing authority and/or UK MAHs (notwithstanding the inclusion of EU legal references where equivalent UK legal references apply).

In this guidance note, all applicable legal requirements set out in the HMRs, and cited in the guidance, are identifiable by the modal verb “must”. Guidance on the implementation of those requirements is provided using the modal verb “should”.

In the subsequent sections of this guidance note, a summary of the key modifications to each of the GVP modules covering major pharmacovigilance processes and the chapters on product- or population-specific considerations is outlined.

Modules covering major pharmacovigilance processes

GVP Module I – Pharmacovigilance systems and their quality systems

Summary of key modifications to GVP Module I – Pharmacovigilance systems and their quality systems

From 1 January 2021, the qualified person responsible for pharmacovigilance (QPPV) for UK authorised products can reside and operate anywhere in the UK or the EU/European Economic Area (EEA). If the QPPV for UK authorised products resides and operates in the EU/EEA, a national contact person for pharmacovigilance must be established in the UK within 12 months from 1 January 2021.

The updated legal framework in relation to quality systems for UK authorised products is outlined in the Module.

Throughout the Module, references to “competent authority(ies)” can be replaced with “licensing authority”.

I.A. Introduction

- [Paragraph 2] This is modified to “The definition of a pharmacovigilance system is provided in the Human Medicines Regulations 2012 (HMR) as amended, regulation 8(1), as a system used by the holder of a marketing authorisation or traditional herbal registration and by the licensing authority to fulfil the tasks and responsibilities set out in Part 11 of the HMR and designed to monitor the safety of authorised or registered medicinal products and detect any change to their risk-benefit balance.”

- [Paragraph 3] The following text is added to the end of this paragraph “Where reference is made throughout this Module to legal provisions in the IR, UK MAHs should note that these apply directly to products authorised in respect of Northern Ireland and equivalent legal provisions are described in HMR Schedule 12A for products authorised in respect of Great Britain only.”

I.C.1. Overall pharmacovigilance responsibilities of the applicant and marketing authorisation holder in the EU

- The title of this section is modified to “Overall pharmacovigilance responsibilities of the applicant and marketing authorisation holder in the UK”.

- [Paragraph 1] This is modified to “The marketing authorisation holder in the UK is responsible for the respective pharmacovigilance tasks and responsibilities laid down in the HMR and, for products authorised in respect of Northern Ireland, the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC, in order to assure responsibility and liability for its authorised medicinal products and to ensure that appropriate action can be taken, when necessary.”

I.C.1.1. Responsibilities of the marketing authorisation holder in relation to the qualified person responsible for pharmacovigilance in the EU

- The title of this section is modified to “Responsibilities of the marketing authorisation holder in relation to the qualified person responsible for pharmacovigilance in the UK”.

- [Paragraph 1] This is modified to “As part of the pharmacovigilance system, the marketing authorisation holder must have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance that resides and operates anywhere in the UK or the EU [HMR regulation 182(2)(a)].”

- [Paragraph 2] This is modified to “The marketing authorisation holder must submit the name and contact details of the QPPV to the licensing authority [HMR regulation 182(3)(a)]. Changes to this information must be submitted in accordance with HMR Schedule 10A(1) (for products authorised in respect of Great Britain only) and Regulation (EC) No 1234/2008 on variations to the terms of marketing authorisation[2] (for products authorised in respect of Northern Ireland). For all UK authorised products, the guidelines published by the Commission under Article 4 of Regulation (EC) No 1234/2008 will apply until such time that the licensing authority publishes guidance on the details of the various categories of variations, on the operation of the procedures laid down in Schedule 10A, and on the documentation to be submitted pursuant to those procedures [HMR regulation 65C(6)].”

- [Paragraph 6] This is modified to “Where the QPPV does not reside and operate in the UK, the licensing authority requires the nomination of a national contact person for pharmacovigilance who resides and operates in the UK and reports into the QPPV [HMR regulation 182(2A)]. Reporting in this context relates to pharmacovigilance tasks and responsibilities and not necessarily to line management. The national contact person must have permanent access to the pharmacovigilance system master file [HMR regulation 182(2A)] and to reports of suspected adverse reactions for UK authorised products. They should have knowledge of pharmacovigilance requirements in the UK and ensure that pharmacovigilance queries raised by the licensing authority, including via inspections, are answered fully and promptly. The national contact person does not necessarily have to be directly employed by the marketing authorisation holder. The details of the national contact person for pharmacovigilance must be notified to the licensing authority [HMR regulation 182(3)(b)]. Any changes to the contact details for this nominated contact person should be notified to the licensing authority immediately and no later than 14 calendar days from the change.”

I.C.1.2. Qualifications of the qualified person responsible for pharmacovigilance in the EU

- The title of this section is modified to “Qualifications of the qualified person responsible for pharmacovigilance for UK authorised products”.

- The requirements and guidance in this section concerning QPPV qualifications continue to apply to the QPPV for UK authorised products who resides and operates anywhere in the UK or the EU/EEA.

[2] See Volume 2A of the Rules Governing Medicinal Products in the EU; http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

I.C.1.3. Role of the qualified person responsible for pharmacovigilance in the EU

- The title of this section is modified to “Role of the qualified person responsible for pharmacovigilance for UK authorised products”.

- [Paragraph 1] This is modified to “The QPPV for UK authorised products is a natural[3] person.”

- [Paragraph 2] This is modified to “The QPPV appointed by the marketing authorisation holder must be appropriately qualified (see I.C.1.2.) and must be at the marketing authorisation holder’s disposal permanently and continuously (see I.C.1.1.) [HMR regulation 182(2)(a)]. The QPPV must reside and operate anywhere in the UK or the EU [HMR regulation 182(2)(a)]. Following European Economic Area (EEA) agreements, the QPPV may also reside and operate in Norway, Iceland or Liechtenstein. Back-up procedures in the case of absence of the QPPV must be in place [HMR Schedule 12A paragraph 2(a)(iv) and IR Art 2(1)(d)] and should be accessible through the QPPV’s contact details. The QPPV should ensure that the back-up person has all necessary information to fulfil the role.”

- The role of the QPPV as described in this section of the guidance continues to apply to the QPPV for UK authorised products that resides and operates in the UK or the EU/EEA. For the avoidance of doubt, this includes the following responsibilities:

  - having an overview of medicinal product safety profiles and any emerging safety concerns;

  - having awareness of any conditions or obligations adopted as part of the marketing authorisations and other commitments relating to safety or the safe use of the products;

  - having awareness of risk minimisation measures in the UK;

  - being aware of and having sufficient authority over the content of risk management plans;

  - being involved in the review and sign-off of protocols of post-authorisation safety studies conducted in the UK or pursuant to a risk management plan agreed in the UK;

  - having awareness of post-authorisation safety studies requested by the licensing authority including the results of such studies;

  - ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP;

  - ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the licensing authority;

[3] A natural person is a real human being, as distinguished from a corporation which is often treated at law as a fictitious person.

- ensuring a full and prompt response to any request from the licensing authority for the provision of additional information necessary for the benefit-risk evaluation of a medicinal product;

- providing any other information relevant to the benefit-risk evaluation to the licensing authority;

- providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals);

- acting as a pharmacovigilance contact point for the licensing authority on a 24-hour basis and also as a contact point for pharmacovigilance inspections.

I.C.1.4. Specific quality system processes of the marketing authorisation holder in the EU

- The title of this section is modified to “Specific quality system processes of the marketing authorisation holder in the UK”.

- [Paragraph 1] The first bullet point is modified to “the submission of adverse reaction data to the licensing authority (for all UK authorised products) and to EudraVigilance (for products authorised in respect of Northern Ireland) within the legal timelines [HMR Schedule 12A paragraph 11(1)(c) and IR Art 11(c)];”

- [Paragraph 1] The second bullet point is modified to “for products authorised in respect of Northern Ireland, the monitoring of the use of terminology referred to in IR Art 25(1) either systematically or by regular random evaluation [IR Art 25(3)];”

- [Paragraph 1] The last bullet point is modified to “that the product information is kept up-to-date by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the UK national web-portal (for all UK authorised products) and the European medicines web-portal (for products authorised in respect of Northern Ireland) [HMR Schedule 12A paragraph 11(1)(f) and IR Art 11(1)(g)].”

I.C.1.5. Quality system requirements for pharmacovigilance tasks subcontracted by the marketing authorisation holder

- Paragraph 5 in relation to centrally authorised products no longer applies to UK MAHs.

I.C.2. Overall pharmacovigilance responsibilities within the EU regulatory network

- The principles in this section continue to apply to the licensing authority.

I.C.2.1. Role of the competent authorities in Member States

- The title of this section is modified to “Role of the licensing authority”.

- This section is modified to “The licensing authority must operate a pharmacovigilance system for the fulfilment of its pharmacovigilance tasks [HMR regulation 179]. In this

context, the licensing authority is responsible for the safety monitoring of each medicinal product.

The licensing authority is responsible for granting, varying, suspending and revoking a marketing authorisation. The pharmacovigilance tasks and responsibilities of the licensing authority for each process are detailed in the respective Modules of GVP.

For products authorised in respect of Northern Ireland through the mutual recognition or the decentralised procedure, one EU Member State acts as the Reference Member State. For practical reasons, the competent authority of the Reference Member State should coordinate communication with the marketing authorisation holder on pharmacovigilance matters and monitor the compliance of the marketing authorisation holder with legal pharmacovigilance requirements. These arrangements do not replace the legal responsibilities of the marketing authorisation holder with respect to the licensing authority, individual competent authorities and the Agency.

Nationally authorised products in respect of Northern Ireland, including those authorised through the mutual recognition or the decentralised procedure, may become subject to regulatory procedures at EU level on pharmacovigilance grounds. If a Commission Decision for a nationally authorised product exists as an outcome of such a procedure, the licensing authority is responsible for the implementation of the Commission Decision and also for its follow-up.

The licensing authority is responsible for pharmacovigilance inspections of organisations in its territory in relation to medicinal products."

I.C.2.2. Role of the European Commission

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

I.C.2.3. Role of the European Medicines Agency

I.C.2.3.1. General role of the Agency and the role of the Agency's secretariat

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

I.C.2.3.2. Role of the Pharmacovigilance Risk Assessment Committee (PRAC)

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

I.C.2.3.3. Role of the Committee for Medicinal Products for Human Use (CHMP)

- This section no longer applies to the licensing authority and UK MAHs.

I.C.2.3.4. Role of the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

I.C.2.4. Specific quality system processes of the quality systems of competent authorities in Member States and the Agency

- The title of this section is modified to “Specific quality system processes of the quality system of the licensing authority”.

- The general principles in this section continue to apply to the licensing authority. For the avoidance of doubt, the licensing authority must put in place the following additional specific quality system processes for:

  - for products authorised in respect of Northern Ireland, monitoring and validating the use of terminology referred to in IR Art 25(1), either systematically or by regular random evaluation [IR Art 25(3)];

  - assessing and processing pharmacovigilance data in accordance with the timelines provided by legislation [HMR Schedule 12A paragraph 15(b) and IR Art 15(1)(b)];

  - ensuring effective communication among regulatory bodies in countries other than the United Kingdom who have the same or similar functions as the licensing authority, as well as with patients, healthcare professionals, marketing authorisation holders and the general public [HMR Schedule 12A paragraph 15(d)]. In addition, ensuring effective communication within the EU regulatory network in relation to products authorised in respect of Northern Ireland [IR Art 15(1)(d)];

  - guaranteeing that the licensing authority informs the Agency, the European Commission and the competent authorities in Member States of its intention to make announcements relating to the safety of a medicinal product or an active substance contained in a medicinal product authorised in respect of Northern Ireland (see Module XV) [IR Art 15(1)(e)];

  - arranging for the essential documents describing its pharmacovigilance system to be kept for as long as the system exists and for at least a further 5 years after it has been formally terminated [HMR Schedule 12A paragraph 16(3) and IR Art 16(2)];

  - ensuring that pharmacovigilance data and documents relating to individual authorised medicinal products are retained for as long as the product is authorised and for at least further 10 years after the UK marketing authorisation has expired [HMR Schedule 12A paragraph 16(4) and IR Art 16(2)].

- Paragraphs 8, 9 and 10, regarding literature monitoring in accordance with Article 27 of Regulation (EC) No 726/2004, interaction between competent authorities, and quality audits of the Member States’ and Agency’s pharmacovigilance systems, no longer apply to the licensing authority in respect of products authorised for sale or supply in Great Britain only.

I.C.2.5. Quality system requirements for pharmacovigilance tasks delegated or transferred by competent authorities in Member States

- This section no longer applies to the licensing authority and UK MAHs.

I.C.2.6. Transparency of the quality system of the EU regulatory network

- This section no longer applies to the licensing authority in respect of products authorised for sale or supply in Great Britain only.

I.C.3. Data protection in the EU

- The title of this section is modified to “Data protection in the UK”.

- This section is modified to “All legal requirements of the HMR, including those relating to the record management described in I.B.10., must apply without prejudice to the obligations of the licensing authority and marketing authorisation holders relating to their processing of personal data under Regulation (EU) 2016/679 (General Data Protection Regulation) (as incorporated into UK law) and the Data Protection Act 2018.”

I.C.4. Preparedness planning in the EU for pharmacovigilance in public health emergencies

- The principles in this section continue to apply to the licensing authority and UK MAHs.

The following section is inserted at the end of the module:

“I.C.5. Transitional provision

As established in HMR regulation 182(2B), there is a temporary exemption as to the requirement to nominate a contact person for pharmacovigilance at a national level where the QPPV for UK authorised products does not reside and operate in the UK. UK MAHs will have 12 months from 1 January 2021 to nominate a national contact person for pharmacovigilance where the QPPV for UK authorised products does not reside and operate in the UK.”

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

Summary of the key modifications to GVP Module II – Pharmacovigilance system master file (Rev 2)

Holders of UK marketing authorisations must maintain a PSMF that describes the pharmacovigilance system that is applied to their UK authorised products and make this available upon request of the licensing authority. The requirements for the content and format of the PSMF are detailed in Chapter 1 of the IR for products authorised in respect of Northern Ireland, and in Part 1 of Schedule 12A of the HMR for products authorised in respect of Great Britain only. The content and format requirements in Schedule 12A of the HMR are aligned with the EU requirements in the IR. Any differences between the requirements in the IR and HMR are explained in these modifications to EU GVP Module II.

The location and registration requirements for the PSMF that covers UK nationally authorised products have changed.

The PSMF requirements for centrally authorised products in the EU are not covered within the scope of this guidance note and are, instead, described in EU GVP Module II. For

products authorised in respect of Northern Ireland through the EU centralised procedure, the PSMF must be located in the EU in accordance with Article 7(1) of the IR.

Throughout the Module, references to “competent authority(ies)” can be replaced with “licensing authority”.

II.A. Introduction

- [Paragraph 1] This is modified to “The legal requirement for a marketing authorisation holder to maintain and make available upon request a pharmacovigilance system master file (PSMF) is stated in regulation 182(2)(b) of the Human Medicines Regulations 2012 (HMR), as amended.”

- [Paragraph 2] This is modified to “The PSMF definition is provided in HMR regulation 8(1) and the minimum requirements for its content and maintenance are set out in the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 (IR) for products authorised in respect of Northern Ireland and in Schedule 12A of HMR for products authorised in respect of Great Britain only. The detailed requirements provided in Chapter I of the IR and Schedule 12A Part 1 of HMR are further supported by the guidance in EU GVP Module II and this guidance note.”

- Paragraphs 3 and 7 no longer apply to the licensing authority and UK MAHs.

- [Paragraph 4] This is modified to “The PSMF must be permanently and immediately available for inspection electronically in the UK at the single point from which reports of suspected adverse reactions referred to in regulation 187 of the HMRs are accessible [HMR regulation 182(2)(b)]. For products authorised in respect of Northern Ireland, the PSMF must be located either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the EU where the qualified person responsible for pharmacovigilance operates [IR Art 7(1)].”

- [Paragraph 5] This is modified to “It is a requirement of the marketing authorisation application that summary information about the pharmacovigilance system is submitted to the licensing authority [HMR Schedule 8, paragraph 12]. This summary includes information on the UK location from which the PSMF can be electronically accessed (see II.B.2.1.).”

II.B. Structures and processes

- Throughout this section, “EU” is replaced with “UK” with the exception of the fourth sentence which is modified to: “Irrespective of the location of other activities, the qualified person for pharmacovigilance (QPPV’s) residence and the location at which he/she carries out his/her tasks must be in the UK or the EU/EEA, and the PSMF must be available electronically from the UK.”

II.B.2.1. Summary of the applicant’s pharmacovigilance system

- [Paragraph 1] This is modified to “The requirements relating to the summary of the applicant’s pharmacovigilance system are described in HMR Schedule 8 paragraph 12. The summary must include the following elements in module 1.8.1 of the dossier:

- proof that the applicant has at his disposal an appropriately qualified person responsible for pharmacovigilance who resides and operates in the UK or an EU Member State;

- the country (which must be either the United Kingdom or an EU Member State) in which the appropriately qualified person resides and carries out his/her tasks;

- the contact details of the appropriately qualified person;

- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Part 11; and

– a reference to the physical location where the pharmacovigilance system master file for the medicinal product can be accessed electronically, which must be in the United Kingdom."

– [Paragraph 2] This is modified to "Applicants for, and holders of simplified registrations of traditional herbal medicinal products are not required to submit a pharmacovigilance system summary, however, they are required to operate a pharmacovigilance system and prepare, maintain and make available on request a PSMF [HMR regulations 177(1), 182(2)(b)]."

II.B.2.2. Location, registration and maintenance

– [Paragraph 1] This is modified to "The PSMF must be permanently and immediately available for inspection electronically at the single point from which reports of suspected adverse reactions referred to in HMR regulation 187 are accessible [HMR regulation 182(2)(b)]. In addition, for products authorised in respect of Northern Ireland, the PSMF must be located either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the EU where the qualified person responsible for pharmacovigilance operates [IR Art 7(1)], irrespective of the format (paper-based or electronic format file). Following European Economic Area (EEA) agreements, the PSMF may also be located in Norway, Iceland or Liechtenstein."

– [Paragraph 2] This is modified to "At the time of UK marketing authorisation application, the applicant should submit to the licensing authority information on the UK location from which the PSMF can be electronically accessed, and include in the application the UK PSMF number, which is the unique code assigned by the licensing authority to the master file. All PSMFs should be registered with the licensing authority and be assigned a unique number. In addition, all PSMFs covering products authorised in respect of Northern Ireland must be registered in the Article 57 database with the PSMF location information (as per Article 7(1) of the IR) and the PSMF reference number, which is the unique code assigned by the EudraVigilance (EV) system to the master file when the EudraVigilance Medicinal Product Report Message (XEVPRM) is processed. Further to the granting of a marketing authorisation, the PSMF will be linked by the marketing authorisation holder to the EVMPD product code(s)."

– Paragraph 3 continues to apply to products authorised in respect of Northern Ireland. The following text is added to the end of this paragraph "Marketing authorisation holders must also ensure that information provided to the licensing authority about their medicinal products for human use is up-to-date, including the information about the

qualified person responsible for pharmacovigilance (QPPV), specifically name and contact details (telephone and fax numbers, postal address and email addresses), and the UK location from which the PSMF can be electronically accessed. Changes to this information must be notified by the marketing authorisation holder via submission of a minor variation of type IA_{IN} immediately and no later than 14 calendar days from the change, in order to have the product licence information updated and to allow continuous supervision by the licencing authority. This is in accordance with HMR Schedule 10A(1) (for products authorised in respect of Great Britain only) and Regulation (EC) No 1234/2008 on variations to the terms of marketing authorisation[4] (for products authorised in respect of Northern Ireland). For all UK authorised products, the guidelines published by the Commission under Article 4 of Regulation (EC) No 1234/2008 will apply until such time that the licensing authority publishes guidance on the details of the various categories of variations, on the operation of the procedures laid down in Schedule 10A, and on the documentation to be submitted pursuant to those procedures [HMR regulation 65C(6)]."

- The guidance in Paragraph 4 applies to both the location of the PSMF (as per Article 7(1) of the IR) and the UK location from which the PSMF can be electronically accessed.

- Paragraph 5 continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

II.B.3. The representation of pharmacovigilance systems

- [Paragraph 1 (text before start of bullets)] This is modified to "The PSMF, as per the definition in HMR regulation 8(1), must describe the pharmacovigilance system for one or more medicinal products of the marketing authorisation holder. For different categories of medicinal products, the marketing authorisation holder may, if appropriate, apply separate pharmacovigilance systems [HMR Schedule 12A paragraph 1(2) and IR Art 1(2)]. Each such system must be described in a separate PSMF. Those files must cumulatively cover all medicinal products of the marketing authorisation holder for which a UK marketing authorisation or traditional herbal registration has been granted in accordance with the HMR."

- [Paragraph 1, bullet point 5] This is modified to "Submission of summary information to the licensing authority cannot contain multiple locations for the electronic accessibility of a single PSMF. The address of the location from which the PSMF can be electronically accessed, provided to fulfil the requirement of HMR Schedule 8 paragraph 12(e), should be an office address which reflects the single point in the UK from which all reports of suspected adverse reactions to the product are accessible [HMR regulations 182(2)(b), 187(4)]. This address may be different to that of the applicant/marketing authorisation holder, for example, a different office of the marketing authorisation holder or a third party."

- [Paragraph 1, bullet point 6] This is modified to "Similarly, the QPPV details aligned to a product in the licensing authority's database may be those of a contract QPPV responsible for the pharmacovigilance system for a particular medicinal product, and not necessarily a QPPV directly employed by the marketing authorisation holder."

[4] See Volume 2A of the Rules Governing Medicinal Products in the EU; http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

- The following bullet point is added below bullet point 6: “Where the QPPV for UK authorised products does not reside and operate in the UK, the marketing authorisation holder must nominate a contact person for pharmacovigilance at a national level who reports to the QPPV, resides and operates in the UK and who has permanent access to the PSMF [HMR regulation 182(2A) and Schedule 12A paragraph 7(2)].”

II.B.4. Information to be contained in the pharmacovigilance system master file

- [Paragraph 1] This is modified to “The PSMF must contain at least all of the documents listed in Article 2 of Commission Implementing Regulation (EU) No 520/2012 or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 2.”

- [Paragraph 2] The principles in this paragraph continue to apply, although UK MAHs should note that the content of the PSMF should reflect the global availability of safety information for medicinal products authorised in the UK.

II.B.4.1. PSMF section on qualified person responsible for pharmacovigilance (QPPV)

- [Paragraph 1] This is modified to “For the QPPV, contact details must be provided in the marketing authorisation application [HMR Schedule 8 paragraph 12(c)] and/or via submission of a minor variation of type IA_{IN} to the licensing authority.”

- [Paragraph 2] This is modified to “The information relating to the QPPV for UK authorised products provided in the PSMF [IR Art 2(1), or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 2(a)] must include:

    - a description of the responsibilities demonstrating that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance with pharmacovigilance tasks and responsibilities;

    - a summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance;

    - contact details;

    - details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance; and

    - responsibilities of the contact person for pharmacovigilance where such a person has been nominated at national level in accordance with HMR regulation 182(2A), including contact details.”

II.B.4.2. PSMF section on the organisational structure of the marketing authorisation holder

- [Under ‘Delegated activities’, paragraph 1] This is modified to “The PSMF, where applicable, must contain a description of the activities and/or services subcontracted by the MAH relating to the fulfillment of pharmacovigilance obligations [IR Art 2(6), or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A

paragraph 2(f)]. This includes arrangements with other parties in any country, worldwide, if applicable to the pharmacovigilance system applied to products authorised in the UK."

II.B.4.3. PSMF section on the sources of safety data

- [Paragraph 1] The principles in this paragraph continue to apply, although UK MAHs should note that the description of the main units for safety data collection should include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorised in the UK.

- [Paragraph 2] This is modified to "Flow diagrams indicating the main stages, timeframes and parties involved may be used. However it is represented, the description of the process for ICSRs from collection to reporting to the licensing authority and, for products authorised in respect of Northern Ireland, to the Agency should indicate the departments and/or third parties involved."

- [Paragraph 3] The principles in this paragraph continue to apply, although UK MAHs should note that the list of study sources of safety data should be comprehensive for products authorised in the UK, irrespective of indication, product presentation or route of administration.

II.B.4.4. PSMF section on computerised systems and databases

- [Paragraph 1] This is modified to "The location, functionality and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose must be described in the PSMF [IR Art 2(3), or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 2(c)]."

II.B.4.5. PSMF section on pharmacovigilance processes

- [Paragraph 4] The principles in this paragraph continue to apply. The PSMF must include the list of procedures referred to in Article 11(1) of Commission Implementing Regulation (EU) No 520/2012 or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 11(1), under the topic compliance management. In addition, the MAH should include a list of any UK-specific procedures relevant to the fulfilment of pharmacovigilance responsibilities. The list may be located in the PSMF Annexes.

II.B.4.6. PSMF section on pharmacovigilance system performance

- [Paragraph 1] This is modified to "The PSMF should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The PSMF should include a description of the following monitoring activities:

    - An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting to the licensing authority, and to EudraVigilance for products authorised in respect of Northern Ireland, over the past year;

- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by the licensing authority, and the Agency for products authorised in respect of Northern Ireland, regarding the quality of ICSR reporting, PSURs or other submissions;

- An overview of the timeliness of PSUR reporting to the licensing authority and to the Agency for products authorised in respect of Northern Ireland (the annex should reflect the latest figures used by the marketing authorisation holder to assess compliance);

- An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and licensing authority deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;

- Where applicable, an overview of adherence to UK risk management plan commitments, or other obligations or conditions of UK marketing authorisation(s) relevant to pharmacovigilance."

II.B.4.8. Annex to the PSMF

– This section is modified to "An annex to the PSMF must contain the following documents:

- A list of medicinal products nationally authorised in the UK covered by the PSMF, including the name of the medicinal product, the international non-proprietary name of the active substance(s) and the specific region of the UK in which the authorisation is valid [IR Art 3(1), or for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 3(a)];

  The list of medicinal products authorised in the UK should also include:

  – the authorisation number(s);

  – the Reference Member State (where the product has been authorised through the mutual recognition or the decentralised procedure);

  – the presence on the market in the UK [HMR regulation 73(1)] (commercial and non-commercial supply);

  – countries other than the UK where the product is authorised or on the market.

  The list should be organised per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimisation measures contained in the risk management plan or laid down as conditions of the marketing authorisation, non-standard PSUR periodicity, or

  - for products authorised in respect of Northern Ireland:

    – referral under Article 31 of Directive 2001/83/EC;

    – or inclusion in the list described in Article 23 of Regulation (EC) No 726/2004)

- for products authorised in respect of Great Britain only:
  - inclusion in the list described in HMR regulation 202A or that described in Article 23 of Regulation (EC) No 726/2004.

The monitoring information may be provided as a secondary list.

For marketing authorisations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system or third-party agreements exist to delegate the system, reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of PSMFs.

Where pharmacovigilance systems are shared, all products that utilise the pharmacovigilance system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organised per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;

- A list of written policies and procedures for the purpose of complying with Article 11(1) of Commission Implementing Regulation (EU) No 520/2012 [IR Art 3(2)] or, for products authorised for sale or supply in Great Britain only, paragraph 11(1) of HMR Schedule 12A [HMR Schedule 12A paragraph 3(b)];

- A list of contractual agreements covering delegated activities including the medicinal products and territory(ies) concerned in accordance with Article 6(2) of Commission Implementing Regulation (EU) No 520/2012 (see II.B.4.3.) [IR Art 3(3)] or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 6(1) (see II.B.4.3.) [HMR Schedule 12A paragraph 3(c)];

- A list of tasks that have been delegated by the qualified person for pharmacovigilance [IR Art 3(4), or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 3(d)];

- A list of all completed audits, for a period of five years, and a list of audit schedules [IR Art 3(5), or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 3(e)];

- Where applicable, a list of performance indicators in accordance with Article 9 of Commission Implementing Regulation (EU) No 520/2012 [IR Art 3(6)] or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 9(1) [HMR Schedule 12A paragraph 3(f)];

- Where applicable, a list of other PSMFs that cover UK nationally authorised products held by the same marketing authorisation holder [IR Art 3(7), or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 3(g)];

  This list should include the UK PSMF number(s), and the name of the QPPV responsible for the pharmacovigilance system used. If the pharmacovigilance system

is managed by another party that is not a marketing authorisation holder, the name of the service provider should also be included.

- A logbook in accordance with Article 5(4) of Commission Implementing Regulation (EU) No 520/2012 [IR Art 3(8) or, for products authorised for sale or supply in Great Britain only, HMR Schedule 12A paragraph 3(h)]. Other change control documentation should be included as appropriate. Documented changes must include at least the date, person responsible for the change and the nature of the change."

II.B.6. Pharmacovigilance system master file presentation

– This section is modified to: "The PSMF must be continuously accessible to the QPPV and, where applicable, to the nominated contact person for pharmacovigilance in the UK [IR Art 7(2) and HMR Schedule 12A paragraph 7(2)], as well as to the licensing authority upon request [HMR regulation 182(2)(b)]. The information must be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements [IR Art 4(1) and HMR Schedule 12A paragraph 4(1)]. Although provision of the document within 7 days of request by the licensing authority is stated in regulation 182(5) of HMR, marketing authorisation holders should be aware that immediate access to the PSMF may also be required by the licensing authority at the stated location in the UK where the PSMF can be electronically accessed."

II.B.6.1. Format and layout

– The format and layout of the PSMF that describes the pharmacovigilance system operated for UK authorised products is consistent with that of the EU PSMF (provided for by Directive 2001/83/EC as amended, Article 104(3)(b)).

– [Paragraph 4, bullet point 1] This is modified to "The unique number assigned by the licensing authority to the PSMF when the request to register the PSMF is processed."

– [Paragraph 4, bullet point 4] This is modified to "The list of PSMFs for the MAH (concerning UK nationally authorised products with a different pharmacovigilance system)."

– [Paragraph 6, bullet point 3] This is modified to "Contact details supplementary to those submitted to the licensing authority in the summary of the pharmacovigilance system, if appropriate".

II.C.1.1. Marketing authorisation holders and applicants

– [Paragraph 1] This is modified to "Marketing authorisation holders must have a pharmacovigilance system in place to ensure the monitoring and supervision of one or more medicinal products. They are also responsible for introducing and maintaining a PSMF that records the pharmacovigilance system in place with regard to one or more authorised products [HMR regulation 182(2)(b)]. In accordance with regulation 182(2)(a) and Schedule 8 paragraph 12 of the HMR, a single QPPV must be appointed to be

responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF."

- [Paragraph 3] This is modified to "The applicant/marketing authorisation holder for all UK authorised products is responsible for ensuring that the PSMF is accessible electronically from the single point within the UK from which the reports referred to in regulation 187(4) are accessible (at any marketing authorisation holder or contractual partner site, including the site of a contractor or marketing partner) and for registering the location from which the master file can be accessed electronically with the licensing authority in the marketing authorisation application. Where the PSMF covers products authorised in respect of Northern Ireland, the PSMF must be located in accordance with IR Art 7(1) and its location should be registered in the Article 57 database. The PSMF must describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current."

- [Paragraph 5] This is modified to "Marketing authorisation holders are responsible for notifying the licensing authority immediately of any change in the QPPV details, the details of the location at which the PSMF can be accessed electronically and the details of the nominated contact person for pharmacovigilance in the UK, if applicable [HMR regulations 182(3)(a)(b) and (3A)(b)]. The licensing authority must update its regulatory database accordingly."

II.C.1.2. National competent authorities

- [Paragraph 1] The licensing authority continues to be obliged to supervise the pharmacovigilance systems of marketing authorisation holders.

- Paragraphs 2 and 3 no longer apply to the licensing authority.

II.C.1.3. The European Medicines Agency

- This section no longer applies to the licensing authority.

II.C.2. Accessibility of the pharmacovigilance system master file

- [Paragraph 1] This is modified to "The PSMF must be kept up to date and be permanently available to the QPPV and, where applicable, to the nominated contact person for pharmacovigilance in the UK [IR Art 4(1) and Art 7(2) and HMR Schedule 12A paragraphs 4(1) and 7(2)]. It must also be permanently available for inspection at the site in the UK where it can be accessed electronically [HMR regulation 182(2)(b)] (the stated location), irrespective of whether the inspection has been notified in advance or is unannounced."

II.C.3. Transparency

- This section continues to apply to PSMFs that cover products authorised in respect of Northern Ireland.

GVP Module III – Pharmacovigilance inspections

Summary of the key modifications to GVP Module III – Pharmacovigilance inspections

The licensing authority will continue to operate a programme of pharmacovigilance inspections to verify compliance with the UK statutory instrument for all products authorised in the UK and, additionally, with EU regulations for products authorised in respect of Northern Ireland. The licensing authority will no longer be a supervisory authority responsible for conducting pharmacovigilance inspections of holders of centrally authorised products on behalf of the EU.

Information on non-compliance identified during inspections conducted by the licensing authority of marketing authorisation holders of products authorised in respect of Northern Ireland will continue to be shared with EEA States, the Agency and the EU Commission.

Throughout the Module, references to “competent authority(ies)” can be replaced with “licensing authority”.

III.A. Introduction

- [Paragraph 2] The legal basis for pharmacovigilance inspections of UK MAHs is described in the Human Medicines Regulations 2012 (HMR), regulation 327. This regulation empowers inspectors to determine whether there has been a contravention of any provision of the HMR which the licensing authority must or may enforce by virtue of HMR regulations 323 and 324. Inspectors are also empowered to inspect information and documents relating to compliance with conditions imposed under HMR regulation 59 (conditions of a UK marketing authorisation: general), 60 (conditions of UK marketing authorisation: exceptional circumstances) or 61 (conditions of a UK marketing authorisation: new obligations post-authorisation).

- [Paragraph 4] This is modified to “For marketing authorisation holders of centrally authorised products, it is the responsibility of the licensing authority in respect of Northern Ireland to verify the fulfilment of requirements concerning the national implementation of specific risk-minimisation measures, national communications concerning safety, locally conducted safety studies, or issues linked to the national health care system. A broader examination of pharmacovigilance applied to particular products of national interest may also be appropriate if this was not covered within the scope of a supervisory authority inspection. The supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the pharmacovigilance system master file is located [REG Art 18(3)].”

- [Paragraph 5] This is modified to “For marketing authorisation holders of nationally authorised products in the UK, including those authorised in Northern Ireland through the mutual recognition or the decentralised procedure, it is the responsibility of the licensing authority to ensure by means of inspection that the legal requirements governing medicinal products are complied with.”

- Paragraphs 7 and 10 continue to apply to the licensing authority for inspections of pharmacovigilance systems that cover products authorised in respect of Northern Ireland.

- [Paragraph 9] This is modified to: “If the outcome of an inspection of pharmacovigilance systems that cover products authorised in respect of Northern Ireland is that the marketing authorisation holder does not comply with the pharmacovigilance obligations, the licensing authority will inform the EEA States, the Agency and the EU Commission [HMR regulation 331(1)(c)].”

- [Paragraph 11] This is modified to “Where appropriate, the licensing authority must take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties [HMR regulations 209, 210 and 210A].”

III.B.1.3. Pre-authorisation inspections

- The legal basis for the licensing authority to conduct pre-authorisation inspections is HMR regulation 327(1)(c). The guidance in this section continues to apply to the licensing authority.

III.B.3. Sites to be inspected

- [Paragraph 2] This is modified to “The sites to be inspected may be located in the UK or outside the UK. Inspections of sites outside the UK might be appropriate where the main pharmacovigilance centre, databases and/or activities are located outside the UK and it would be otherwise inefficient or impossible to confirm compliance from a site within the UK.”

III.B.4.1. Routine pharmacovigilance inspections

- [Paragraph 1, text before bullets] This is modified to “Pharmacovigilance inspections conducted as part of the routine risk-based inspection programme should examine compliance with UK legislation and guidance, and the scope of such inspections should include the following elements, as appropriate:”

- [Paragraph 1] The scope of routine pharmacovigilance inspections is modified to include:

    - “risk management:

        - fulfilment of conditions of a marketing authorisation;

        - implementation of approved changes to safety communications and product information, including internal distribution and external publication;

        - implementation of additional risk minimisation activities.”

- [Paragraph 1, bullet point 4, sub-bullet point 1] The legal requirement for reporting suspected unexpected serious adverse reactions (SUSARs) and non-interventional study cases is described in the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, and HMR regulation 188(1)(1A) respectively.

III.B.5. Inspection process

- The Union procedures on pharmacovigilance inspections[5] no longer apply to the licensing authority.

III.B.7. Regulatory actions and sanctions

- [Paragraph 1] The text in relation to penalties imposed by the Agency or the Commission no longer applies to the licensing authority. The licensing authority must take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties.

- [Paragraph 2, bullet point 4] This is modified to “infringement notice: these are statutory notices in accordance with HMR regulation 206 which the licensing authority may issue stating the legislation and guideline that has been breached, reminding marketing authorisation holders of their pharmacovigilance obligations or specifying the steps that the marketing authorisation holder must take and in what timeframe in order to rectify the non-compliance and in order to prevent a further case of non-compliance;”.

- [Paragraph 2, bullet points 10 and 11] Penalties in relation to a breach of a provision of HMR Part 11, Regulation (EC) No 726/2004, Commission Implementing Regulation (EU) No 520/2012 and Schedule 12A are outlined in HMR regulations 209, 210 and 210A, respectively.

III.B.8. Record management and archiving

- This is modified to “The principles and requirements for record keeping and archiving of documents obtained or resulting from the pharmacovigilance inspections referred to in III.B.5 are described in IR Article 16, HMR Schedule 12A paragraph 16 and in GVP Module I.”

III.B.9. Qualification and training of inspectors

- [Paragraph 1] This is modified to “Inspectors who are involved in the conduct of pharmacovigilance inspections should be appointed by the licensing authority in order to determine whether there has been a contravention of a provision of the HMR which the licensing authority is required or empowered to enforce by virtue of HMR regulations 323 and 324.”

- [Paragraph 2] The Union procedures on pharmacovigilance inspections no longer apply to the licensing authority.

III.B.10. Quality management of pharmacovigilance inspection process

- [Paragraph 2] The Union procedures on pharmacovigilance inspections no longer apply to the licensing authority.

[5] https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/compliance/pharmacovigilance-inspections/pharmacovigilance-inspection-procedures-human

III.C.1. Sharing of information

- This section continues to apply to the licensing authority for inspections of pharmacovigilance systems that cover products authorised in respect of Northern Ireland.

III.C.2. Role of the European Medicines Agency

III.C.2.1. General Role of the Agency

- This section continues to apply to the licensing authority for inspections of pharmacovigilance systems that cover products authorised in respect of Northern Ireland.

III.C.2.2. Role of the PRAC

- This section continues to apply to the licensing authority for inspections of pharmacovigilance systems that cover products authorised in respect of Northern Ireland.

III.C.2.3. Role of the CHMP

- This section no longer applies to the licensing authority.

III.C.3. Role of the European Commission

- This section continues to apply to the licensing authority for inspections of pharmacovigilance systems that cover centrally authorised products authorised in respect of Northern Ireland.

III.C.4.1. General Considerations

- The general principles in this section continue to apply to the licensing authority.

III.C.4.2. Role of the Supervisory Authority

- This section no longer applies to the licensing authority.

III.C.4.3. Inspection Programmes

- Paragraphs 1 to 3 no longer apply to the licensing authority.

III.C.5. Role of the Marketing Authorisation Holders and Applicants

- [Paragraph 1, text before bullets] This is modified to “Marketing authorisation holders with authorised products and applicants who have submitted new applications for a marketing authorisation are subject to pharmacovigilance inspections (see III.B.1.). Therefore, both have responsibilities in relation to inspections, including but not limited to the following:”

- [Paragraph 1, second bullet point] The legal requirements for the maintenance and provision of the pharmacovigilance system master file for UK authorised products are described in HMR regulations 182(2)(b) and 182(5).

- [Paragraph 1, sixth bullet point] This is modified to “to ensure that relevant pharmacovigilance data is accessible from at least one point in the UK [HMR regulation 187(4)];”

III.C.6. Inspection Fees

- This is modified to “An inspection fee(s) (and inspectors’ expenses where applicable) will be charged in accordance with The Medicines (Products for Human Use) (Fees) Regulations 2016 (S.I. 2016 No. 190), as amended.”

GVP Module IV – Pharmacovigilance audits (Rev 1)

Summary of key modifications to GVP Module IV – Pharmacovigilance audits (Rev 1)

The legal references in relation to audit have been updated.

IV.A. Introduction

- [Paragraph 1] This is modified to “The legal requirement for the licensing authority and UK marketing authorisation holders to perform audits of their pharmacovigilance systems, including risk-based audits of their quality systems, is described in the Human Medicines Regulations 2012 (HMR) as amended, regulations 180 and 184, respectively. Additional legal requirements in relation to audit are described in IR Art 13(1), Art 17(1), for products authorised in respect of Northern Ireland, and HMR Schedule 12A, paragraphs 13(1) and 17(1), for products authorised in respect of Great Britain only.”

- [Paragraph 3] This is modified to “For products authorised in respect of Northern Ireland, the minimum requirements of the pharmacovigilance systems and the quality system are set out in the Commission Implementing Regulation (EU) No 520/2012 (IR) on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC. The specificities of the risk-based audits of the quality system [for pharmacovigilance activities] are as described in the Implementing Measures [IR Art 8,10,11,12,13(1) for marketing authorisation holders, and IR Art 8,14,15,16,17(1) for the licensing authority]. For products authorised in respect of Great Britain only, these minimum requirements are described in HMR Schedule 12A (Further provision as to the performance of pharmacovigilance activities). The specificities of the risk-based audits of the quality system [for pharmacovigilance activities] are as described in HMR Schedule 12A [paragraphs 8,10,11,12,13 for marketing authorisation holders, and paragraphs 8,14,15,16,17 for the licensing authority]. Risk-based audits of the pharmacovigilance system should cover all areas listed in the HMR and the IR.”

IV.C.1.1. Requirement to perform an audit

- [Paragraph 1] This is modified to “The marketing authorisation holder in the UK is required to perform regular risk-based audit(s) of their pharmacovigilance system [HMR

regulation 184], including audit(s) of its quality system to ensure that the quality system complies with the quality system requirements [HMR Schedule 12A paragraphs 8, 10, 11, 12 and 13(1)(2) and IR Art 8,10,11,12,13(1)]. The dates and results of audits and follow-up audits must be documented [HMR Schedule 12A paragraph 13(3) and IR Art 13(2)]."

IV.C.1.1.1. The qualified person responsible for pharmacovigilance in the EU (QPPV)

- The title of this section is modified to "The qualified person responsible for pharmacovigilance for UK authorised products (QPPV)".

- The guidance in this section applies to the QPPV responsible for the pharmacovigilance system operated for UK authorised products. The QPPV should be notified of any audit findings relevant to the pharmacovigilance system used for UK authorised products, irrespective of where the audit was conducted.

IV.C.1.2. Competent authorities in Member States and the European Medicines Agency

- The title of this section is modified to "Licensing authority".

IV.C.1.2.1. Requirement to perform an audit

- This is modified to "The licensing authority must perform a regular audit of its pharmacovigilance system [HMR regulation 180]. Included in its obligation to perform audits of its pharmacovigilance system/tasks, the licensing authority must perform risk-based audits of the quality system as well, at regular intervals according to a common methodology to ensure that the quality system complies with the requirements [HMR Schedule 12A paragraphs 8, 14, 15, 16 and 17(1) and IR Art 8,14,15,16,17(1)]. The dates and results of audits and follow-up audits must be documented [HMR Schedule 12A paragraph 17(2) and IR Art 17(2)]."

IV.C.1.2.2. Common methodology

- This section no longer applies to the licensing authority.

IV.C.1.2.3. The Pharmacovigilance Risk Assessment Committee (PRAC)

- This section no longer applies to the licensing authority.

IV.C.2.2. Reporting by competent authorities in Member States and the Agency

- The title of this section is modified to "Reporting by the licensing authority".

- [Paragraph 2] This is modified to "The licensing authority must report the results [of audits of its pharmacovigilance system relating to products authorised in respect of Northern Ireland] to the Commission on 21 September 2021 at the latest and then every 2 years thereafter [HMR regulation 180(1A)(3)]."

GVP Module V – Risk management systems (Rev 2)

Summary of key modifications to GVP Module V – Risk management systems (Rev 2)

For holders of UK and EU marketing authorisations for the same medicinal product, the version of the RMP that is submitted to EU national competent authorities can also be submitted to the licensing authority. This document should conform to the format and content requirements described in the Commission's GVP guidance on risk management systems (Module V) sections V.B.3 to V.B.10. Where the licensing authority has made a specific request for information to be included, or where the risk management system in the UK differs from that in the EU, this information should be provided to the licensing authority in a UK-specific annex.

For those UK MAHs that do not hold an EU marketing authorisation for the medicinal product, the RMP should conform to the Commission's GVP guidance on risk management systems, taking into account the modified format and content requirements described in this UK guidance note (Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority) in sections V.B.3. to V.B.10.

The national system for submission of a risk management plan to the licensing authority should be followed and the licensing authority is responsible for the assessment of the RMP.

Throughout the Module, the different legal references for products authorised in respect of Northern Ireland and for products authorised in respect of Great Britain only are highlighted. References to "competent authority(ies)" can be replaced with "licensing authority".

V.A. Introduction

- [Paragraph 3] This is modified to "The Human Medicines Regulations 2012 (HMR) as amended, regulations 59(2)(b) and (f) include provisions for post-authorisation safety studies and post-authorisation efficacy studies to be a condition of the marketing authorisation in certain circumstances and for these studies to be included in the risk management system [HMR regulation 59(6)]. The legislation also includes provisions for additional risk minimisation activities to be included in the risk management system as a condition to the marketing authorisation [HMR regulation 59(2)(a)]. Marketing authorisation applicants are encouraged to plan from very early on in a product's life cycle how they will further characterise and minimise the risks associated with the product in the post-authorisation phase."

- [Paragraph 4] This is modified to "Guidance on templates and submission of EU RMPs is kept up-to-date on the Agency's website[6].

- [Paragraph 7] This is modified to "The following articles provide the main references in relation to the legal basis for risk management for products authorised in respect of Northern Ireland, but additional articles may also be relevant:

[6] https://www.ema.europa.eu/en

- HMR Schedule 8 paragraphs 12 and 13, regulations 59(2)(6), 61(1)(14), 182(2), 203(2)(d);
- IR: Article 30, Article 31, Article 32, Article 33, Annex I;
- Regulation (EC) No 1901/2006 Article 34(2);
- Regulation (EC) No 1394/2007 Article 14(2)."

– The following paragraph is added to the end of this section:

"The following articles provide the main references in relation to the legal basis for risk management for products authorised in respect of Great Britain only, but additional articles may also be relevant:

- HMR Schedule 8 paragraphs 12 and 13, regulations 59(2) and (6), 61(1) and (14), 182(2) and 203(2)(d);
- HMR Schedule 12A paragraphs 22, 23, 24 and 25;
- HMR regulation 59(4A) and (4B);
- HMR regulation 59(4D) and (4E)."

V.B.2. Responsibilities for risk management

– [Paragraph 2, bullet point 1] The references to DIR 8(3)(iaa) and DIR Art 104(3)(c) are replaced with HMR Schedule 8 paragraph 13 and regulation 182(2)(c), respectively.

– [Paragraph 2, bullet point 2] The reference to DIR Art 104(3)(e) is replaced with HMR regulation 182(2)(e).

Note: Sections V.B.3. to V.B.10. that follow are modified for UK marketing authorisation holders that do not hold EU marketing authorisations for the same medicinal product. Holders of EU and UK marketing authorisations should continue to follow the Commission's GVP guidance on RMP format and content as described in GVP Module V sections V.B.3 to V.B.10. References throughout these sections to "competent authority" are replaced with "licensing authority".

V.B.3. Overview of the format and content of the risk management plan (RMP)

– [Paragraph 1] The RMP format is included in IR Annex I for products authorised in respect of Northern Ireland and HMR Schedule 12A, paragraph 25 for products authorised in respect of Great Britain only.

– [Paragraph 1] The following text is added to the end of this paragraph "Guidance on the format of the RMP in the EU is available on the Agency's website[7]; this guidance continues to apply to UK MAHs."

[7] https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans

- [Paragraph 3] The reference to DIR Art 8(3) is replaced with HMR Schedule 8 paragraph 13(b).

- [Paragraph 4] Article 14(2) of Regulation (EC) No 1394/2007, which provides for a specific framework for risk management planning for advanced therapy medicinal products (ATMP), continues to apply to products authorised in respect of Northern Ireland. HMR regulation 59(4D)(4E) applies to products authorised in respect of Great Britain only.

- [Paragraph 9] This is modified to “The UK RMP should be submitted as part of an eCTD submission.”

- [Paragraph 12, bullet point 4] The references to “QPPV” are replaced with “QPPV for UK authorised products”.

V.B.4. RMP part I “Product(s) overview”

- [Paragraph 1, bullet point 4] This no longer applies to UK MAHs.

- [Paragraph 1, bullet point 6] This no longer applies to UK MAHs.

- [Paragraph 1, bullet point 7] This is modified to “invented name(s) in the UK;”.

- [Paragraph 1, bullet point 13] This is modified to “whether the product is subject to additional monitoring in the UK (at initial marketing authorisation application conclusion or with RMP updates)”.

V.B.5. RMP part II “Safety specification”

- [Paragraph 2] Reference to “EU” is replaced with “UK”.

V.B.5.1.2. Advanced therapy medicinal products

- The categorisation of advanced therapy medicinal products in Regulation (EC) No 1394/2007 continues to apply to products authorised in respect of Northern Ireland. The categorisation in HMR regulation 2A(1) applies to products authorised in respect of Great Britain only. Reference in this section to “EU” is replaced with “UK”.

V.B.5.2. RMP part II, module SI “Epidemiology of the indication(s) and target population(s)”

- References to “EU” are replaced with “UK”.

V.B.5.6. RMP part II, module SV “Post-authorisation experience”

- References to “EU” are replaced with “UK”.

V.B.5.7. RMP part II, module SVI “Additional EU requirements for the safety specification”

- The title of this section is modified to “Additional UK requirements for the safety specification”.

- Reference to “EU-RMP” is replaced with “UK RMP”.

- The reference to DIR Art 71(2) for special medical prescription is replaced with HMR regulation 62(4).

V.B.6.1. RMP part III section “Routine pharmacovigilance activities”

- [Paragraph 1] Reference to “DIR and REG” is replaced with “HMR”.

- [Paragraph 2] The role of the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual recognition and Decentralised Procedures – Human (CMDh) no longer applies to UK MAHs. The licensing authority may make recommendations for specific activities related to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions which differ from the normal requirements for routine pharmacovigilance. The remaining text in this paragraph continues to apply.

V.B.6.3. RMP part III section “Summary table of additional pharmacovigilance activities”

- [Paragraph 1] This is modified to “This RMP section outlines the pharmacovigilance activities designed to identify and characterise risks associated with the use of a medicinal product. Some may be imposed as conditions to the marketing authorisation, either because they are key to the risk-benefit profile of the product (in accordance with HMR regulations 59 or 61) (category 1 studies in the pharmacovigilance plan), or because they are specific obligations in the context of a conditional marketing authorisation (in accordance with HMR regulation 59(4C)) or a marketing authorisation under exceptional circumstances (in accordance with HMR regulation 60) (category 2 studies in the pharmacovigilance plan). If the condition or the specific obligation is a non-interventional PASS, it will be subject to the supervision set out in HMR regulations 198 to 202 and the format and content of such non-interventional PASS should be as described in IR Annex III (for products authorised in respect of Northern Ireland) and HMR Schedule 12A paragraphs 28 to 32 (for products authorised in respect of Great Britain only) (see GVP Module VIII).”

- [Table V.3. Attributes of additional pharmacovigilance activities] This is modified as follows:

	Type of activity	Study category (PhV plan)	Status	Supervised under	
				HMR regulation 198	HMR regulations 199-201
Imposed PASS	"Interventional"	1	Mandatory and subject to penalties	No	No
	Non-interventional			Yes	Yes
Specific obligation	"Interventional"	2	Mandatory and subject to penalties	No	No
	Non-interventional			Yes	Yes
Required	"Interventional"	3	Legally enforceable	No	No
	Non-interventional			Yes	No

- [Table V.3 footnote] The first sentence is modified to "Clinical interventional studies are subject to the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended."

- [Paragraph 3] This is modified to "Studies required in jurisdictions outside the UK should not be included in the RMP unless they are also imposed as a condition to the marketing authorisation, or as a specific obligation or are required by the licensing authority. Studies not required by the licensing authority should not be included in the pharmacovigilance plan in the RMP. This is without prejudice to safety concerns arising from any such studies, which should be reported as per the applicable legislation."

V.B.8. RMP part V "Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)"

- [Under 'Legal status', paragraphs 2 and 3] The legal basis for the conditions or restrictions under which a medicinal product may be made available to patients in the UK can be found in HMR regulation 62(3) for medicinal products subject to medical prescription and HMR regulation 62(4) for medicinal products only available upon a restricted or special medical prescription.

- [Under 'Legal status', paragraph 6] The concept of categorisation at Member State level no longer applies to the licensing authority.

- [Under 'Additional risk minimisation activities', paragraph 3] This paragraph no longer applies to UK MAHs.

- [Under 'Evaluation of the effectiveness of risk minimisation activities', paragraph 1] The following sentence no longer applies to UK MAHs "Where relevant, such information may be presented by EU region."

V.B.9. RMP part VI "Summary of the risk management plan"

- [Paragraph 1] This is modified to "A summary of the RMP for each authorised medicinal product must be made publicly available and must include the key elements of the risk management plan [HMR regulation 203(2)(d), Schedule 12A paragraph 23(1) and IR Art 31(1)]."

- [Paragraph 2] This is modified to "Part VI of the RMP must be provided by the marketing authorisation applicant/holder for medicinal products which have an RMP. Based on the information contained in part VI of the RMP, a summary of the RMP should be included in the public assessment report published on the licensing authority's website."

V.B.10.1. RMP annex 1

- This section no longer applies to UK MAHs.

V.C.1. Requirements for the applicant/ marketing authorisation holder in the EU

- The title of this section is modified to "Requirements for the applicant/ marketing authorisation holder in the UK".

- [Paragraph 1] Reference to DIR Art 8(3)(iaa) is replaced with HMR Schedule 8 paragraph 13.

- References in this section to "Agency" and "competent authority" are replaced with "licensing authority".

V.C.1.1.1. New applications under Article 10(1), i.e. "generic"

- The title of this section is modified to "New applications under HMR regulation 51, i.e. 'generic'".

- [Paragraph 1] The reference to DIR Art 10(1) is replaced with HMR regulations 51, 51A and 51B.

- [Paragraph 1, bullet point 2, sub-point 2] For the avoidance of doubt, where the originator product does not have an RMP, UK MAHs of generic products should continue to refer to the safety concerns of the substance published on the CMDh website[8].

V.C.1.1.2. New applications under Article 10c, i.e. "informed consent"

- The title of this section is modified to "New applications under HMR regulation 56, i.e. 'informed consent'".

- [Paragraph 1] The reference to DIR Art 10c is replaced with HMR regulation 56.

[8] http://www.hma.eu/464.html

V.C.1.1.3. New applications under Article 10(3), i.e. “hybrid”

- The title of this section is modified to “New applications under HMR regulations 52, 52A and 52B, i.e. ‘hybrid’”.

- [Paragraph 1] The reference to DIR Art 10(3) is replaced with HMR regulations 52, 52A and 52B.

V.C.1.1.4. New applications under Article 10b, i.e. involving “fixed combination” medicinal products

- The title of this section is modified to “New applications under HMR regulation 55, i.e. involving ‘fixed combination’ medicinal products”.

V.C.1.1.5. New applications under Article 10a, i.e. “well established medicinal use”

- The title of this section is modified to “New applications under HMR regulation 54, i.e. ‘well established medicinal use’”.

- [Paragraph 1] The reference to DIR Art 10a is replaced with HMR regulation 54.

V.C.1.1.6. New applications under Article 10(4), i.e. “biosimilar products”

- The title of this section is modified to “New applications under HMR regulations 53, 53A and 53B, i.e. ‘biosimilar products’”.

V.C.2. Submission of a risk management plan to competent authorities in the EU

- The title of this section is modified to “Submission of a risk management plan to the licensing authority in the UK”.

- [Paragraph 1] This is modified to “The national system for submission of a risk management plan to the licensing authority should be followed[9].”

- Paragraph 2 no longer applies to the licensing authority and UK MAHs.

V.C.2.1. Risk management plan updates

- Under ‘RMP updates with the PSUR’, paragraph 2 continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland that are subject to the EU single assessment procedure.

V.C.3. Assessment of the risk management plan within the EU regulatory network

- The title of this section is modified to “Assessment of the risk management plan within the UK”.

- Paragraphs 1 and 3 no longer apply to the licensing authority and UK MAHs.

[9] https://mhrabpm.appiancloud.com/suite/

- [Paragraph 2] This is modified to “The licensing authority is responsible for the assessment of the RMP. The licensing authority may impose an obligation on a marketing authorisation holder to operate a risk management system for each medicinal product, as referred to in HMR regulation 183(2), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the licensing authority must also oblige the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned [HMR regulation 183(8)]”.

- [Paragraph 4] This is modified to “When necessary, the licensing authority will ensure that all marketing authorisation holders of medicinal products containing the same active substance make similar changes to their risk minimisation measures when changes are made to those of the reference medicinal product.”

V.C.4. Transparency

- [Paragraph 1] This is modified to “The licensing authority must make publicly available, by means of the national medicines web-portal, public assessment reports and summaries of risk management plans [HMR regulation 203(2)(a) and (d)].”

- Paragraphs 2 and 3 no longer apply to the licensing authority.

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

Summary of the key modifications to GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

The ICSR reporting requirements for UK authorised products have changed; the Module includes updated guidance on which ICSRs must be reported to the licensing authority and which must be reported to EudraVigilance.

The monitoring of the medical literature by the European Medicines Agency continues to apply to UK MAHs for products authorised in respect of Northern Ireland. In accordance with Article 107(3) of Directive 2001/83/EC and to avoid the submission of duplicate ICSRs, the marketing authorisation holder must only submit those ICSRs described in the medical literature which is not reviewed by the Agency, for products authorised in respect of Northern Ireland containing active substances which are not included in the list monitored by the Agency.

Throughout the Module, references to “competent authority(ies)” can be replaced with “licensing authority”.

VI.A. Introduction

- [Paragraph 1] This is modified to “This Module of GVP addresses the legal requirements detailed in The Human Medicines Regulations 2012 (HMR) as amended, which are applicable to the licensing authority and marketing authorisation holders as regards the collection, data management and submission of individual reports of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use

authorised in the UK. These legal requirements are outlined in HMR regulations 178, 179, 185 and 186 for the licensing authority and regulations 187 and 188 for UK MAHs. In addition, the provisions in the Commission Implementing Regulation (EU) No 520/2012 (IR) Chapters IV and V apply to products authorised in respect of Northern Ireland and those in HMR Schedule 12A Parts 5 and 6 apply to products authorised in respect of Great Britain only."

VI.B.1.1.2. Literature reports

- [Paragraph 6] The text regarding the submission of ICSRs from the scientific and medical literature not monitored by the European Medicines Agency continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

VI.C. Operation of the EU network

- The title of this section is modified to "Operation of the UK and EU network".

- [Paragraph 1] This is modified to "Section VI.C of this Module highlights the UK and EU specific requirements, as defined in the HMR, in relation to the collection, management and submission of reports of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the UK, irrespective of the products' conditions of use within or outside the terms of the marketing authorisation in the UK. These requirements are applicable to the licensing authority and/or to marketing authorisation holders in the UK."

- [Paragraph 2] This is modified to "The definitions and general principles detailed in Sections VI.A. and VI.B. should be applied in conjunction with the guidance provided in this Section. In accordance with HMR Schedule 12A Part 5, the licensing authority may publish a list of which of the internationally agreed terminology, formats and standards are to be used for the description, classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information in the UK. Until such time that a list is published, UK MAHs should follow Chapter IV of the Commission Implementing Regulation (EU) No 520/2012 on the use of terminology, formats and standards."

- [Paragraph 3] The reference to Article 107 is replaced with HMR regulation 188 regarding the legal basis for marketing authorisation holders to submit information on adverse reactions that occur in the UK and information on serious suspected adverse reactions that occur in countries other than the UK.

- [Paragraph 4] This is modified to "The guidance provided in this Module also applies to

  - homeopathic and herbal medicinal products with the exception of homeopathic medicinal products authorised under the special simplified registration procedure detailed in HMR Part 6 [HMR regulation 177(1)], and

  - medicinal products supplied in the context of compassionate use as defined in Article 83(2) of Regulation (EC) No 726/2004, subject to and without prejudice to the applicable national laws of EU Member States. As the case may be, this guidance may also apply to named patient use as defined under HMR regulation 167 (see VI.C.1.2.2. for ICSRs management in compassionate use and named patient use)."

- [Paragraph 5] This is modified to "For products authorised in respect of Great Britain only that are a combination of a medical device and a medicinal product, the following guidance applies. Where the medical device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable (as defined in regulation 5 of the UK Medical Devices Regulations 2002, as amended (UK MDR)), that single product shall be governed by the requirements for submission of reports of suspected adverse reactions provided in the HMR. The relevant essential requirements, as set out in regulation 9 of the UK MDR, shall apply as far as safety and performance-related device features are concerned. Where a device is intended to administer a medicinal product within the meaning of HMR regulation 2(1), that device shall be governed by the UK MDR, without prejudice to the provisions of the HMR with regard to the medicinal product. This means that the device must be CE marked[10] or UKCA marked as a medical device and follow the requirements for medical device vigilance given in the UK MDR. A medical device incorporating a medicinal product or substance, where the action of the medicinal product or substance is ancillary to that of the device, follows the legal requirements of EU Directive 90/385/EEC and EU Directive 93/42/EEC, which are transposed into UK law by virtue of the UK MDR."

- The following paragraph is added to the end of this section:

"For products authorised in respect of Northern Ireland that are a combination of a medical device and a medicinal product, the UK MDR will continue to apply until the Medical Device Regulations (2017/745) and the in vitro Diagnostic Medical Device Regulations (2017/746) come into effect, which will be 26 May 2021 and 26 May 2022, respectively, in line with the EU's implementation timeline. Until these regulations come into effect, the guidance relating to the submission of suspected adverse reactions described in paragraph 5 applies to products authorised in respect of Northern Ireland that are a combination of a medical device and a medicinal product."

VI.C.1. Management of individual safety reports for clinical trials, post-authorisation studies, compassionate use and named patient use in the EU

- The title of this section is modified to "Management of individual safety reports for clinical trials, post-authorisation studies, compassionate use and named patient use in the UK".

- References throughout this section to Directive 2001/20/EC are replaced with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, and references to Directive 2001/83/EC and Regulation (EC) No 726/2004 are replaced with the HMR.

- [Paragraph 2] This is modified to "In the UK, post-authorisation safety or efficacy studies can be imposed by the licensing authority during the evaluation of the initial marketing authorisation application in accordance with HMR regulation 59(2)(b) and (f), or they can be requested during the post-authorisation phase in line with HMR regulation 61(1). They can also be conducted voluntarily by the marketing authorisation holders."

[10] Note that the CE mark will be recognised for medical devices in Great Britain until 30 June 2023. From 1 July 2023, to place a device on the Great Britain market, manufacturers will need to meet the requirements for placing a UKCA mark on their device.

- [Paragraph 7] This is modified to “The rules for the submission of valid ICSRs to the licensing authority and the EudraVigilance database depend on the types of organised collection systems where the suspected adverse reactions occurred and the guidance provided in VI.C.6.2. should be followed.”

VI.C.2.1. Responsibilities of Member States

- The title of this section is modified to “Responsibilities of the licensing authority”.

- [Paragraph 1] This is modified to “The licensing authority must have in place a system for the collection and recording of unsolicited and solicited reports of suspected adverse reactions that occur in its territory and which are brought to its attention by healthcare professionals, consumers, or marketing authorisation holders [HMR regulations 179(1) and 185]. In this context, the licensing authority must establish procedures for collecting and recording all reports of suspected adverse reactions that occur in its territory.”

- [Paragraph 2] This is modified to “The licensing authority must take all appropriate measures to encourage healthcare professionals and consumers in the UK to report suspected adverse reactions. In addition, the licensing authority may impose specific obligations on healthcare professionals. To this end, the licensing authority in the UK must facilitate the reporting of suspected adverse reactions by means of alternative straightforward reporting systems, accessible to healthcare professionals and consumers, in addition to web-based formats [HMR regulation 178(b)]. Information on the different ways of reporting suspected adverse reactions related to medicinal products must be made publicly available, including by means of the national medicines web-based portal [HMR regulation 203(2)(f)]. To increase awareness of the reporting systems, organisations representing consumers and healthcare professionals may be involved as appropriate.”

- Paragraph 3 no longer applies to the licensing authority.

- [Paragraph 7] This is modified to “The licensing authority must ensure that the reports of suspected adverse reactions arising from an error associated with the use of a medicinal product (see VI.A.1.2. for medication error definition) that are brought to its attention are made available to any statutory body with functions in relation to patient safety within the UK [HMR regulation 186(2) and (3)]. To facilitate such reporting, it may be necessary to implement data exchange agreements or other arrangements, as appropriate. Further guidance concerning the management and assessment of reports of medication errors is provided in the Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors.[11]”

- [Paragraph 8] This is modified to “Pharmacovigilance data and documents relating to individual authorised medicinal products must be retained by the licensing authority as long as the product is authorised and for at least 10 years after the marketing authorisation has expired [HMR Schedule 12A paragraph 16(3) and IR Art 16(2)] (see VI.C.6.2.4. and GVP Module I for guidance on ICSRs data quality).”

[11] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medication-errors

VI.C.2.2. Responsibilities of the marketing authorisation holder in the EU

- The title of this section is modified to “Responsibilities of the marketing authorisation holder in the UK”.

- [Paragraph 1] In this paragraph “EU” is replaced with “UK” and the legal references are replaced with HMR regulations 182(1) and 187(1).

- [Paragraph 3]This is modified to “The marketing authorisation holder must establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports [HMR regulation 188(1)(c)]. They must also collect follow-up information on these reports and submit the updates to the licensing authority’s database (for all UK authorised products) and the EudraVigilance database (for products authorised in respect of NI) [HMR regulation 188(1)(d) and (1A)(c)]. The marketing authorisation holder must establish mechanisms enabling the traceability and follow-up of adverse reaction reports while complying with the data protection legislation [HMR Schedule 12A paragraph 12(3) and IR Art 12 (1)]. In support of the operation of the follow-up procedures, business process maps and process descriptions are provided in VI.App.1.1. and VI.App.1.2.. Further guidance on the follow-up of ICSRs is provided in VI.B.3. and in VI.C.6.2.2.7..”

- [Paragraph 4] The principles described in this paragraph concerning the follow-up of ICSRs apply to ICSRs made available to a marketing authorisation holder directly by the licensing authority.

- [Paragraph 7] In this paragraph, references to “EU” are replaced with “UK”.

VI.C.2.2.1. Spontaneous reports

- In this section, reference to “EU” is replaced with “UK” and the legal reference is modified to HMR regulation 187(1)(a) and (3).

VI.C.2.2.2. Solicited reports

- In this section, reference to “EU” is replaced with “UK” and the legal reference is modified to HMR regulation 187(1)(b).

VI.C.2.2.3.1. Monitoring of the medical literature by the European Medicines Agency

- This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

VI.C.2.2.3.2. Exclusion criteria for the submission of ICSRs published in the medical literature

- [Paragraph 1] This is modified to “The following exclusion criteria for the submission of ICSRs to the licensing authority (for all UK authorised products) and the EudraVigilance database (for products authorised in respect of Northern Ireland) by a marketing authorisation holder may be applied for cases published in the medical literature:”.

- [Paragraph 1, sub-paragraph c.] This is modified to “which is based on an analysis from the licensing authority’s database or a competent authority database within the EU, respectively. However, the submission requirements remain for those ICSRs which are based on the analysis from a competent authority database outside the UK;”.

VI.C.2.2.7. Period between the submission of the marketing authorisation application and the granting of the marketing authorisation

- [Paragraph 1] The text in relation to applications assessed under the centralised procedure no longer applies to the licensing authority and UK MAHs.

VI.C.2.2.9. Period during a public health emergency

- The following text is added to the end of this section “Arrangements for amended submission requirements in the UK will be appropriately notified on the licensing authority’s website.”

VI.C.2.2.10. Reports from class action lawsuits

- [Paragraph 2] The final sentence is modified to “The request should be made to the licensing authority’s pharmacovigilance department.”

VI.C.2.2.12. Reporting of off-label use

- [Paragraph 2, section a., sub-paragraph 1] The final sentence is modified to “Valid ICSRs must be submitted to the licensing authority and EudraVigilance database in accordance with the time frames and modalities provided in VI.C.3., VI.C.4. and VI.C.6.2.3.3.”.

- [Paragraph 2, section b., sub-paragraph 1] This is modified to “The potential obligations regarding the collection of data on the off-label use of a medicinal product are set out in HMR regulation 75(2), which requires the marketing authorisation holder to report to the licensing authority any other new information which might influence the evaluation of the benefits and risks of the medicinal product, including data on the use of the product where such use is outside the terms of the marketing authorisation.”

- Paragraph 3 no longer applies to the licensing authority and UK MAHs.

VI.C.3. Submission time frames of ICSRs in EU

- The title of this section is modified to “Submission time frames of ICSRs for UK authorised products”.

- [Paragraph 2] This is modified to “According to HMR regulation 188(1)(1A),

    - serious valid ICSRs must be submitted by the marketing authorisation holder to the licensing authority (for all UK authorised products) and to EudraVigilance (for products authorised in respect of Northern Ireland) within 15 days from the date of receipt of the reports;

- non-serious valid ICSRs must be submitted by the marketing authorisation holder to the licensing authority (for all UK authorised products) and to EudraVigilance (for products authorised in respect of Northern Ireland) within 90 days from the date of receipt of the reports."

– [Paragraph 3] The ICH E2B(R2)/(R3) requirements apply to reports submitted in the UK and the EU.

VI.C.4. Submission modalities of ICSRs in EU

– The title of this section is modified to "Submission modalities of ICSRs for UK authorised products".

– [Paragraph 1] This is modified to "In addition to the guidance provided in VI.B.8., the licensing authority and the marketing authorisation holder should continue to use the formats, standards and terminologies for the electronic submission of suspected adverse reactions as referred to in Chapter IV of the Commission Implementing Regulation (EU) No 520/2012 (or those published by the licensing authority in accordance with HMR Schedule 12A Part 5, as applicable). ICSRs must be used for the submission to the licensing authority's database and the EudraVigilance database of reports of suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time [HMR Schedule 12A paragraph 19 and IR Art 27]. The licensing authority and the marketing authorisation holder must also ensure that all submitted ICSRs are well documented and as complete as possible in accordance with the requirements provided in HMR Schedule 12A paragraph 20 and IR Art 28."

– [Paragraph 3] This is modified to "In line with the provisions set out in HMR regulation 188(1)(1A), the following submission requirements must apply to valid unsolicited and solicited ICSRs reported by healthcare professionals and non-healthcare professionals in relation to medicinal products for human use authorised in the UK in accordance with the HMR. This is relevant irrespective of the condition of use of the suspected medicinal product and of the expectedness of the adverse reaction.

<u>For all UK authorised products:</u>

a. Serious ICSRs

- The marketing authorisation holder must submit all serious ICSRs that occur within or outside the UK, including those received from competent authorities outside the UK, to the licensing authority.

- The licensing authority should make available to the marketing authorisation holders of the suspected medicinal products, all serious ICSRs that occur within the UK reported directly to it.[12]

b. Non-Serious ICSRs

- The marketing authorisation holder must submit all non-serious ICSRs that occur in the UK to the licensing authority.

[12] https://www.gov.uk/guidance/send-and-receive-information-on-adverse-drug-reactions-adrs

- The licensing authority should make available to the marketing authorisation holders of the suspected medicinal products, all non-serious ICSRs that occur within the UK reported directly to it.

For products authorised in respect of Northern Ireland:

c. Serious ICSRs

- The marketing authorisation holder must submit all serious ICSRs that occur within or outside the UK, including those received from competent authorities outside the EU, to the EudraVigilance database.

d. Non-Serious ICSRs

- The marketing authorisation holder must submit all non-serious ICSRs that occur in an EEA State or Northern Ireland to the EudraVigilance database."

– Paragraph 5 no longer applies to the licensing authority.

VI.C.5. Collaboration with the World Health Organization and the European Monitoring Centre for Drugs and Drug Addiction

– [Paragraph 1] This is modified to "The licensing authority must make available to the WHO (in practice the Uppsala Monitoring Centre (UMC) as the WHO Collaborating Centre for International Drug Monitoring) all suspected adverse reaction reports occurring in the UK that are submitted to the licensing authority's database. In this regard, ICSRs from the UK submitted to the licensing authority's database are transmitted to the WHO electronically in ICH-E2B format."

– Paragraph 2 no longer applies to the licensing authority and UK MAHs.

VI.C.6. Electronic exchange of safety information in the EU

– The title of this section is modified to "Electronic exchange of safety information in the UK and the EU".

– [Paragraph 2] This is modified to "The information provided here is relevant for the electronic exchange of ICSRs in the UK between marketing authorisation holders and the licensing authority, and for the electronic submission of information on medicinal products to the Agency."

VI.C.6.1. Applicable guidelines, definitions, international formats, standards and terminologies

– [Paragraph 1] This is modified to "For the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, the licensing authority and marketing authorisation holders should adhere to the guidelines, definitions, international formats, standards and terminologies provided in Chapter IV and V of the Commission Implementing Regulation (EU) No 520/2012 (or those published by the licensing

authority in accordance with HMR Schedule 12A Part 5, as applicable). In addition, the following guidelines should be applied:

- the ICH Guidelines detailed in VI.B.8.;
- the guidelines applicable for the ICH-E2B(R2) and ICH-E2B(R3) formats:"

– The subsequent table describing ICH-E2B guidelines continues to apply to the licensing authority and UK MAHs.

VI.C.6.2. Electronic submission of individual case safety reports

– [Paragraph 1] This is modified to "The submission of valid ICSRs electronically by marketing authorisation holders is mandatory for all medicinal products authorised in the UK [HMR regulation 188(1)(1A)]. Non-adherence to this requirement constitutes a non-compliance with UK legislation."

– [Paragraph 2] This is modified to "The responsibilities in case of communication failure (including adherence to compliance for submission of ICSRs) are detailed in the business continuity plan available on the licensing authority's website[13] and in the EU Individual Case Safety Report (ICSR) Implementation Guide[14]."

– [Paragraph 3] The first sentence is modified to "Technical tools (EVWEB and ICSR Submissions) have been made available by the Agency and the licensing authority respectively to interested electronic data interchange partners, including small and medium-sized enterprises, to facilitate compliance with the electronic submission requirements of ICSRs as defined in UK legislation."

– The following text is added to the end of this section:

"In line with ICH-E2B, unsolicited reports and solicited reports which do not fall under the scope of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended (see VI.C.1.) should be submitted as ICSRs with the following value:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• 'MHRAUK' in the data element M.1.6 'Message receiver identifier' (ICH M2).
ICH-E2B(R3)	• 'MHRAUK' in the data elements N.1.4 'Batch Receiver Identifier' and 'N.2.r.3 Message Receiver Identifier'.

[13] https://www.gov.uk/guidance/send-and-receive-information-on-adverse-drug-reactions-adrs
[14] Ref.: EMA/51938/2013; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.

Depending on their type, these ICSRs should be classified based on one of the following options in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.4 'Type of report': – spontaneous report; – other; – not available to sender (unknown); or – report from study. • When the value of the data element A.1.4 is 'Report from study', the data element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' should be populated with: – individual patient use, e.g. compassionate use or named-patient basis; or – other studies, e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring, post-authorisation study.
ICH-E2B(R3)	• Data element C.1.3 'Type of report': – spontaneous report; – other; – not available to sender (unknown); or – report from study. • When the value of the data element C.1.3 is 'Report from study', the data element C.5.4 'Study type in which the reaction(s)/event(s) were observed' should be populated with: – individual patient use, e.g. compassionate use or named-patient basis; or – other studies, e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring, post-authorisation study.

Cases of suspected unexpected serious adverse reactions (SUSARs), related to investigational medicinal products studied in clinical trials which fall under the scope of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended (see VI.C.1.), should be reported by the sponsor. The ICSRs should be submitted with the following value in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• 'MHRAUK' in the data element M.1.6 'Message receiver identifier' (ICH M2).
ICH-E2B(R3)	• 'MHRAUK' in the data elements N.1.4 'Batch Receiver Identifier' and 'N.2.r.3 Message Receiver Identifier'.

These ICSRs should be classified as follows in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.4 'Type of report': – report from study. • When the value of the data element A.1.4 is 'Report from study', the data element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' should be populated with: – clinical trials.
ICH-E2B(R3)	• Data element C.1.3 'Type of report': – report from study. • When the value of the data element C.1.3 is 'Report from study', the data element C.5.4 'Study type in which the reaction(s)/event(s) were observed' should be populated with: – clinical trials."

VI.C.6.2.1. EudraVigilance Database Modules

– This section continues to apply to UK MAHs in relation to the reporting of post-authorisation ICSRs to EudraVigilance for products authorised in respect of Northern Ireland.

VI.C.6.2.1.1. Adverse reaction data collected in the EudraVigilance Post-Authorisation Module

– This section continues to apply to UK MAHs in relation to the reporting of post-authorisation ICSRs to EudraVigilance for products authorised in respect of Northern Ireland.

VI.C.6.2.1.2. Adverse reaction data collected in the EudraVigilance Clinical Trial Module

– This section no longer applies to the licensing authority and sponsors of clinical trials in the UK.

VI.C.6.2.2. Preparation of individual case safety reports

– Throughout this section, references to sub-paragraphs in IR Article 28 have an equivalent sub-paragraph in HMR Schedule 12A paragraph 20, which are applicable to products authorised in respect of Great Britain only.

VI.C.6.2.2.7. Follow-up information

– [Paragraph 4] "EudraVigilance database" is replaced with "licensing authority's database or the EudraVigilance database".

VI.C.6.2.2.8. Amendment of cases

- [Paragraph 1] “EudraVigilance” is replaced with “the licensing authority or EudraVigilance”.

VI.C.6.2.2.9. Nullification of cases

- The following text is added to the end of this section “If the original case was sent to EudraVigilance before the end of the Transition period and the latest version is to be nullified on or after the 1 January 2021, then the marketing authorisation holder should send the nullification report to the licensing authority.”

VI.C.6.2.2.10. Data protection laws

- [Paragraph 1] This is modified to “To detect, assess, understand and prevent adverse reactions and to identify, and take actions to reduce the risks of, and increase the benefits from medicinal products for the purpose of safeguarding public health, the processing of personal data concerning the patient or the primary source within the licensing authority’s database is possible while respecting UK legislation in relation to data protection (Regulation (EU) 2016/679 (General Data Protection Regulation) (as incorporated into UK law) and the Data Protection Act 2018).”

- [Paragraphs 2 and 3] The principles concerning pseudonymisation continue to apply to the licensing authority and UK MAHs.

VI.C.6.2.2.11. Handling of languages

- [Paragraph 2] The text in this paragraph continues to apply to products authorised in respect of Northern Ireland. The following text is added to the end of this paragraph “For products authorised in respect of Great Britain only, in accordance with HMR Schedule 12A paragraph 20(6), suspected adverse reactions must be reported in English to the licensing authority. Where suspected adverse reactions are reported by the primary source in narrative and textual descriptions in a language other than English, the summary thereof in English should be provided by the marketing authorisation holder, and the original verbatim text reported by the primary source should be included in the ICSR, if it is requested by the licensing authority.”

- Paragraph 3 no longer applies to the licensing authority and UK MAHs.

- [Paragraph 5 and associated table] The guidance in the table applies where the licensing authority has requested provision of the original verbatim text in a language other than English for the suspected adverse reaction and the additional description of the case.

VI.C.6.2.3.2. Suspected adverse reaction reports published in the medical literature

- [Paragraph 1] The text that refers to the monitoring of the medical literature by the European Medicines Agency continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

VI.C.6.2.3.7. Reports of suspected adverse reactions originating from organised data collection systems and other systems

- [Paragraph 3] The text in this paragraph continues to apply to products authorised in respect of Northern Ireland. The following text is added to the end of this paragraph “All ICSRs reportable to the licensing authority and which originate from organised data collection systems and other systems, including those that fall under the scope of the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, should be submitted to MHRAUK (see VI.C.6.2. for guidance on electronic submission requirements).”

VI.C.6.2.4. Data quality of individual case safety reports transmitted electronically and duplicate management

- The principles in this section continue to apply to the licensing authority’s database.

- [Paragraph 6] This is modified to “Specific quality system procedures and processes must be in place in order to ensure:

  - the submission of accurate and verifiable data on serious and non-serious suspected adverse reactions to the licensing authority and EudraVigilance databases within the 15 or 90-day time frame [HMR Schedule 12A paragraph 11(1)(c) and IR Art 11(1)(c)];

  - the quality, integrity and completeness of the ICSRs submitted, which should also be entire and undiminished in their structure, format and content [HMR Schedule 12A paragraphs 11(1)(d) and 15(a), and IR Art 11(1)(d) and Art 15(1)(a)];

  - the detection of duplicates of suspected adverse reactions reports in collaboration with the licensing authority and the Agency [HMR regulation 188(1)(e) and (1A)(d)].”

- [Paragraph 7] This is modified to “To confirm that the quality system enables for the detection and management of duplicate ICSRs and the submission to the licensing authority and EudraVigilance databases of ICSRs of the highest quality within the correct time frames, the marketing authorisation holder must perform risk-based audits of the quality system at regular intervals [HMR regulation 184(1)]. Corrective action, including a follow-up audit of deficiencies must be taken where necessary. The dates and results of audits and follow-up audits must be documented [HMR Schedule 12A paragraph 13(3), and IR Art 13 (2) and Art 17(2)].”

- Paragraphs 9, 10, 11, 12 and 13 continue to apply to UK MAHs for products authorised in respect of Northern Ireland.

- [Paragraph 14] This is modified to “Guidance on the detection of duplicate ICSRs is provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports.”

VI.C.6.2.6. Electronic submission of ICSRs through the headquarter of a marketing authorisation holder

- [Paragraph 1, bullet point 2] “EudraVigilance” is replaced with “the licensing authority and EudraVigilance”.

VI.C.6.3. Electronic submission of information on medicinal products

- This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

VI. Appendix 1 Process for follow-up of ICSRs

- The principles for follow-up of ICSRs outlined in Figures VI.2. and VI.3. (Business process maps) and Tables VI.2. and VI.3. (Process descriptions) continue to apply to the licensing authority and UK MAHs.

- [Figure VI.2 and Table VI.2] Steps referring to submission of ICSRs to EudraVigilance (steps 3.1, 6.1 and 12.1) no longer apply to the licensing authority, and only apply to UK MAHs for products authorised in respect of Northern Ireland. For reports received by UK MAHs, the text in steps 3.1, 6.1 and 12.1 is modified as follows “Submit the initial/follow-up valid ICSR (UK and rest of world (ROW) serious and UK non-serious) to the licensing authority’s database (for all UK authorised products) and (UK and ROW serious and EEA/NI non-serious) to EudraVigilance (EV) (for products authorised in respect of Northern Ireland) within the relevant time frames (15 or 90 days, as applicable). Non-serious non-UK ICSRs should not be submitted to the licensing authority’s database or EV.”

- [Figure VI.3 and Table VI.3] Steps referring to submission of initial ICSRs (step 2) and follow-up ICSRs (step 13.1) are modified to submission of valid ICSRs (UK and ROW serious and UK non-serious) to the licensing authority’s database (for all UK authorised products) and (UK and ROW serious and EEA/NI non-serious) to EudraVigilance (EV) (for products authorised in respect of Northern Ireland). Step 3 concerning the re-routing of ICSRs no longer applies.

VI. Appendix 2 Detailed guidance on the monitoring of the medical literature

- The guidance on the monitoring of the medical literature continues to apply to the licensing authority and UK MAHs. References to the European Medicines Agency’s monitoring of selected medical literature for suspected adverse reactions to medicinal products containing certain active substances continue to apply to UK MAHs for products authorised in respect of Northern Ireland.

VI.App.2.10. Electronic submission of copies of articles on suspected adverse reactions published in the medical literature

- [Paragraph 1] This is modified to “In accordance with HMR Schedule 12A paragraph 20(5)(a) and Article 28(3) of the Commission Implementing Regulation (EU) No 520/2012, upon request of the licensing authority or the Agency respectively, the marketing authorisation holder that transmitted the initial report must provide a copy of the relevant article taking into account copyright restrictions, and a full translation of that article into English.”

- [Table VI.4: ICH-E2B(R2)] Literature articles reportable to the licensing authority should be provided in PDF format and sent via e-mail to the following address: pharmacovigilanceservice@mhra.gov.uk.

VI. Appendix 3 Modalities for the submission of ICSRs in EU

– The title of this Appendix is modified to “Modalities for the submission of ICSRs in UK”.

VI.App.3.1. Modalities applicable to competent authorities in Member States and to marketing authorisation holders

– The title of this sub-appendix is modified to “Modalities applicable to the licensing authority and marketing authorisation holders”.

– Figure VI.4. (Business process map - ICSRs submission in EU by competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs)) continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

– Table VI.6. (Process description - ICSRs submission in EU by competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs)) continues to apply to UK MAHs for products authorised in respect of Northern Ireland. For serious ICSRs, references to “EEA” are replaced with “UK”. For non-serious ICSRs, references to “EEA” are replaced with “EEA or Northern Ireland”.

– Table VI.6A (Process description - ICSRs submission in UK by marketing authorisation holders (MAHs)) is added to the end of VI.App.3.1.as follows:

No.	Step	Description	Responsible Organisation
1	**Start.**	**Receipt by the MAH of a report of suspected adverse reaction related to a medicinal product (ADR report). Go to step 2.**	**MAH**
2	Create ICSR.	Create an individual case safety report (ICSR). Go to step 2.1.	MAH
2.1	Is ICSR valid?	Is the report a valid ICSR in accordance with VI.B.2.? If no, follow-up on the ICSR as described in VI.App.1.1. If yes, go to step 3.	MAH
3	Is ICSR serious?	Is the ICSR serious? If No go to step 3.1. If Yes, go to step 4.	MAH
3.1	Is ICSR from UK?	Is the ICSR from UK? If No go to step 3.2. If Yes, go to step 4.	MAH

No.	Step	Description	Responsible Organisation
3.2	End.	The ICSR is not serious and it is not from the UK. It should not be sent to the licensing authority.	MAH
4	Submit ICSR to licensing authority.	Submit the ICSR (UK and non-UK serious, and UK non-serious) to the licensing authority in ICH-E2B(R2/R3) format as an XML message within the relevant time frame (15 or 90 days, as applicable). Non-serious non-UK ICSRs should not be submitted to the licensing authority. Go to step 5. See guidance in the licensing authority's Business Continuity Plan[15] in case of system failure in safety message generation, submission, receipt, processing and rerouting.	MAH
5	Message received in licensing authority's database.	Receive the message in the licensing authority's database. Go to step 6.	Licensing authority
6	Technical Validation (Business Rules).	Every message received in the licensing authority's database is validated against the licensing authority's Business Rules and an acknowledgement message (ACK) is created specifying whether the message & ICSR(s) therein are correct. The acknowledgement message is sent to the sender (Go to step 7). - All messages will receive an E2B(R2) acknowledgement. - A correct ICSR will have an E2B(R2) ACK code 01 (ACK_B.1.8). - An ICSR not correct will have an E2B(R2) ACK code 02 (ACK_B.1.8). - A message will receive a transmission acknowledgement code 03 (ACK_A.1.6) if the message is not correctly formatted.	Licensing authority
7	ACK message sent.	The acknowledgement message created in step 6 is transmitted to the sender no later than 2 business days following the receipt of the ICSR.	Licensing authority

[15] https://www.gov.uk/guidance/send-and-receive-information-on-adverse-drug-reactions-adrs

No.	Step	Description	Responsible Organisation
		Go to step 11 for the licensing authority's next step. Go to step 8 for MAH's next step.	
8	Receive ACK message.	Receive the ACK message. Associate it with the relevant ICSR and check that it was considered valid. Go to step 9.	MAH
9	Is ICSR ACK positive?	Is a positive acknowledgement code received for the ICSR? If yes, go to step 9.1. If no, then the regulatory timeline clock has not stopped and the ICSR should be corrected and re-transmitted to the licensing authority's database within the relevant regulatory timelines. Day 0 remains as the day that the first information was received. Go to step 10 to correct the ICSR. Neither an ICSR not correct (with an E2B(R2) ACK code 02 or E2B(R3) ACK code "CR"), nor a message not correct (with an E2B(R2) transmission acknowledgement code 03 or E2B(R3) transmission acknowledgement code "AR") constitute new information.	MAH
9.1	End.	End the process for this ICSR. Normal follow-up activities should continue and if any follow-up report is received, return to step 1.	MAH
10	Correct ICSR.	Correct the ICSR to remove the errors identified in the ACK. Go to step 10.1.	MAH
10.1	Resubmit corrected ICSR.	Resubmit the corrected ICSR to the licensing authority's database. Go back to step 5 for the receipt of the corrected ICSR in the licensing authority's database.	MAH
11	Store ICSR in licensing authority's database.	Once the ICSR has been technically validated (step 6) and the acknowledgement message is transmitted to the sender (step 7), the ICSR is stored in the licensing authority's database. Go to step 12.	Licensing authority
12	Was ICSR ACK positive?	Did the technical validation of the ICSR in step 6 create a positive ACK code?	Licensing authority

No.	Step	Description	Responsible Organisation
		If no, perform no further processing on this version of the ICSR and go to step 12.1 If Yes, go to step 13.	
12.1	Await corrected case.	The sender should correct every ICSR with an error ACK and retransmit it within the appropriate regulatory timelines. The licensing authority periodically assesses all ICSRs with an error ACK for which a corrected version has not been transmitted and contact the sender to inform of these missing corrected ICSRs. If a sender fails to correct the ICSRs, this information is incorporated into data quality assessments and the appropriate committee is informed. The ICSR stored in the licensing authority's database (step 11) while waiting for corrected version. Go back to step 5 upon receipt of the corrected ICSR.	Licensing authority
13	End.	The ICSR is now stored in the licensing authority's database. It is available for signal detection and data quality analyses following duplicate detection and recoding. See guidance in the licensing authority's Business Continuity Plan in case of system failure in safety message generation, submission, receipt, processing and rerouting.	Licensing authority

VI.App.3.2. Requirements applicable to marketing authorisation holders

– Table VI.7. (ICSRs submission requirements applicable to marketing authorisation holders) is modified as follows and applies to UK MAHs for products authorised in respect of Northern Ireland:

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
• Centralised • Mutual recognition,	UK	All serious	• EudraVigilance database	15 days
	EEA/Northern Ireland	All non-serious	• EudraVigilance database	90 days

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
decentralised or subject to referral • Purely national	Non-UK	All serious	• EudraVigilance database	15 days

– Table VI.7A. (ICSRs submission requirements in the UK applicable to marketing authorisation holders) is added to the end of VI.App.3.2. and applies to UK MAHs for all UK nationally authorised products:

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
• Mutual recognition or decentralised	UK	All serious	• Licensing authority	15 days
		All non-serious	• Licensing authority	90 days
• Purely national	Non-UK	All serious	• Licensing authority	15 days

VI.App.3.3. Requirements applicable to competent authorities in Member States

– This section no longer applies to the licensing authority.

VI.App.3.4. Rerouting to competent authorities in Member States of ICSRs submitted to EudraVigilance by marketing authorisation holders

– This appendix no longer applies to the licensing authority.

VI. Appendix 4 Submission of ICSRs to the World Health Organization (WHO)

– This appendix no longer applies to the licensing authority.

VI. Appendix 6 Data quality monitoring of ICSRs transmitted electronically

– This appendix continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

VI. Appendix 7 Duplicate detection and management of ICSRs

– This appendix continues to apply to UK MAHs for products authorised in respect of Northern Ireland. Duplicate management of suspected adverse reaction reports applicable to the licensing authority is described in the modifications to GVP Module VI Addendum I.

GVP Module VI Addendum I – Duplicate management of suspected adverse reaction reports

Summary of the key modifications to GVP Module VI Addendum I – Duplicate management of suspected adverse reaction reports

The ICSR reporting requirements for UK authorised products have changed; the Addendum includes updated guidance on what to do if possible duplicates in the licensing authority's database have been detected.

VI. Add I.1. Introduction

- [Paragraph 1] Reference to Articles 107(5) and 107a(3) of Directive 2001/83 is replaced with the Human Medicines Regulations 2012 (HMR) as amended, regulations 188(1)(e) and (1A)(d).

- [Paragraph 3] The last sentence is modified to "Case handling refers e.g. to coding practices, obtaining follow-up information and processing of personal data in line with Regulation (EU) 2016/679 (General Data Protection Regulation) (as incorporated into UK law) and the Data Protection Act 2018."

- [Paragraph 4] The first sentence is modified to "Detection and handling of duplicates by the licensing authority and marketing authorisation holders form an important element of good case management and the collaboration of marketing authorisation holders with the licensing authority and the Agency in the detection of duplicates is mandated by HMR regulations 188(1)(e) and (1A)(d)."

- Paragraph 5 no longer applies.

VI. Add I.3.1. What to do if possible duplicates in EudraVigilance have been detected

- This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

The following section is added after section VI. Add I.3.1.:

"VI. Add I.3.1A. What to do if possible duplicates in the licensing authority's database have been detected

- "If a marketing authorisation holder identifies two or more duplicates where that marketing authorisation holder is the source of all the original electronic cases, these should be handled by the marketing authorisation holder. A master case should be assigned and, if new information is added, then this should be reported to the licensing authority using the master case details; any merged and subsequently closed cases should be nullified by the marketing authorisation holder and transmitted to the licensing authority.

  If follow-up information is received, then marketing authorisation holders should use the master case reference to submit an updated case.

- If a marketing authorisation holder identifies two or more potential duplicates and that marketing authorisation holder is not the source of all the original electronic cases, then the reviewer should send an email to pharmacovigilanceservice@mhra.gov.uk with information on which cases are suspected to be duplicates. The licensing authority will send feedback on whether or not the cases are duplicates and which is the master case. The marketing authorisation holder should then update its own database to reflect the changes, e.g. merge the cases as necessary.

  If follow-up information is submitted, marketing authorisation holders can use their original case reference details and the additional information will be linked to the master case within the licensing authority's database.

The information that the licensing authority needs is either the case numbers (either Worldwide unique case safety IDs or Safety report IDs) or local report numbers (those starting with ADR) of the suspected duplicates in a cluster.

To report suspected duplicates, the licensing authority encourages that the sender sends each suspected cluster of duplicates as a single row in a table similar to the format below:

Table VI. Add I.2A. Licensing authority preferred format for receiving notification of suspected duplicates

Cluster 1	ADR 23568948	ADR 23785698		
Cluster 2	ADR 24124589	ADR 24986545	ADR 22874859	ADR 22249789
Cluster 3	ADR 25787895	ADR 23951487	ADR 24789654"	

VI. Add I.3.2. Confirmation of duplicate cases

– [Paragraph 2] The first sentence is modified to "HMR regulations 188(1)(e) and (1A)(d) require marketing authorisation holders to collaborate with the licensing authority and the Agency in the detection of duplicates of suspected adverse reaction reports."

VI. Add I.4.2. Process maps and descriptions for allocation or creation of a master case

– [Table VI. Add I.3. Step 9] The text following the * is modified as follows "If the original case was sent to EudraVigilance before the end of the Transition period and the latest version is to be sent on or after 1 January 2021, then you should send it to the licensing authority and to EudraVigilance."

– [Table VI. Add I.4. Step 9] The third sentence is modified as follows "If the original case was sent to EudraVigilance before the end of the Transition period and the latest version is to be sent on or after 1 January 2021, then you should send it to the licensing authority."

GVP Module VII – Periodic safety update report (Rev 1)

Summary of the key modifications to GVP Module VII – Periodic safety update reports (Rev 1)

The PSUR reporting requirements for UK authorised products have changed; the Module includes updated guidance on when to submit PSURs to the licensing authority and when to submit PSURs to the Agency. There is also updated guidance on the PSUR assessment procedure.

For holders of EU and UK marketing authorisations for the same medicinal product, the version of the PSUR that includes the EU regional appendix can be submitted to the licensing authority. This document should conform to the format and content requirements described in the Commission's GVP guidance on periodic safety update reports (Module VII) section VII.C.5. Where the licensing authority has made a specific request for information to be included, this information should be provided in a UK regional appendix.

For those UK MAHs that do not hold an EU marketing authorisation for the medicinal product, the PSUR should include a UK regional appendix which conforms to the requirements described in this guidance note (Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders) section VII.C.5.

For products authorised in respect of Great Britain only, the licensing authority may determine a UK reference date from which submission dates are calculated in respect of products that contain the same active substance or the same combination of active substances.

VII.A. Introduction

- [Paragraph 2] The legal requirements for submission of PSURs are established in The Human Medicines Regulations 2012 (HMR) as amended.

- [Paragraph 3] This is modified to "For products authorised in respect of Northern Ireland, the format of PSURs must follow the structure described in the IR Article 35. For products authorised in respect of Great Britain only, the format of PSURs must follow the structure described in HMR Schedule 12A paragraph 27. This Module provides guidance on the preparation, submission and assessment of PSURs."

- [Paragraph 5] Further details and guidance for the submission of PSURs in the UK, including the list of UK and Union references dates and frequency of submission are provided in the modifications to VII.C.

- [Paragraph 6] For the avoidance of doubt, the legal basis for the submission of PSURs to the licensing authority is described in HMR regulation 191 and the national system for submission of a PSUR to the licensing authority should be followed[16]. The timelines for submission described in this paragraph continue to apply to UK MAHs.

[16] https://mhrabpm.appiancloud.com/suite/

- [Paragraph 9] This is modified to “The amended HMR also waives the obligation to submit PSURs routinely for generic medicinal products (authorised under HMR regulation 51), well-established use medicinal products (authorised under HMR regulation 54) and traditional herbal medicinal products (authorised under HMR regulation 127) [HMR regulation 192]. For such products, PSURs must be submitted where there is a condition in the marketing authorisation or when requested by the licensing authority on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs for an active substance after its authorisation.”

- [Paragraph 10] This is modified to “The licensing authority must assess PSURs to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products [HMR regulation 195]. This includes PSURs for different medicinal products containing the same active substance or the same combination of active substances as per the principles regarding harmonisation of PSUR frequency or date of submission outlined in HMR regulation 193.”

- Paragraphs 11 and 13 no longer apply to UK MAHs for products authorised in respect of Great Britain only.

VII.B.5. Format and contents of the PSUR

- [Paragraph 6] This is modified to “A PSUR must be prepared following the full modular structure set out in Annex II of the IR [IR Art 35] for products authorised in respect of Northern Ireland, and HMR Schedule 12A paragraph 27 for products authorised in respect of Great Britain only.”

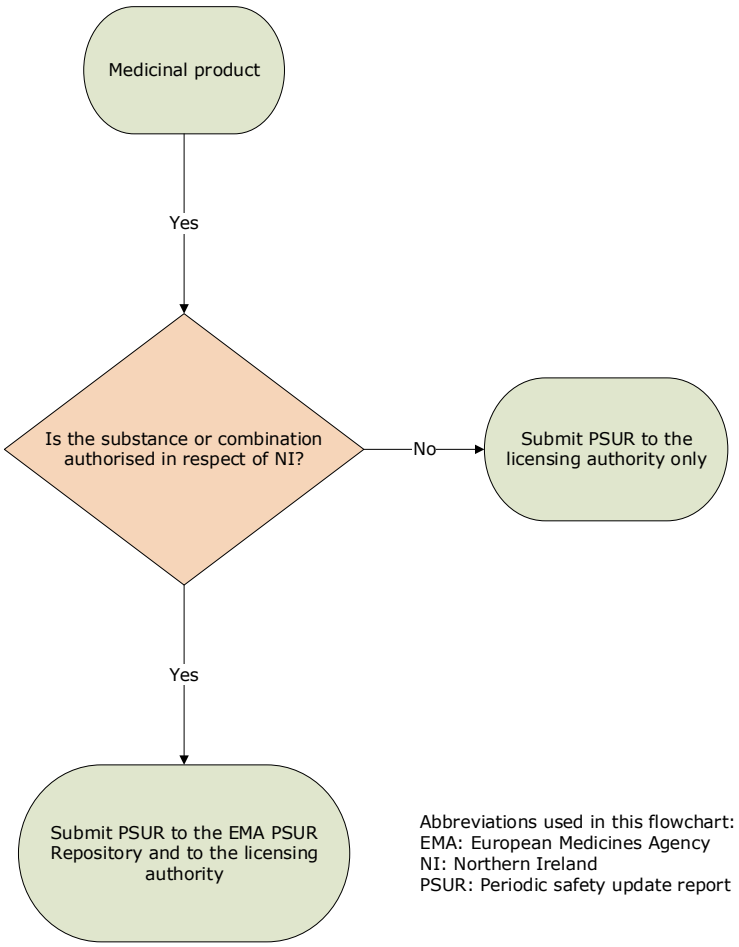
- [Footnote 6] This is modified to “For PSURs submitted in the UK, it is at the discretion of the QPPV responsible for the pharmacovigilance system operated for UK authorised products to determine the most appropriate person to sign the document according to the marketing authorisation holder structure and responsibilities. No delegation letters should be submitted.”

The following section is added before section VII.C.1. PSUR process in the EU – General process:

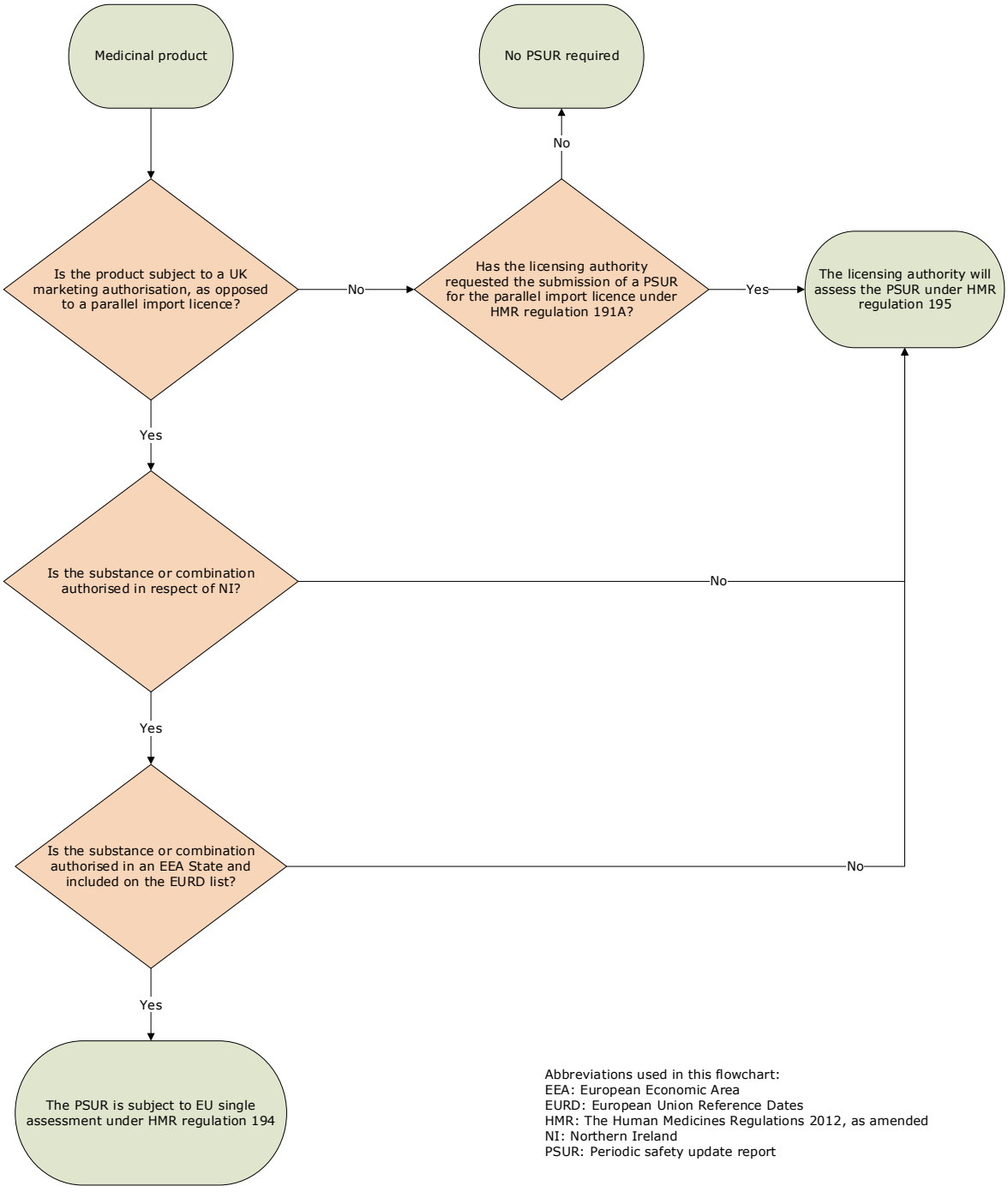
“VII.C.1A. PSUR submission and assessment process for UK authorised products – General process

The following flowchart (Figure VII.2A.) reflects the general process for PSUR submission for UK authorised products.

Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority



The following flowchart (Figure VII.2B.) reflects the general process for PSUR assessment for UK authorised products.



VII.C.1. PSUR process in the EU – General process

– This section and the associated flow chart (Figure VII.2.) continue to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland that are subject to the EU single assessment procedure.

VII.C.2. Standard submission schedule of PSURs

- [Paragraph 1] This is modified to “Marketing authorisation holders for products authorised in the UK before 21 July 2012 and for which the frequency and dates of submission of PSURs are not laid down as a condition to the marketing authorisation or determined otherwise in the list of UK or Union reference dates, must submit PSURs according to the following submission schedule [HMR regulation 191(10)].

  - immediately upon the request of the licensing authority;
  - at 6 months intervals once the product is authorised, even if it is not marketed;
  - once a product is marketed within the EEA or Northern Ireland (for products authorised in respect of Northern Ireland) or in Great Britain (for products authorised in respect of Great Britain only), 6 monthly PSUR submission should be continued following initial placing on the market for 2 years, then once a year for the following 2 years and thereafter at 3-yearly intervals.”

VII.C.3. List of European Union reference dates and frequency of submission of PSURs

- The title of this section is modified to “Lists of UK and European Union reference dates and frequency of submission of PSURs”.

VII.C.3.1. Objectives of the EU reference dates list

- The title of this section is modified to “Objectives of the UK and EU reference dates lists”.

- [Paragraph 1] The following text is added to the end of this paragraph “This list of Union reference dates applies to products authorised in respect of Northern Ireland. For products authorised in respect of Great Britain only, the licensing authority may determine a UK reference date from which submission dates are calculated in respect of products that contain the same active substance or the same combination of active substances. Where the UK reference date differs from the EU reference date, the licensing authority must publish a list of UK reference dates and the frequency and date of submission of PSURs. If the active substance or combination of active substances is not on the list of UK reference dates, then the EU reference date and the frequency and date of submission of PSURs made public by means of the European medicines web-portal shall apply [HMR regulation 193(6B)].”

- [Paragraph 2] The objectives of the list of EU reference dates as described in this paragraph also apply to the list of UK reference dates and frequency of submission of PSURs.

VII.C.3.2. Description of the EU reference dates list

- The title of this section is modified to “Description of the UK and EU reference dates lists”.

- The following text is added to the end of this section “For products authorised in respect of Great Britain only, the licensing authority may determine a UK reference date from

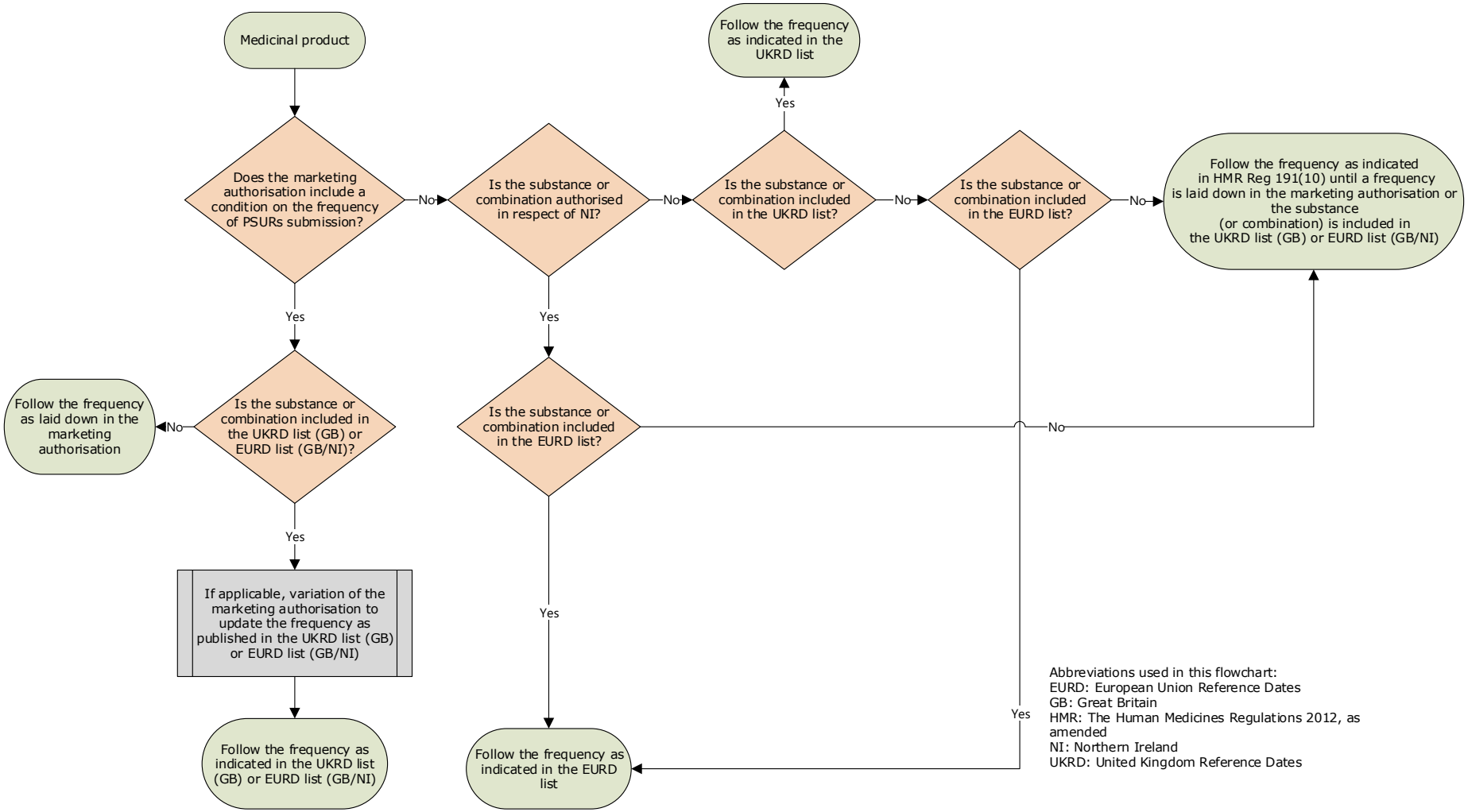
which submission dates are calculated and, where it so determines, must publish a list of UK reference dates on its web-portal [HMR regulation 193(7)]. Any change to the dates of submission and frequency on PSURs is to take effect 6 months after the date of such publication [HMR regulation 193(8)]. Until the licensing authority determines a UK reference date, the EU reference date and frequency of PSUR submission published by the Agency under Article 107c(7) of the 2001 Directive is deemed to be the UK reference date [HMR regulation 193(6A)]."

VII.C.3.3. Application of the list of EU reference dates to submission of PSURs

- The title of this section is modified to "Application of the list of UK and EU reference dates to submission of PSURs".

VII.C.3.3.1. Submission of PSURs for medicinal products: general requirement

– Figure VII.3. is modified as follows:



VII.C.3.3.2. Submission of PSURs for generic, well-established use, traditional herbal and homeopathic medicinal products

- [Paragraph 1] This is modified to “By way of derogation, generics (authorised under HMR regulation 51), well-established use (authorised under HMR regulation 54) and traditional herbal (authorised under HMR regulation 127) medicinal products are exempted from submitting PSURs except in the following circumstances [HMR regulation 192]:

  - the marketing authorisation provides for the submission of PSURs as a condition;

  - PSUR(s) is (are) requested by the licensing authority on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation has been granted (e.g. when the “reference” medicinal product is no longer marketed). Where the licensing authority requests submission of PSURs for products authorised in respect of Northern Ireland, the assessment reports of the requested PSURs must be communicated to the Agency [HMR regulation 192(9)].”

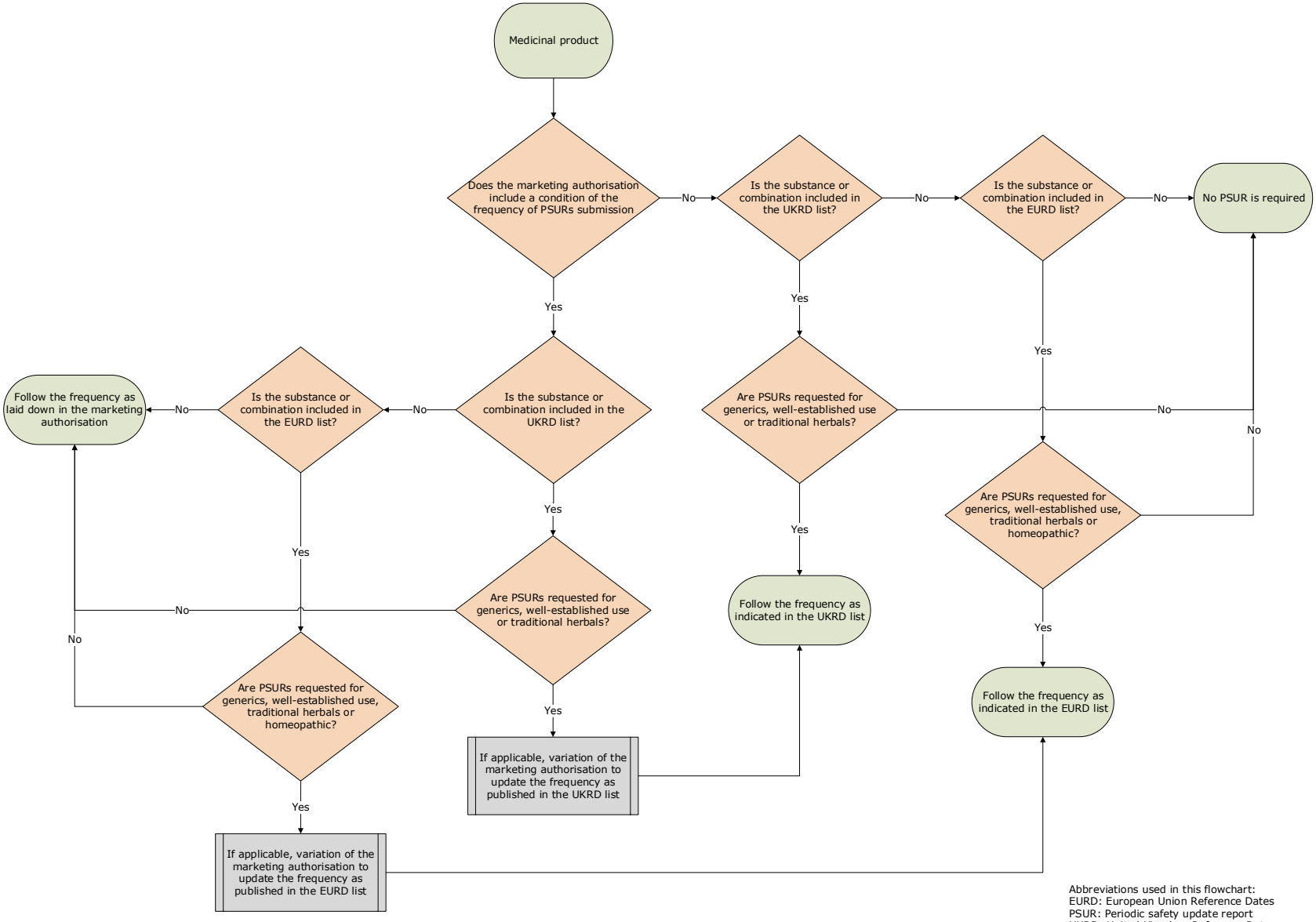
- [Paragraph 2] For the avoidance of doubt, the legislative provision laid down in HMR regulation 192 is applied by specifying in the list of UK or EU reference dates the substances for which PSURs for generic, well-established use and traditional herbal medicinal products are required.

- [Paragraph 4] This is modified to “The application of the list of UK or EU reference dates for the submission of PSURs for generic, well-established use and traditional herbal medicinal products does not undermine the right of the licensing authority to request the submission of PSURs at any time under the provision laid down in HMR regulation 192(4).”

- The title of Figure VII.4. is modified to “Conditions for PSURs submission for generic, well-established use, traditional herbal and homeopathic medicinal products authorised in respect of Northern Ireland”.

- The following figure is inserted after Figure VII.4.

“Figure VII.4A. Conditions for PSURs submission for generic, well-established use and traditional herbal medicinal products authorised in respect of Great Britain only”


Medicinal product
Does the marketing authorisation include a condition of the frequency of PSURs submission
No
Is the substance or combination included in the UKRD list?
No
Is the substance or combination included in the EURD list?
No
No PSUR is required
Yes
Yes
Yes
Follow the frequency as laid down in the marketing authorisation
No
Is the substance or combination included in the EURD list?
No
Is the substance or combination included in the UKRD list?
Are PSURs requested for generics, well-established use or traditional herbals?
No
No
Yes
Yes
Yes
Yes
Are PSURs requested for generics, well-established use, traditional herbals or homeopathic?
No
Are PSURs requested for generics, well-established use or traditional herbals?
Follow the frequency as indicated in the UKRD list
Yes
No
Are PSURs requested for generics, well-established use, traditional herbals or homeopathic?
Follow the frequency as indicated in the EURD list
Yes
Yes
If applicable, variation of the marketing authorisation to update the frequency as published in the UKRD list
If applicable, variation of the marketing authorisation to update the frequency as published in the EURD list
Abbreviations used in this flowchart:
EURD: European Union Reference Dates
PSUR: Periodic safety update report
UKRD: United Kingdom Reference Dates

VII.C.3.3.4. Submission of PSURs on demand of a competent authority in a Member State

- The title of this section is modified to “Submission of PSURs on demand of the licensing authority”.

- The legal basis for the licensing authority to request the submission of a PSUR is outlined in HMR regulations 191(10)(a) and 192(4).

VII.C.3.5.1. General principles

- The general principles in this section also apply to the licensing authority in respect of the list of UK reference dates.

- Figure VII.5 continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

VII.C.3.5.2. Requests from marketing authorisation holders to amend the list of EU reference dates

- The title of this section is modified to “Requests from marketing authorisation holders to amend the lists of UK and EU reference dates”.

- The following text is added to the end of this section “Marketing authorisation holders for products authorised in respect of Great Britain only must be allowed to submit a request in writing to the licensing authority to amend the UK reference date from which submission dates are calculated or change the frequency and date of submission of the PSUR in the UK [HMR regulation 193(2) and (3)].”

VII.C.3.6. Publication of the list

- The following text is added to the end of this section “The licensing authority must publish a list of UK reference dates and the frequency and date of submission of the PSUR, where different requirements exist in the UK [HMR regulation 193(7)].”

VII.C.4. Processes for PSUR Assessment in the EU network

- The title of this section is modified to “Process for PSUR Assessment in the UK and in the EU network”.

- Paragraph 1 is omitted.

- [Paragraph 2] This is modified to “For medicinal products authorised in respect of Northern Ireland that are not authorised in an EEA State and are not included in the EURD list (therefore are not subject to the EU single assessment procedure), for medicinal products imported into the UK under a parallel import licence and for medicinal products authorised in respect of Great Britain only, the assessment of PSURs is conducted by the licensing authority (see VII.C.4.1.). The licensing authority must assess PSURs to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of the medicinal product [HMR regulation 195].”

- [Paragraph 3] This is modified to “For medicinal products authorised in respect of Northern Ireland that are also authorised in more than one Member State, containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holders and for which the frequency and dates of submission of PSURs have been harmonised in the list of EU reference dates, an EU single assessment of all PSURs is conducted with recommendation from the PRAC in accordance with the procedure described in VII.C.4.2.2..”

- [Paragraph 4] This is modified to “Further to the EU single assessment of the PSUR and opinion from the CHMP or position from the CMDh, as applicable, following the recommendation from the PRAC, the licensing authority must take the necessary measures to vary, suspend or revoke the marketing authorisation(s), in accordance with outcome of the assessment [HMR regulation 194(2)] (see VII.C.4.2.3. and VII.C.4.2.4.).”

- [Paragraph 5] This is modified to “The outcome of the PSUR assessment results in a legally binding decision in case of any action to vary, suspend, revoke the marketing authorisations of the medicinal products containing the concerned active substance or combination of active substances, on the basis of the licensing authority’s assessment, or the position of the CMDh or the opinion of the CHMP following the recommendations from the PRAC. Furthermore, marketing authorisation holders are reminded of their obligation to keep their marketing authorisation up to date in accordance with HMR regulation 76(2). The recommendations are therefore implemented in a harmonised and timely manner for all products within the scope of the procedure across the UK and the EU.”

- [Paragraph 6] This is modified to “Amendments to the SmPC, package leaflet and labelling as a result of the PSUR assessment should be implemented through the appropriate variation for nationally authorised products, including those authorised through the mutual recognition and decentralised procedures.”

VII.C.4.1. PSURs for purely nationally authorised products

- The title of this section is modified to “PSURs assessed by the licensing authority”.

- [Paragraph 1] This is modified to “It is the responsibility of the licensing authority to evaluate the PSURs for:

  - medicinal products authorised in respect of Northern Ireland that are not authorised in an EEA State and are not included in the EURD list (therefore are not subject to the EU single assessment procedure);

  - medicinal products imported into the UK under a parallel import licence;

  - medicinal products authorised in respect of Great Britain only.

- [Paragraphs 3 and 4] References to “competent authority in the Member State” are replaced with “licensing authority”.

VII.C.4.2. Medicinal products authorised in more than one Member State

VII.C.4.2.1. Assessment of PSURs for a single centrally authorised medicinal product

- This section no longer applies to the licensing authority and UK MAHs.

VII.C.4.2.2. Assessment of PSURs for medicinal products subject to different marketing authorisations containing the same active substance (EU single assessment)

- This section and Figure VII.7 continue to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland that are subject to the EU single assessment procedure.

VII.C.4.2.3. Single assessment including at least one centrally authorised product leading to a CHMP opinion

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland that are subject to the EU single assessment procedure.

VII.C.4.2.4. Single assessment not including centrally authorised product leading to a CMDh position

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland that are subject to the EU single assessment procedure.

VII.C.5. EU-specific requirements for periodic safety update reports

- The title of this section is modified to “UK-specific requirements for periodic safety update reports”.

- Throughout sections VII.C.5.1. to VII.C.5.5., references to “EU” are replaced with “UK”.

VII.C.6.1. Quality systems and record management systems at the level of the marketing authorisation holder

- [Paragraph 1] This is modified to “Specific quality system procedures and processes must be in place in order to ensure the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, for products authorised in respect of Northern Ireland, and via the UK national web-portal, for all UK authorised products [HMR regulation 76(2)].”

- [Paragraph 2] This is modified to “It is the responsibility of the marketing authorisation holder to check regularly the list of UK and EU reference dates and frequency of submission published in the UK and European medicines web-portals to ensure compliance with the PSUR reporting requirements for their medicinal products (see VII.C.3.).”

- [Paragraph 3] This is modified to “Systems should be in place to schedule the production of PSURs according to:

  - the list of UK or EU reference dates and frequency of PSURs submission; or
  - the conditions laid down in the marketing authorisation; or
  - the standard PSUR submission schedule established according to HMR regulation 191(10) for products authorised before 21 July 2012 (without any conditions in their marketing authorisation or not included in the list of UK or EU references dates and frequency of submission or not affected by the derogation established in HMR regulation 192); or
  - ad hoc requests for PSURs by the licensing authority.”

- [Paragraph 6, bullet point 3] This is modified to “awareness of the PSUR and assessment report conclusions, licensing authority decisions, and, for products authorised in respect of Northern Ireland covered by the EU single assessment procedure, PRAC recommendations, CHMP opinions, CMDh positions and European Commission decisions in order to ensure that appropriate action takes place.”

VII.C.6.2. Quality systems and record management systems at the level of the European Medicines Agency

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland that are subject to the EU single assessment procedure.

VII.C.6.3. Quality systems and record management systems at the level of the competent authorities in Member States

- The title of this section is modified to “Quality systems and record management systems at the level of the licensing authority”.

- [Paragraph 1] This is modified to “The licensing authority must have in place a pharmacovigilance system [HMR regulation 179] for the surveillance of medicinal products and for receipt and evaluation of all pharmacovigilance data including PSURs. For the purpose of operating its tasks relating to PSURs in addition to the pharmacovigilance system the licensing authority should implement a quality system (see Module I).”

- [Paragraph 2] This is modified to “The licensing authority should monitor marketing authorisation holders for compliance with regulatory obligations for PSURs.”

- [Paragraph 3] This is modified to “No PSUR assessment at EU level is foreseen for medicinal products authorised in respect of Northern Ireland that are not authorised in an EEA State and are not included in the EURD list, for medicinal products imported into the UK under a parallel import licence and for medicinal products authorised in respect of Great Britain only; therefore the licensing authority should have procedures in place for the assessment of PSURs related to those medicinal products.”

- Paragraph 4 continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland that are subject to the EU single assessment procedure.

- Paragraphs 5 and 6 no longer apply to the licensing authority.

VII.C.7. Transparency

VII.C.7.1. Publication of PSUR-related documents on the European medicines and national medicines web-portals

- The existing text in this section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland that are subject to the EU single assessment procedure.

- The following text is added to the end of this section and applies to all UK MAHs "The following must be made publicly available by means of the national medicines web-portal [HMR regulation 193(7)]:

  - list of UK reference dates and frequency of submission of PSURs (see VII C.3.)."

- The following should be made publicly available by means of the national medicines web-portal:

  - final PSUR assessment conclusions."

VII.C.8. Renewal of marketing authorisations

- [Paragraph 1] This is modified to "Marketing authorisations need to be renewed after 5 years on the basis of a re-evaluation of the risk-benefit balance in order to continue to be valid to place the product on the market. This renewal is irrespective of whether the marketing authorisation is suspended. For products authorised in respect of Northern Ireland via the mutual recognition or decentralised procedures, further details on the procedure and the documentation requirements can be found in the current version of the "CMDh Best Practice Guide on the processing of renewals in the MRP/DCP" (CMDh/004/2005)."

- Paragraph 3 no longer applies to the licensing authority and UK MAHs.

- [Paragraph 4] This is modified to "Conditional marketing authorisations should be renewed annually [HMR regulation 65B]."

VII.C.9. Transition and interim arrangements

VII.C.9.1. Submission and availability of documents before the Agency's repository is in place

- This section no longer applies to the licensing authority and UK MAHs.

VII.C.9.2. Quality systems and record management systems at the level of the competent authorities in Member States

- This section no longer applies to the licensing authority and UK MAHs.

VII.C.9.3. Publication of the EU list of Union reference dates and start of the EU PSUR single assessment procedure

- This section no longer applies to the licensing authority and UK MAHs.

GVP Module VIII – Post-authorisation safety studies (Rev 3)

Summary of the key modifications to GVP Module VIII – Post-authorisation safety studies (Rev 3)

The requirements for submission of post-authorisation safety study (PASS) protocols, substantial amendments to the study protocol and final study reports for UK authorised products have changed; the Module includes updated guidance on what must be reported to the licensing authority and what must be reported to the European Medicines Agency. There is also updated guidance on the assessment of PASS protocols and final study reports.

VIII.A. Introduction

- [Paragraph 1] This is modified to “The Human Medicines Regulations 2012 (HMR), as amended include provisions for post-authorisation safety studies applicable in the UK.”

- [Paragraph 2] This is modified to “A post-authorisation safety study (PASS) is defined in HMR regulation 8(1) as any study relating to a medicinal product to which a marketing authorisation or traditional herbal registration relates that is conducted with the aim of--

  (a) identifying, characterising or quantifying a safety hazard;

  (b) confirming the safety profile of the medicinal product; or

  (c) measuring the effectiveness of risk management measures.”

- [Paragraph 5] This is modified to “Non-interventional PASS concerned by the guidance can be:

  - imposed as an obligation in accordance with HMR regulation 59 (conditions of a UK marketing authorisation [or parallel import licence]: general) or HMR regulation 61 (conditions of a UK marketing authorisation: new obligations post-authorisation) (category 1 of studies in GVP Module V);

  - imposed as a specific obligation in the framework of a conditional authorisation (in accordance with HMR regulation 59(4C)) or a marketing authorisation granted under exceptional circumstances in accordance with HMR regulation 60 (conditions of a UK marketing authorisation: exceptional circumstances) (category 2 of studies in GVP Module V);

- required in the risk management plan (RMP) to investigate a safety concern or to evaluate the effectiveness of risk minimisation activities (category 3 of studies in GVP Module V); or

- conducted voluntarily by a marketing authorisation holder."

– [Paragraph 6] This is modified to "Non-interventional PASS must be conducted in accordance with the following provisions:

- Regulation 198 applies to non-interventional PASS initiated, managed or financed by an MAH voluntarily or pursuant to imposed obligations.

- Regulations 199 to 202 and Schedule 12A paragraphs 28 to 32 apply to non-interventional PASS conducted pursuant to an obligation imposed by the licensing authority."

– [Paragraph 9] This is modified to "If a PASS is interventional, the provisions of the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, shall apply."

VIII.B.2. Study registration

– This section of the guidance continues to apply to products authorised in respect of Northern Ireland for non-interventional PASS conducted pursuant to an obligation imposed by the licensing authority, as well as non-interventional PASS required in the risk management plan agreed in the UK or conducted voluntarily in the UK.

VIII.B.3. Study protocol

– [Paragraph 2] This is modified to "For non-interventional PASS imposed as an obligation by the licensing authority, the draft study protocol must be submitted by the marketing authorisation holder to the licensing authority and to PRAC (unless the study is to be conducted in the UK only) for products authorised in respect of Northern Ireland, and to the licensing authority for products authorised in respect of Great Britain only [regulation 199(2)] (see VIII. C.2.)."

– [Paragraph 3] This is modified to "For non-interventional PASS conducted voluntarily, the marketing authorisation holder may be required by the licensing authority to submit the protocol to the licensing authority and to the competent authorities of the Member States in which the study is conducted for products authorised in respect of Northern Ireland, and to the licensing authority for products authorised in respect of Great Britain only [regulation 198(2)]. Requirements and recommendations for submission of the study protocol to the Agency and national competent authorities are specified in GVP Module VIII Addendum I."

– [Paragraph 5] This is modified to "Where applicable, the marketing authorisation holder's pharmacovigilance contact person at national level in the UK should be informed of any study sponsored or conducted by the marketing authorisation holder in the UK and have access to the protocol."

VIII.B.3.1. Format and content of the study protocol

- [Paragraph 1] This is modified to “For non-interventional PASS conducted pursuant to an obligation imposed by the licensing authority, the study protocol must follow the format described in this section of the guidance [HMR Schedule 12A paragraph 30 and IR Annex III]. This format should also be followed for non-interventional PASS required in the risk management plan agreed in the UK or conducted voluntarily in the UK.”

VIII.B.3.2. Substantial amendments to the study protocol

- [Paragraph 1] Explanatory note: If changes to the protocol lead to the study being considered an interventional clinical trial, the licensing authority should be informed immediately. The study must subsequently be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

- [Paragraph 2] This is modified to “For non-interventional PASS conducted pursuant to an obligation imposed by the licensing authority, any substantial amendments to the study protocol must be submitted to the licensing authority and to the PRAC (unless the study is to be conducted in the UK only) for products authorised in respect of Northern Ireland, and to the licensing authority for products authorised in respect of Great Britain only, before their implementation [regulation 200(2)] (see VIII.C.2.1.).”

VIII.B.4.1. Data relevant to the risk-benefit balance of the product

- [Paragraph 1] This is modified to “The marketing authorisation holder must monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the medicinal product concerned [HMR regulation 198(3)(b)]. The marketing authorisation holder must communicate to the competent authorities of the EEA States in which the study is conducted (for products authorised in respect of Northern Ireland) and to the licensing authority (for all UK authorised products) any new information that arises at any point during the study which might influence the evaluation of the risk-benefit balance for that product [regulation 198(3)(c)]. Any new information that may affect the risk-benefit balance of the medicinal product should be communicated immediately in writing as an emerging safety issue to the licensing authority (for all UK authorised products) (signalmanagement@mhra.gov.uk) and to the Agency (for products authorised in respect of Northern Ireland) (P-PV-emerging-safety-issue@ema.europa.eu) via email. Information affecting the risk-benefit balance of the medicinal product may include an analysis of adverse reactions and aggregated data.”

VIII.B.4.3.1. Progress report and interim report of study results

- [Paragraph 3] This is modified to “Upon request from the licensing authority, progress reports for PASS imposed as an obligation or conducted voluntarily must be submitted to the competent authorities of the Member States in which the study is conducted for products authorised in respect of Northern Ireland and to the licensing authority for all UK authorised products [HMR regulation 198(2)]. Requests for progress reports may be made before the study commences or any time during the study conduct. They may be guided by the communication of risk-benefit information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the product. Requirements and recommendations for submission of progress reports are specified in GVP Module VIII Addendum I.”

VIII.B.4.3.2. Final study report

- [Paragraph 1] This is modified to “For non-interventional PASS conducted pursuant to an obligation imposed by the licensing authority, the final study report must follow the format described in this section [HMR Schedule 12A paragraph 32 and IR Annex III] and must be submitted within 12 months of the end of data collection [HMR regulation 201(2)] (see VIII.C.2.). This format and timeline should also be followed for non-interventional PASS required in the risk management plan agreed in the UK or conducted voluntarily in the UK.”

- [Paragraph 4, point 2] This is modified to “**Abstract**: stand-alone summary in the format presented below [HMR Schedule 12A paragraph 31 and IR Annex III].”

VIII.B.6. Data protection

- [Paragraph 1] This is modified to “The legislation on data protection must be followed in accordance with Regulation (EU) 2016/679 (General Data Protection Regulation (GDPR)) (as adopted into UK law by section 3 of EU Withdrawal Act 2018, and the Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations 2019 (SI 2019/419)). When processing personal data, organisations based in the UK will need to comply with this version of the GDPR (known as the UK GDPR) and the requirements of the Data Protection Act 2018 (which is amended by SI 2019/419 and the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) (No. 2) Regulations 2019 (SI 2019/485)).”

VIII.C.1. Procedure for imposing post-authorisation safety studies

- This is modified to “In the UK, the conduct of any post-authorisation safety study (PASS) can be imposed by the licensing authority as applicable during the evaluation of the initial marketing authorisation application [regulation 59] or during the post-authorisation phase [regulation 61], whenever there are concerns about the risks of an authorised medicinal product for which PASS results would significantly impact on the risk-benefit of the product. This obligation must be duly justified, must be notified in writing and must include the objectives and timeframe for the submission and conduct of the study. The request may also include recommendations on key elements of the study (e.g. study design, setting, exposure(s), outcome(s), study population).”

VIII.C.1.1. Request for a post-authorisation safety study as part of the initial marketing authorisation application

- This is modified to “A marketing authorisation may be granted subject to the conduct of a PASS. The condition to conduct a PASS can be imposed by the licensing authority as applicable during the evaluation of the initial marketing authorisation application [HMR regulation 59].”

VIII.C.1.2. Request for a post-authorisation safety study during a post-authorisation regulatory procedure

- This is modified to “The need for a PASS could be identified by the Agency (for products authorised in respect of Northern Ireland) or by the licensing authority (for all UK authorised products) during a post-authorisation regulatory procedure, for example, an

extension or a variation to a marketing authorisation, a renewal procedure or a PSUR procedure. With respect to the licensing authority, if, during the evaluation of a post-authorisation procedure the need for a PASS is identified, the licensing authority must give written notice to the MAH of the imposition of the obligation, the justification for the imposition, the objectives and timeframe for submission and conduct of the study, and the opportunity to present written observations. If the imposition of a PASS is confirmed, the licensing authority must vary the marketing authorisation to include the PASS as a condition of the marketing authorisation [HMR regulation 61]. For products authorised in respect of Northern Ireland, the PRAC may adopt an advice or a recommendation with an assessment report to the CHMP or the Member States as applicable."

VIII.C.1.3. Request for a post-authorisation safety study due to an emerging safety concern

- This is modified to "After the granting of the marketing authorisation, the Agency (for products authorised in respect of Northern Ireland) or the licensing authority (for all UK authorised products), may impose on the marketing authorisation holder an obligation to conduct a post-authorisation safety study if there are concerns about the risk of the authorised medicinal product. With respect to the licensing authority, if the need for a PASS is identified, the licensing authority must give written notice to the MAH of the imposition of the obligation, the justification for the imposition, the objectives and timeframe for submission and conduct of the study, and the opportunity to present written observations. If the imposition of a PASS is confirmed, the licensing authority must vary the marketing authorisation to include the PASS as a condition of the marketing authorisation [HMR regulation 61]. For products authorised in respect of Northern Ireland, the PRAC may adopt an advice or a recommendation with an assessment report to the CHMP or the Member States as applicable."

VIII.C.1.4. Joint post-authorisation safety studies

- This section is modified to "If safety concerns apply to more than one medicinal product authorised in respect of Northern Ireland, the licensing authority must, following consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct a joint PASS [regulation 61(6)]. If safety concerns apply to more than one medicinal product authorised in respect of Great Britain only, the licensing authority must encourage the marketing authorisation holders concerned to conduct a joint PASS [regulation 61(6A)]. Requests to the marketing authorisation holders should contain the justification for the request of a joint study and may include core elements for the study protocol. The licensing authority or the Agency should support interactions between the concerned marketing authorisation holders and provide suggestions for the joint study proposal."

VIII.C.1.5. Written observations in response to the imposition of an obligation

- The principles in this section continue to apply to the licensing authority and UK MAHs. The legal basis for written observations in response to the imposition of the obligation is described in HMR regulation 61(9). The legal basis to vary the marketing authorisation to include the obligation as a condition of the marketing authorisation and to update the risk management plan, where applicable, is described in HMR regulation 61(12) and (14), respectively.

VIII.C.2. Supervision of non-interventional post-authorisation safety studies conducted pursuant to an obligation

- This section is modified to “For products authorised in respect of Northern Ireland, non-interventional PASS conducted pursuant to obligations imposed by the licensing authority (categories 1 and 2 of studies in GVP Module V) are supervised and assessed by the licensing authority (where the study is conducted in the UK only) or the PRAC. For products authorised in respect of Great Britain only, non-interventional PASS conducted pursuant to obligations imposed by the licensing authority are supervised and assessed by the licensing authority [HMR regulation 199].”

VIII.C.2.1. Roles and responsibilities of the marketing authorisation holder

- [Paragraph 1] This is modified to “If the study is a non-interventional study (see VIII.A.), the marketing authorisation holder must ensure that the study meets the requirements applicable to non-interventional PASS set out in HMR regulations 198 to 202, Schedule 12A paragraphs 28 to 32, IR Art 36 – 38 (for products authorised in respect of Northern Ireland) and this Module. The marketing authorisation holder must ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this fulfilment can be audited, inspected and verified (see VIII.B.6. and VIII.B.7.).”

- [Paragraph 2] This is modified to “For products authorised in respect of Northern Ireland, following the imposing as a condition to the marketing authorisation to conduct a non-interventional PASS, the marketing authorisation holder must develop a study protocol and submit it to the licensing authority and to the PRAC (unless the study is to be conducted in the UK only) for review. For products authorised in respect of Great Britain only, the study protocol must be submitted to the licensing authority [HMR regulation 199(2)]. The marketing authorisation holder has the responsibility to ensure that the study is not a clinical trial, in which case the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, shall apply.”

- [Paragraph 3] This is modified to “For products authorised in respect of Northern Ireland, the imposed study may commence only when the written endorsement from the licensing authority (where the study is to be conducted in the UK only) or the PRAC has been issued. For products authorised in respect of Great Britain only, the imposed study may commence only when the written endorsement from the licensing authority has been issued [HMR regulation 199(5)(6)]. When a letter of endorsement has been issued by the PRAC, the marketing authorisation holder must forward the protocol to the national competent authority of the Member State(s) in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol [HMR regulation 199(8)].”

- [Paragraph 4] This is modified to “Prior to submission of the protocol, the marketing authorisation holder may submit a request to the licensing authority for a pre-submission meeting in order to clarify specific aspects of the requested study (such as study objectives, study population, definition of exposure and outcomes) and to facilitate the development of the protocol in accordance with the objectives determined by the licensing authority.”

- [Paragraph 5] This is modified to “After a non-interventional imposed PASS has been commenced, the marketing authorisation holder must submit any substantial

amendments to the protocol, before their implementation, to the licensing authority and to the PRAC (unless the study is to be conducted in the UK only) for products authorised in respect of Northern Ireland, and to the licensing authority for products authorised in respect of Great Britain only [HMR regulation 200(2)] (see VIII.A.1. for the definition of a substantial amendment)."

- [Paragraph 6] This is modified to "For products authorised in respect of Northern Ireland, upon completion of the study, the marketing authorisation holder must submit a final study report, including a public abstract, to the licensing authority and to the PRAC (unless the study was conducted in the UK only) as soon as possible and not later than 12 months after the end of data collection, unless a written waiver has been granted by the licensing authority or the PRAC, as appropriate. For products authorised in respect of Great Britain only, the marketing authorisation holder must submit a final study report, including a public abstract, to the licensing authority as soon as possible and not later than 12 months after the end of data collection, unless a written waiver has been granted by the licensing authority [HMR regulation 201(2)]."

- [Paragraph 7] The following text is added to the end of this paragraph "When the licensing authority is responsible for supervision of the PASS (in instances where the protocol has only been submitted to the licensing authority), the marketing authorisation holder should request the waiver in writing to the licensing authority at least three months before the due date for the submission of the report. The request should include a justification for the waiver. The request should be assessed by the licensing authority and granted or rejected by the licensing authority on the basis of the justification and timeline submitted by the marketing authorisation holder."

- Paragraph 8 no longer applies to the licensing authority and UK MAHs.

VIII.C.2.2. Roles and responsibilities of the PRAC and the national competent authority

- The title of this section is modified to "Roles and responsibilities of the PRAC and the licensing authority".

- [Paragraph 1] This is modified to "Within 60 days from submission of the draft protocol, the licensing authority (in instances where the protocol has only been submitted to the licensing authority) or the PRAC, as appropriate, must issue a letter endorsing the draft protocol, a letter of objection or a letter notifying the marketing authorisation holder that the study is a clinical trial within the meaning of the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended. The letter of objection must set out in detail the grounds for the objection in any of the following cases:

  - it is considered that the conduct of the study promotes the use of a medicinal product;

  - it is considered that the design of the study does not fulfil the study objectives [HMR regulation 199(5)]."

- [Paragraph 2] This is modified to "If the study proves to be interventional, the PRAC or the licensing authority should issue an explanatory statement to the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive

2001/20/EC or the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended."

- [Paragraph 4] This is modified to "In case of submission of an amended study protocol, the licensing authority (in instances where the protocol has only been submitted to the licensing authority) or the PRAC, as appropriate, must assess the amendments and inform the marketing authorisation holder of its endorsement or objection. The licensing authority will provide the marketing authorisation holder with a letter of endorsement or objection to the protocol amendment as soon as it is reasonably practicable. The letter of objection will provide a timeline by which the marketing authorisation holder should resubmit an amended version of the protocol [HMR regulation 200(5)]."

- Paragraph 5 no longer applies to the licensing authority.

- Paragraph 6 applies in relation to products authorised in respect of Northern Ireland where PRAC is involved in the oversight of the study.

VIII.C.2.3. Roles and responsibilities of the Agency

- This section continues to apply to the licensing authority and UK MAHs in relation to products authorised in respect of Northern Ireland where PRAC is involved in the oversight of the study.

VIII.C.3. Changes to the marketing authorisation following results from a non-interventional post-authorisation safety study

- [Paragraph 1] This is modified to "The marketing authorisation holder must submit a final study report to the licensing authority and to the PRAC (unless the study is to be conducted in the UK only) for products authorised in respect of Northern Ireland, and to the licensing authority for products authorised in respect of Great Britain only within 12 months of the end of data collection unless a written waiver has been granted [HMR regulation 201(2)]."

- [Paragraph 2] This is modified to "The marketing authorisation holder must evaluate whether the study results have an impact on the marketing authorisation and must, if necessary, submit to the licensing authority an application to vary the marketing authorisation [HMR regulation 201(5)]."

- [Paragraph 3] This is modified to "Following the review of the final study report, the PRAC or the licensing authority may recommend variation, suspension or revocation of the marketing authorisation [HMR regulation 202]."

- Paragraph 4 no longer applies to the licensing authority or UK MAHs.

- Paragraph 5 continues to apply to the licensing authority and UK MAHs in relation to products authorised in respect of Northern Ireland where PRAC is involved in the oversight of the study.

The following is added to the end of the Module:

VIII. Appendix 2. Figures on the PASS process for UK authorised products

Figure VIII.1. Study protocol or substantial amendment submission requirements

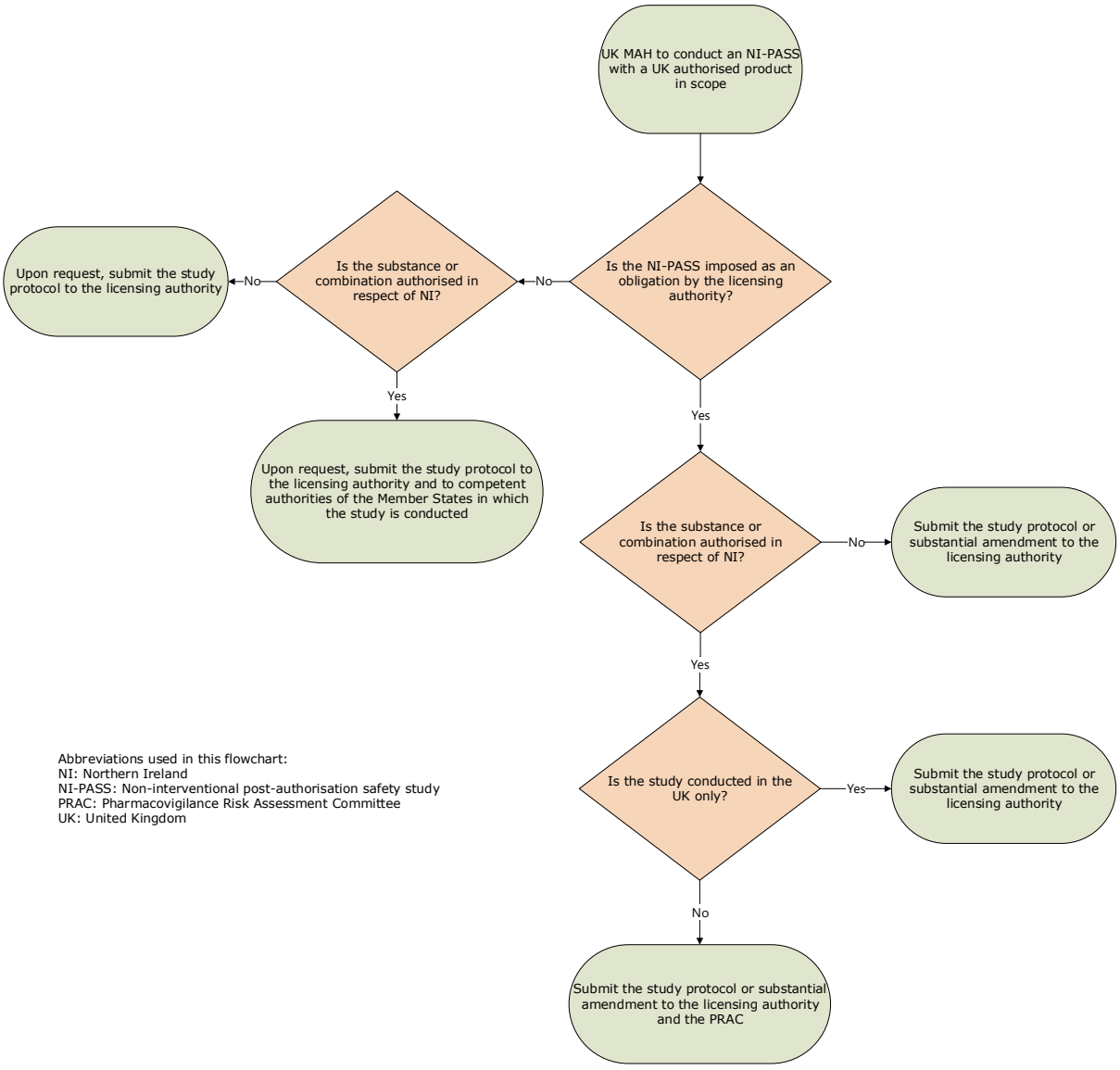
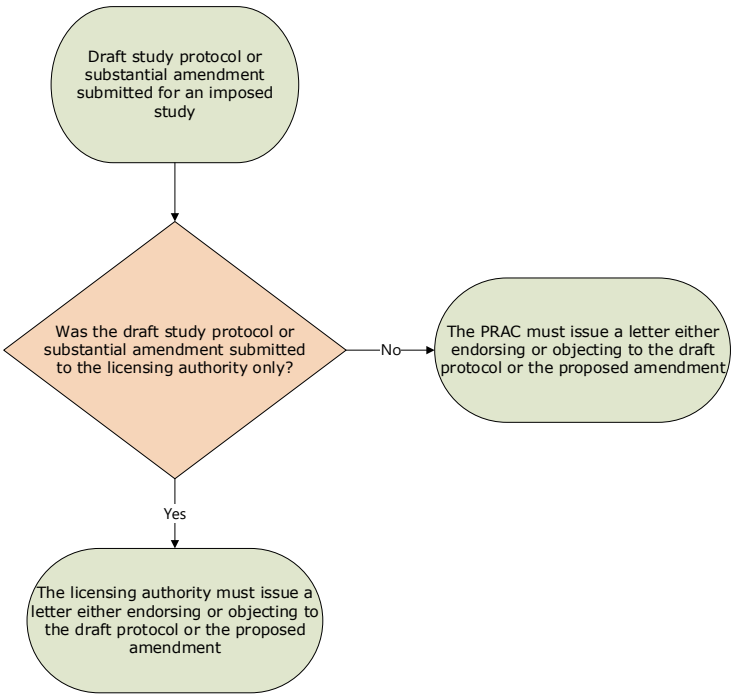
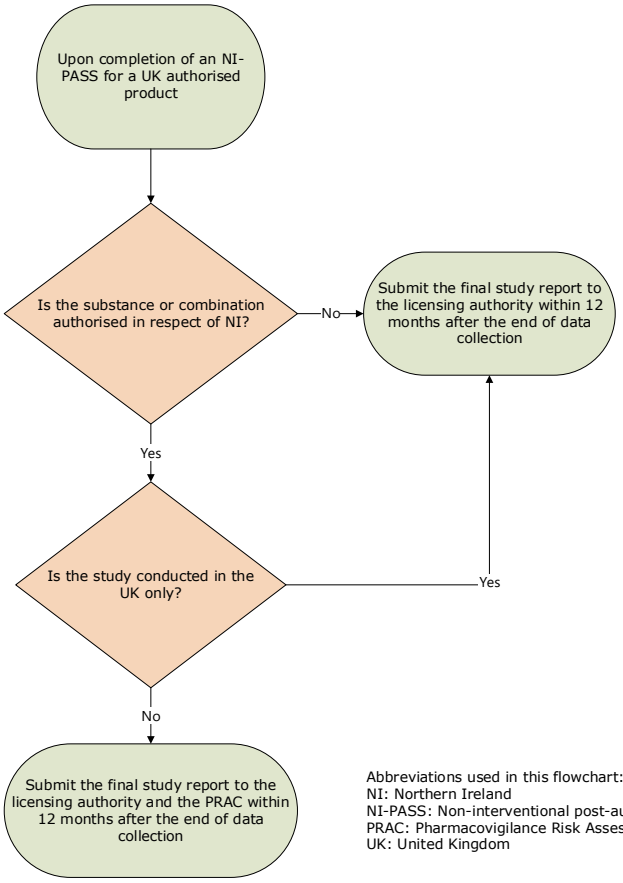


Figure VIII.2. Assessment of the draft study protocol or substantial amendment for imposed studies



Abbreviations used in this flowchart:
PRAC: Pharmacovigilance Risk Assessment Committee

Figure VIII.3. Final study report submission requirements



Abbreviations used in this flowchart:
NI: Northern Ireland
NI-PASS: Non-interventional post-authorisation safety study
PRAC: Pharmacovigilance Risk Assessment Committee
UK: United Kingdom

GVP Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev 3)

- GVP Module VIII Addendum I continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

GVP Module IX – Signal management (Rev 1)

Summary of the key modifications to GVP Module IX – Signal management (Rev 1)

The requirements for submission of emerging safety issues have changed; the module includes updated guidance on what must be reported to the licensing authority and what must be reported to the European Medicines Agency.

There are new requirements on reporting signals from any data source for UK authorised products to the licensing authority. Guidance is provided on the routes and timeframes for reporting these to the licensing authority.

IX.A. Introduction

- [Paragraph 1] This is modified to “The Human Medicines Regulations 2012 (HMR), as amended, includes provisions for signal management in the UK [HMR regulations 179(3), 182(4), 189(1) and 190(1)].”

- [Paragraph 4] The reference to the centralised procedure no longer applies to UK MAHs.

- [Paragraph 8] The guidance documents ‘EMA Questions and Answers on Signal Management’ and ‘Screening for Adverse Reactions in EudraVigilance’ no longer apply to the licensing authority or UK MAHs in respect of products authorised for sale or supply in Great Britain only.

IX.A.1.1. General terminology

- Paragraph 4 under ‘Signal’ no longer applies to UK MAHs in respect of products authorised for sale or supply in Great Britain only.

- [Under ‘Emerging safety issue’ Paragraph 1, bullet point 3] This is modified to “major safety-related regulatory actions outside the UK, e.g. a restriction of the use of the medicinal product or its suspension.”

IX.A.1.2. Terminology specific to the EU signal management process with oversight of the Pharmacovigilance Risk Assessment Committee (PRAC)

- This section no longer applies to UK MAHs in respect of products authorised for sale or supply in Great Britain only.

IX.C.1.1. Responsibilities of the marketing authorisation holder in the EU

- The title of this section is modified to “Responsibilities of the marketing authorisation holder in the UK”.

- [Paragraph 1] This is modified to “The marketing authorisation holder in the UK should continuously monitor the safety of their medicinal products and inform the licensing authority of any new information that might have an impact on the marketing authorisation [HMR regulation 75(2)]. This includes information that meets the definition of an emerging safety issue (see IX.A.1.1. and IX.C.2.)”.

- Paragraph 2 continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

- [Paragraph 3] This is modified to “Signals detected through other sources should be handled according to the marketing authorisation holder’s own signal management process, taking into account the general principles outlined in IX.B.. Such signals should be reported to the licensing authority, taking into account the general obligations of the marketing authorisation holder to keep their product information up to date throughout the product’s lifecycle by variation applications and to present comprehensive signal information in PSURs (see GVP Module VII).”

- [Paragraph 4] This is modified to “Signals, from any source, that meet the definition of emerging safety issues (see IX.A.1.1.) should be notified to the Agency (for products authorised in respect of Northern Ireland) and to the licensing authority (for all UK authorised products) in accordance with the process outlined in IX.C.2..”

- [Paragraph 5] This is modified to “The marketing authorisation holder must collaborate with the licensing authority and, where applicable, the Agency for the assessment of the signals by providing the additional information requested [HMR regulation 75(4)].”

- [Paragraph 6] This is modified to “Marketing authorisation holders must keep their product information up-to-date in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web portal (for products authorised in respect of Northern Ireland) [IR Art 11(1)(f), HMR regulation 76(2)] and the UK web-portal established in accordance with regulation 203(1) (for all UK authorised products) [HMR Schedule 12A paragraph 11(1)(f), regulation 76].”

IX.C.1.2. Responsibilities within the EU regulatory network

- The title of this section is modified to “Responsibilities of the licensing authority”.

- [Paragraph 1] This is modified to “The licensing authority must be responsible for monitoring the data that it collects by virtue of operating its pharmacovigilance system under HMR Part 11 [HMR regulation 189(1)].”

- [Paragraph 2] This is modified to “The licensing authority should validate and prioritise signals it has detected or that have been brought to its attention from any source (see IX.B.3. and IX.B.4.).”

- Paragraphs 3 and 4 no longer apply to the licensing authority.

IX.C.2. Emerging safety issues

- [Paragraph 1] This is modified to “For all UK authorised products, when the marketing authorisation holder in the UK becomes aware of an emerging safety issue from any source (see IX.A.1.1.), they should notify it in writing to the licensing authority to the mailbox signalmanagement@mhra.gov.uk. For products authorised in respect of Northern Ireland, they should also notify the Agency using the mailbox P-PV-emerging-safety-issue@ema.europa.eu [HMR regulation 190(1)]. This should be done as soon as possible and no later than 3 working days after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue.”

- [Paragraph 4] This is modified to “Upon being notified of an emerging safety issue, the licensing authority and/or the Agency should promptly assess the urgency and potential impact of the issue and agree on appropriate next steps and the potential regulatory procedure to address the matter raised.”

- [Paragraph 5] This is modified to “For signals notified as emerging safety issues, a standalone signal notification (see IX.C.4.3.) is not required).”

- [Paragraph 6] This is modified to “The marketing authorisation holder must collaborate with the licensing authority and, where applicable, the Agency in the assessment of the emerging safety issue [HMR regulation 75(4)].”

- [Paragraph 8] This is modified to “For all UK authorised products, should the marketing authorisation holder decide as a result of the emerging safety issue to take any of the following actions: temporary or permanent cessation or suspension of marketing of a medicinal product, withdrawal of a medicinal product from the market, request for the withdrawal of a marketing authorisation or non-application for the renewal of a marketing authorisation, the notification of such action must be done in parallel to the licensing authority (withdrawcancel@mhra.gov.uk) in accordance with the requirements set out in HMR regulation 73(3) and (5A). For products authorised in respect of Northern Ireland, such action must also be notified to the Agency (withdrawnproducts@ema.europa.eu) [HMR regulation 73(5C)].”

- [Paragraph 9] This is modified to “For all UK authorised products, new safety information related to quality defects or suspected falsified medicinal products which might influence the evaluation of the benefits and risks of the medicinal product and which may give rise to an abnormal restriction in supply should not be notified as an emerging safety issue. These must be notified to the licensing authority (dmrc@mhra.gov.uk) in accordance with HMR regulation 75(2). For products authorised in respect of Northern Ireland, such information should also be notified to the Agency (qdefect@ema.europa.eu).”

IX.C.3. Monitoring of EudraVigilance data

- This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

IX.C.3.1. Principles for access

- This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

IX.C.3.2. Periodicity of monitoring

- This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

IX.C.3.3. Analysis of EudraVigilance data

- This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

IX.C.4. Notifications and procedural options for signals detected by the marketing authorisation holder in the EU based on the continuous monitoring of EudraVigilance data

- The title of this section is modified to “Notifications and procedural options for signals detected by the marketing authorisation holder in the UK based on the continuous monitoring of EudraVigilance data and other data sources”.

- [Paragraph 1] This is modified to “For products authorised in respect of Northern Ireland, where a marketing authorisation holder detects a new signal when monitoring the EudraVigilance database, it shall validate it and shall forthwith inform the Agency [IR Art 21(2)]. For all UK authorised products, where a marketing authorisation holder detects a new signal from any data source, it must validate it and forthwith inform the licensing authority [HMR regulation 190(1).”

- [Paragraph 2] This is modified to “For this purpose, signal validation by the marketing authorisation holder should include a thorough analysis of ICSR data available to them. This analysis should be complemented, for validated signals, by the MAH’s assessment of all other relevant data available to them (e.g. literature, clinical trials, databases with larger datasets) (see IX.B.3.). By definition, a signal should provide new information on an association (see IX.A.1.1.) and therefore, the marketing authorisation holder should check, wherever possible, whether a risk may already be addressed in the product information of other UK medicinal products containing the active substance of interest (except for product-specific issues), in which case the product information should be aligned as appropriate through an application for variation of the terms of marketing authorisation. The marketing authorisation holder should also take into account the information published or communicated by the Agency and the licensing authority in relation to signals (see IX.C.9.).”

IX.C.4.1. Variation of the terms of marketing authorisation

- [Paragraph 1] This is modified to “A marketing authorisation holder may conclude, based on their assessment of a signal detected, that the product information and/or the RMP should be updated through a variation. In such cases, the marketing authorisation holder should submit the variation application to the licensing authority as soon as possible and no later than 3 months after completing the assessment of the signal if it corresponds to an important risk (see GVP Annex I), or within 6 months for adverse reactions or risks not considered important.”

– [Paragraph 2] This is modified to “In such instances, a separate standalone signal notification (see IX.C.4.3.) is not required, as the proposed changes and supportive evidence will be assessed within the variation procedure by the licensing authority[17].”

IX.C.4.2. Inclusion of the signal in the periodic safety update report (PSUR)

– [Paragraph 1] This is modified to “If an active substance is included in the List of Union Reference Dates and Frequency of Submission of Periodic Safety Update Reports (PSURs) (EURD List)[18], or the list of UK reference dates published by the licensing authority in accordance with HMR regulation 193(7), and a PSUR is due to be submitted within 6 months of the completion, by the marketing authorisation holder, of the assessment of a signal detected through any data source, the submission of a separate standalone signal notification (see IX.C.4.3.) is not required. Indeed, the signal will be further assessed by the PRAC / licensing authority as appropriate within the PSUR procedure (see modifications to GVP Module VII). If the data-lock point of the PSUR has elapsed by the time the marketing authorisation holder has completed their assessment of the signal, it should be mentioned in the PSUR section ‘Late-breaking Information’ together with a proposal for further management of the signal (see GVP Module VII).”

– The following text is added to the end of this section “At the time of PSUR submission to the licensing authority, if the PSUR includes a signal that corresponds to an important potential risk (see GVP Annex I), or one that the marketing authorisation holder has been requested to assess by another regulatory authority outside of the UK, the marketing authorisation holder should additionally notify the licensing authority in writing to the mailbox signalmanagement@mhra.gov.uk.”

IX.C.4.3. Standalone signal notification

– [Paragraph 1] This is modified to “For products authorised in respect of Northern Ireland, where a marketing authorisation holder, based on their assessment of a signal detected through EudraVigilance monitoring, and which does not meet the conditions outlined in IX.C.4.1. and IX.C.4.2., concludes that further analysis of the signal is required, they should complete the standalone signal notification form available on the European medicines web-portal and send it to the Agency using the mailbox MAH-EV-signals@ema.europa.eu and to the licensing authority using the mailbox signalmanagement@mhra.gov.uk. For all UK authorised products, where a marketing authorisation holder, based on their assessment of a signal detected through any other data source, and which does not meet the conditions outlined in IX.C.4.1. and IX.C.4.2., concludes that further analysis of the signal by the licensing authority is required, they should complete the standalone signal notification form available on the national web-portal[19] and send it to the licensing authority using the mailbox signalmanagement@mhra.gov.uk.”

IX.C.5. Signal confirmation by the PRAC rapporteur or (lead) Member State

– This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

[17] https://www.gov.uk/guidance/medicines-apply-for-a-variation-to-your-marketing-authorisation
[18] See www.ema.europa.eu
[19] https://www.gov.uk/guidance/send-and-receive-information-on-adverse-drug-reactions-adrs

The following text is inserted after this section:

“IX.C.5A. Signal confirmation, prioritisation and analysis by the licensing authority

Within 30 days of receipt of a standalone signal notification from a marketing authorisation holder, the licensing authority should confirm or not the signal, i.e. decide whether or not it should undergo analysis and prioritisation (see IX.A.1.2.). When further assessment is considered needed, the licensing authority should define a timeframe taking into account the prioritisation of the signal.

Marketing authorisation holders must collaborate with the licensing authority for the assessment of the signals by providing the additional information requested [HMR regulation 75(4)]. Such requests are generally addressed to marketing authorisation holders of the reference medicinal products and usually consist of a cumulative review of relevant data (e.g. from spontaneous reports, clinical trials, scientific literature), together with a discussion and conclusion from the marketing authorisation holder. Marketing authorisation holders that provide data are also invited to comment on the preliminary assessment report.

The licensing authority may decide not to confirm a validated signal if, for example:

- it is already adequately handled through a different procedure (e.g. PSUR, variation) at the time confirmation is considered, including procedures for other medicinal products containing the same active substance (e.g. originator product);
- the validated signal involves an adverse reaction that is already adequately reflected in the product information of other products authorised in the UK with the same active substance;
- the signal has already been subject of review and the data that has arisen since this review does not provide substantial new evidence;
- the available data does not warrant further analysis due to limited evidence or clinical relevance.

The justification for not confirming a signal should be communicated to the marketing authorisation holder.”

IX.C.6. Signal analysis, prioritisation and assessment by the PRAC

– This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

IX.C.7. Recommendations on signals from the PRAC

– This section continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

The following text is inserted after this section:

"IX.C.7A. Recommendations on signals from the licensing authority

Licensing authority recommendations may include any or a combination of the following conclusions:

- the marketing authorisation holder should provide additional data for assessment within a signal procedure;
- the marketing authorisation holder should provide a review of additional data on the signal in the following PSUR or submit an ad-hoc PSUR (see GVP Module VII);
- the marketing authorisation holder should update the product information through an application for a variation to the terms of the marketing authorisation;
- the marketing authorisation holder should be requested to submit an RMP or to update the RMP (see GVP Module V);
- the marketing authorisation holder should implement additional risk minimisation measures such as educational materials (see GVP Module XVI) or the dissemination of a Direct Healthcare Professional Communication (DHPC) (see GVP Module XV);
- the marketing authorisation holder should sponsor a post-authorisation study according to an agreed protocol and submit the final results of that study (see GVP Module VIII);
- an inspection should take place in order to verify that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Part 11 of the HMR;
- any other appropriate action that is not listed above;
- no action is required at this point in time, other than routine pharmacovigilance.

Licensing authority recommendations on signals are published on the national web-portal."

IX.C.8. Record management in the European Pharmacovigilance Issues Tracking Tool (EPITT)

– This section no longer applies to the licensing authority.

IX.C.9. Transparency

– The following text is added to the end of this section "Information on signals for UK authorised products will be published on the national web-portal[20] by the licensing authority."

IX. Appendix 1. Figures on the EU signal management process

– These figures continue to apply to UK MAHs for products authorised in respect of Northern Ireland.

[20] https://yellowcard.mhra.gov.uk

GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions

- GVP Module IX Addendum I continues to apply to the licensing authority and UK MAHs.

GVP Module X – Additional monitoring

Summary of the key modifications to GVP Module X – Additional monitoring

For products authorised in respect of Great Britain only, the licensing authority may establish and make public a list of medicinal products that are subject to additional monitoring. The EU additional monitoring list continues to apply to products authorised in respect of Northern Ireland.

X.A. Introduction

- [Paragraph 2] The concept of additional monitoring has been transposed into the Human Medicines Regulations 2012 (HMR) as amended, regulation 202A, for products authorised in respect of Great Britain only.
- [Paragraph 3] This is modified to “As defined in Article 23 of Regulation (EC) No 726/2004 (REG) and Article 11 of Directive 2001/83/EC (DIR), the Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring (hereafter referred to as “the list”). This EU additional monitoring list applies to products authorised in respect of Northern Ireland. As defined in HMR regulation 202A(1), the licensing authority may establish and make public a list of medicinal products authorised in respect of Great Britain only that are subject to additional monitoring (hereafter referred to as “the list”). These medicinal products will be readily identifiable by an inverted equilateral black triangle ▼ as stipulated in the Implementing Regulation (EU) No 198/2013 and HMR regulation 202A(4). That triangle will be followed by an explanatory statement in the summary of product characteristics (SmPC) as follows:

  “This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.”

X.C.1. Criteria for including a medicinal product in the additional monitoring list

X.C.1.1. Mandatory scope

- The existing text in this section continues to apply to products authorised in respect of Northern Ireland.

- The following text is added to the end of this section “For products authorised in respect of Great Britain only, according to HMR regulation 202A(2), it is mandatory to include the following categories of medicinal products in the list:

  - medicinal products authorised in the UK that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the UK;

- any biological medicinal product not covered by the previous category and authorised in the UK after 1 January 2011;
- products for which a PASS was requested at the time of marketing authorisation (HMR regulation 59(2)(b));
- products authorised with specific obligations on the recording or reporting of suspected adverse drug reactions which are stricter than those referred to in HMR Part 11 (HMR regulation 59(2)(c));
- products for which a PASS was requested following the grant of marketing authorisation (HMR regulation 61(4));
- products which were granted a conditional marketing authorisation (HMR regulation 50I);
- products authorised under exceptional circumstances (HMR regulation 60).”

X.C.1.2. Optional scope

– The existing text in this section continues to apply to products authorised in respect of Northern Ireland.

– The following text is added to the end of this section “For products authorised in respect of Great Britain only, as set out in HMR regulation 202A(3), there is the possibility to include in the list medicinal products subject to conditions not falling under the mandatory scope.

  As reflected in HMR regulation 202A(3), the situations that could form the basis for a request for inclusion in the list are:

  - When a marketing authorisation is granted subject to one or more of the following:
    – conditions or restrictions with regard to the safe and effective use of the medicinal product (HMR regulation 59(2)(d));
    – measures for ensuring the safe use of the medicinal product to be included in the risk management system (HMR regulation 59(2)(a));
    – an obligation to conduct a post-authorisation efficacy study (HMR regulations 59(2)(f), 61(5));
    – the existence of an adequate pharmacovigilance system (HMR regulation 59(2)(e));
    – an obligation to operate a risk management system in relation to a medicinal product which has an authorisation or registration that was granted before 21 July 2012 (HMR regulation 183(2)).”

X.C.2. Criteria for defining the initial time period of maintenance in the additional monitoring list

X.C.2.1. Mandatory scope

- This section is modified to “For medicinal products authorised in respect of Northern Ireland containing new active substances as well as for all biological medicinal products approved after 1 January 2011 the initial period of time for inclusion is five years after the Union Reference Date (URD) referred to in Article 107c(5) of Directive 2001/83/EC. For medicinal products authorised in respect of Great Britain only containing new active substances, as well as for all biological medicinal products approved after 1 January 2011, the initial period of time for inclusion is five years after the UK reference date referred to in HMR regulation 193(6A).”

X.C.2.2. Optional scope

- The principles in this section continue to apply to the additional monitoring list established by the licensing authority.

X.C.3.1. The European Commission

- This section no longer applies to the licensing authority and UK MAHs.

X.C.3.2. The Agency

- This section no longer applies to the licensing authority and UK MAHs for products authorised in respect of Great Britain only.

X.C.3.3. National competent authorities

- The title of this section is modified to “The licensing authority”.

- The text in this section is modified to “The licensing authority should:

  - make publicly available on its national web-portal the list of medicinal products authorised in respect of Great Britain only that are subject to additional monitoring;

  - take into account the lists of all nationally authorised medicinal products subject to additional monitoring in determining the frequency and processes of their signal detection activities;

  - inform the relevant MAH when a medicinal product authorised in respect of Great Britain only has been included to the list of additional monitored products.”

X.C.3.4. The Pharmacovigilance Risk Assessment Committee (PRAC)

- This section no longer applies to the licensing authority and UK MAHs for products authorised in respect of Great Britain only.

X.C.4. Creation and maintenance of the list

- This section no longer applies to the licensing authority and UK MAHs for products authorised in respect of Great Britain only.

X.C.5. Black symbol and explanatory statements

- [Paragraph 1] This is modified to “For medicinal products included in the lists provided for in Article 23 of Regulation (EC) No 726/2004 and HMR regulation 202A, the SmPC must include the statement:

  “This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.”,

  preceded by an inverted equilateral black triangle (Implementing Regulation (EU) No 198/2013 and HMR regulation 202A(4)(a)). A similar statement will also be included in the package leaflet. Once the medicinal product is included or removed from the list, the marketing authorisation holder must update the SmPC and the package leaflet to include or remove, as appropriate, the black symbol, the statement, and the standardised explanatory statement.”

X.C.6. Transparency

- [Paragraph 1] This is modified to “For products authorised in respect of Northern Ireland, pursuant to Article 23 of Regulation 726/2004, the Agency will make publicly available the list of the names and active substances of all medicinal products approved in the EU subject to additional monitoring and the general criteria to include medicinal products in the list. The licensing authority must also make publicly available the list of medicinal products authorised in respect of Northern Ireland that are subject to additional monitoring [HMR regulation 203(2)(e)]. For products authorised in respect of Great Britain only, pursuant to HMR regulation 203(2)(da), the licensing authority must make publicly available the list of the names and active substances of all medicinal products subject to additional monitoring.”

- Paragraph 2 no longer applies to the licensing authority and UK MAHs.

GVP Module XV – Safety communication (Rev 1)

Summary of the key modifications to GVP Module XV – Safety communication

The principles of safety communication outlined in GVP Module XV continue to apply to all UK authorised products. The responsibilities of the marketing authorisation holder in relation to public announcements on pharmacovigilance concerns in relation to the use of a medicinal product have been updated for products authorised in respect of Northern Ireland and products authorised in respect of Great Britain only.

The processes for the submission and assessment of direct healthcare professional communications (DHPC) in the UK have changed.

Throughout the Module, references to “EU” are replaced with “UK” and references to “competent authority(ies)” are replaced with “licensing authority”.

XV.B.4. Content of safety communication

- [Paragraph 1] This is modified to “The information in the safety communication must not be misleading and must be presented objectively [HMR regulation 205(4)]. Safety information should not include any material or statement which might constitute advertising within the scope of HMR Part 14.”

XV.B.5.5. Website

- [Paragraph 2] This is modified to “The licensing authority must set up and maintain a national medicines web-portal [HMR regulation 203(1)]”.

XV.B.5.8. Inter-authority communication

- This section no longer applies to the licensing authority.

XV.B.5.9. Responding to enquiries from the public

- [Paragraph 2] This is modified to “With respect to responding to enquiries from the public, HMR regulations 7(3)(c) and 281(2) apply to all UK authorised products. For products authorised in respect of Northern Ireland, IR Art 11(g) and Art 15(d) apply to marketing authorisation holders and the licensing authority respectively. For products authorised in respect of Great Britain only, Schedule 12A paragraphs 11(g) and 15(d) apply to marketing authorisation holders and the licensing authority respectively.”

XV.C.1. Coordination of safety announcements in the EU

- The title of this section is modified to “Coordination of safety announcements in the UK”.

- Paragraph 1 no longer applies to the licensing authority.

- [Paragraph 2] This is modified to “When issuing safety announcements, the licensing authority may make use of the different tools and channels described in XV.B.5.. For products authorised in respect of Northern Ireland, prior to the publication of a safety announcement, the licensing authority must inform the European Medicines Agency, the European Commission and the competent authorities of Member States not less than 24 hours in advance, unless urgent public announcements are required for the protection of public health [HMR regulation 204].”

- Paragraphs 3 and 4 no longer apply to the licensing authority. The following text is added to the end of this section “The licensing authority is responsible for safety announcements in the UK and will cooperate with the EU, as necessary, in relation to products authorised in respect of Northern Ireland.”

XV.C.1.1. Process for exchange and coordination of safety announcements

- This section is modified to:

"Coordination of safety announcements should be done in cooperation with the concerned marketing authorisation holder(s). Whenever possible, the licensing authority should provide any safety announcement prior to its publication to the concerned marketing authorisation holder(s), together with the timetable for the information being made public. Any information of a personal or commercially confidential nature should be deleted unless its public disclosure is necessary for the protection of public health.

Safety announcements should be shared with international partners, subject to embargo and any specific confidentiality arrangements in place.

The licensing authority should interact with concerned stakeholders in the UK (mainly patients' and healthcare professionals' organisations), who can play a key role in reviewing and disseminating information to the end users (patients and healthcare professionals). It is recommended that the licensing authority keep up-to-date contact details of relevant patients' and healthcare professionals' organisations."

XV.C.1.2. Exchange of safety information produced by third parties

- This section no longer applies to the licensing authority.

XV.C.1.3. Requirements for the marketing authorisation holder in the EU

- The title of this section is modified to "Requirements for the marketing authorisation holder in the UK".

- [Paragraph 1] This is modified to "As soon as a marketing authorisation holder in the UK intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, the marketing authorisation holder must inform the following bodies [HMR regulation 205(2)(3)]:

  - for products authorised in respect of Northern Ireland, the licensing authority, the Agency and the European Commission;

  - for products authorised in respect of Great Britain only, the licensing authority.

  This should apply to announcements intended for the UK as well as outside the UK (when they concern medicinal products authorised in the UK). Informing the authorities at the same time as the public (i.e. without advance notice to the authorities) should only occur exceptionally and under justified grounds. Whenever possible, the information should be provided under embargo at least 24 hours prior to its publication."

- [Paragraph 2] This is modified to "The marketing authorisation holder must ensure that information to the public is presented objectively and is not misleading [HMR regulation 205(4)]."

- [Paragraph 3] This is modified to "Whenever a marketing authorisation holder becomes aware that a third party intends to issue communications that could potentially impact the risk-benefit balance of a medicinal product authorised in the UK, the marketing authorisation holder should inform the following bodies and make every effort to share the content of the communications with the licensing authority:

- for products authorised in respect of Northern Ireland, the licensing authority and the Agency;

- for products authorised in respect of Great Britain only, the licensing authority [regulations 73(5A)(c) and 75(2)(d)]."

XV.C.1.5. Languages and translations

– This section no longer applies to the licensing authority and UK MAHs.

XV.C.2. Direct healthcare professional communications (DHPCs) in the EU

– The title of this section is modified to "Direct healthcare professional communications (DHPCs) in the UK".

– This section is modified to "A direct healthcare professional communication (DHPC) (see XV.B.5.1.) is usually disseminated by one or a group of marketing authorisation holders for the respective medicinal product(s) or active substance(s), either at the request of the licensing authority or on the marketing authorisation holder's own initiative. The marketing authorisation holder should seek the agreement of the licensing authority regarding the content of a DHPC (and communication plan) prior to dissemination."

XV.C.2.1. Processing of DHPCs

– This section is modified to:

"The situations when a DHPC is necessary or should be considered are provided in XV.B.5.1.. When drafting a DHPC, the template (see GVP Annex II) and the guidance provided in the annotations in the template should be followed as appropriate.

The roles and responsibilities of the licensing authority, the Agency and marketing authorisation holders in the preparation and processing of DHPCs depend on the route of authorisation of the medicinal products concerned:

- for centrally authorised medicinal products, the relevant marketing authorisation holders should submit the draft DHPC and communication plan (including the intended recipients and the timetable for disseminating the DHPC) to the Agency, which should coordinate the review process by its scientific committees (i.e. PRAC and CHMP) and CMDh, and to the licensing authority in respect of Northern Ireland via pharmacovigilanceservice@mhra.gov.uk for information purposes;

- for medicinal products authorised in respect of Northern Ireland through the mutual recognition or decentralised procedure, the marketing authorisation holder should submit the draft DHPC and communication plan (including intended recipients and timetable for dissemination) to the Reference Member State, which should co-ordinate the process with the marketing authorisation holder while keeping the concerned Member States involved in the process, and to the licensing authority in respect of Northern Ireland via pharmacovigilanceservice@mhra.gov.uk for information purposes;

- for all other UK nationally authorised products, the marketing authorisation holder should submit the draft DHPC and communication plan (including intended recipients

and timetable for dissemination) to the licensing authority for review via pharmacovigilanceservice@mhra.gov.uk.

Irrespective of the route of authorisation, the marketing authorisation holder should wait until comments are received on either the draft DHPC or the communication plan from the licensing authority before disseminating the DHPC in the UK. The timing may be adapted according to the urgency of the situation.

For products in respect of Northern Ireland that have been authorised via the centralised, mutual recognition or decentralised procedures, there might be situations where a single DHPC prepared at EU level may not be suitable as there may be differences in Northern Ireland (such as differences in available therapeutic alternatives) which cannot be addressed in a single DHPC. Therefore, once a core EU DHPC is agreed at EU level setting out core EU messages, the final version of the DHPC and communication plan should be sent to the licensing authority for review. The core EU DHPC can then, if necessary, be complemented at national level with additional information to address the different national situation (i.e. in relation to availability and choice of alternative treatments). Although there may be national tailoring of such DHPCs, any core messages agreed at EU level should be preserved (i.e. tailoring should not conflict with these core messages).

For safety information that affects several marketing authorisation holders (i.e. when the DHPC covers several products with the same active substance or products of the same therapeutic class), marketing authorisation holders are strongly encouraged to arrange for one marketing authorisation holder to act on behalf of all concerned marketing authorisation holders as the contact point for the licensing authority. Where generics are involved, the contact point should normally be the marketing authorisation holder of the originator product. If no originator product is marketed, one of the concerned generic companies is encouraged to act as the contact point. Such coordination between concerned marketing authorisation holders aims to ensure that healthcare professionals receive a single DHPC covering all the medicinal products affected by a single safety concern (same active substance or a class review). The marketing authorisation holder acting as contact point for the licensing authority on behalf of all other marketing authorisation holders should be specified in the agreed communication plan to facilitate coordination.

In cases where an authority outside the UK requests the dissemination of a DHPC in their territory for a medicinal product also authorised in the UK, the marketing authorisation holder should notify the licensing authority. This is part of the legal requirement under which the marketing authorisation holder must notify the licensing authority of any new information which may impact the risk-benefit balance of a medicinal product [HMR regulations 73(5A)(c) and 75(2)(d)]. The need for any subsequent communication, e.g. a DHPC in the UK, should be considered and agreed on a case-by-case basis."

- Paragraphs 3 and 6 no longer apply to the licensing authority and UK MAHs.

- [Paragraph 8] The flow chart describing the processing of DHPCs in Figure XV.1. no longer applies in its entirety to the licensing authority and UK MAHs, therefore it is omitted.

XV.C.2.2. Translation and dissemination of DHPCs

- This section no longer applies to the licensing authority and UK MAHs.

XV.C.2.3. Publication of DHPCs

- This section is modified to “The licensing authority may publish the final DHPC. The marketing authorisation holder should inform the licensing authority of the date of the dissemination of the DHPC in the UK, so that the timing for such publication is aligned to that of the dissemination. The licensing authority may also issue an additional safety announcement (see XV.B.5.2.) and disseminate them to relevant healthcare professionals and their organisations as appropriate.

GVP Annex II - Templates

- The templates for Direct Healthcare Professional Communication and the Communication Plan for Direct Healthcare Professional Communication in GVP Annex II continue to apply to UK MAHs.

GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)

Summary of the key modifications to GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators

The roles and responsibilities of UK marketing authorisation holders, the licensing authority and EU agencies and committees have been updated to reflect management of risk minimisation measures at a national level in the UK.

Throughout the Module, references to “EU” are replaced with “UK” and references to “competent authority(ies)” are replaced with “licensing authority”.

XVI.A. Introduction

- [Paragraph 6] This is modified to “HMR regulation 182(2)(d) states that the marketing authorisation holder must “monitor the outcome of the risk minimisation measures which are contained in the risk management plan (if any) for the product or which are laid down as conditions of the authorisation of the product under regulations 59 to 61 (conditions of UK marketing authorisation). HMR regulation 189 includes provisions for the licensing authority to monitor the outcome of risk minimisation measures which are contained in the risk management plan (RMP) or measures that are laid down as conditions.”

XVI.B.5. Coordination

- The principles described in this section continue to apply to the licensing authority and UK MAHs. The legal basis for authorising products referred to as “generics” or “hybrids” is described in HMR regulations 51, 51A and 51B, and 52, 52A and 52B, respectively. If several products authorised according to these regulations of the same active substance are available on the market, there should be a consistent approach in the use of additional risk minimisation measures coordinated and overseen by the licensing authority.

XVI.C. Operation of the EU network

- Paragraphs 1, 2 and 3 no longer apply to the licensing authority and UK MAHs.

- Paragraph 4 continues to apply to UK MAHs in relation to products authorised in respect of Northern Ireland that have been granted in the context of a mutual recognition or decentralised procedure.

XVI.C.1. Roles and responsibilities within the EU regulatory network

- This section no longer applies to the licensing authority and UK MAHs.

XVI.C.1.1. The European Medicines Agency

- This section no longer applies to the licensing authority and UK MAHs.

XVI.C.1.2. The Pharmacovigilance Risk Assessment Committee (PRAC)

- This section no longer applies to the licensing authority and UK MAHs.

XVI.C.1.3. Competent authorities in Member States

- The title of this section is modified to “The Licensing Authority”.

- [Paragraph 1] This is modified to “The licensing authority is responsible for the oversight of the implementation of additional risk minimisation measures imposed as a condition of the marketing authorisation for the safe and effective use of a medicinal product in the UK.”

- [Paragraph 2] This is modified to “For those risk minimisation measures introduced after the initial marketing authorisation, the licensing authority should ensure prompt consideration and agreement of the interventions with the marketing authorisation holder.”

- [Paragraph 3] The role of the PRAC in facilitating harmonised implementation of risk minimisation tools for generic products of the same active substance in the UK no longer applies to the licensing authority.

- [Paragraph 7] This is modified to “The licensing authority must monitor the outcome of risk minimisation measures contained in RMPs and of the conditions referred to in regulations 59, 60 and 61 [regulation 189(1)(c) and (d)].”

- Paragraphs 4, 6 and 9 no longer apply to the licensing authority.

XVI.C.2. Roles and responsibilities of the marketing authorisation holder or applicant in the EU

- The title of this section is modified to “Roles and responsibilities of the marketing authorisation holder or applicant in the UK”.

- The principles described in this section continue to apply to the marketing authorisation holder or applicant in the UK.

- [Paragraph 8] Reference to Articles 21a, 22 or 22a of DIR is replaced with HMR regulations 59, 60 and 61. Reference to DIR Art 104(3)(d) is replaced with HMR regulation 182(2)(d).

XVI.C.5. Transparency

- Paragraph 2 is omitted to reduce repetition.

- Paragraph 3 no longer applies to the licensing authority.

- [Paragraph 4] This is modified to “By means of the national medicines web-portal, the licensing authority must make publicly available at least the following:

  - public assessment report; this must include a summary written in a manner that is understandable to the public [HMR regulations 64(5)(6), 203(2)(a)], and a summary of the risk management plan [HMR regulation 203(2)(d)], with specific focus on risk minimisation activities described therein [HMR Schedule 12A paragraph 23(1)].

  - summary of product characteristics and package leaflets [HMR regulation 203(2)(b)(c)].”

GVP Module XVI Addendum I – Educational materials

Summary of the key modifications to GVP Module XVI Addendum I – Educational materials

Throughout this Addendum, references to ‘competent authorities’ are replaced with ‘licensing authority’ and references to ‘Member State(s)’ are replaced with ‘UK’.

XVI. Add I.1. Introduction

- [Paragraph 2] This is modified to “Drafts of the educational material(s) addressing the key elements should be submitted by the marketing authorisation holder to the licensing authority for assessment and then be implemented in the UK upon approval by the licensing authority.”

- [Paragraph 4] This modified to “This Addendum to GVP Module XVI provides further guidance for marketing authorisation holders on the submission of draft educational material(s) to the licensing authority, as well as guidance for the licensing authority to support the assessment of such materials, in particular with regard to format and content.”

- [Paragraph 5] This is modified to “This Addendum is applicable to all UK authorised products, including those authorised in respect of Northern Ireland through the mutual recognition and decentralised procedures.”

XVI. Add I.3. Submission of educational materials

- [Paragraph 1, text before bullet points] This is modified to “The draft educational material should be submitted to the licensing authority as follows:”

XVI. Add I.5. Content of educational materials

- [Paragraph 2] This is modified to “The educational material should contain the messages of the key elements agreed with the licensing authority and laid down in the conditions of the marketing authorisation (as referred to in HMR regulation 59).”

XVI. Add I.6. Assessment and publication of educational materials by the competent authorities of Member States

- The title of this section is modified to “Assessment and publication of educational materials by the licensing authority”.

- [Paragraph 1] This is modified to “The timelines for the assessment of draft educational materials by the licensing authority may vary, depending on e.g. the aRMM, the kind of requested educational materials, or the quality of the submitted drafts. Nevertheless, an average timeline of 60 days should be considered for assessment.”

Chapters on product- or population-specific considerations

Product- or Population-Specific Considerations I – Vaccines for prophylaxis against infectious diseases

Summary of the key modifications to GVP Chapter PI – Vaccines for prophylaxis against infectious disease

There are changes to the reporting of batch-related issues, quality defects and emerging safety issues for vaccines authorised in the UK.

The continued roles and responsibilities of UK marketing authorisation holders and the licensing authority in relation to vaccine safety are confirmed.

Throughout the Chapter, references to “competent authority(ies)” can be replaced with “licensing authority”.

P.I.A. Introduction

- [Paragraph 6] This is modified to “The legal references for this guidance are The Human Medicines Regulations 2012 (HMR) as amended for all UK authorised products, and additionally the Commission Implementing Regulation (EU) No 520/2012 for products authorised in respect of Northern Ireland.”

P.I.C.1. Roles and responsibilities

- [Paragraph 2] The legal obligations that apply to vaccines authorised nationally in the UK are laid down in the Human Medicines Regulations 2012 as amended.

P.I.C.1.3. Marketing authorisation holders

- [Paragraph 2] Reference to “Member States” is replaced with “UK”.

P.I.C.1.4. Competent authorities in Member States

- The principles in this section continue to apply to the licensing authority.

P.I.C.1.5. European Medicines Agency

- For products authorised in respect of Northern Ireland, the Agency has a continued responsibility for EudraVigilance data monitoring, signal detection and signal validation for centrally authorised vaccines, and for active substances contained in several vaccines where at least one is centrally authorised (see GVP Module IX).

P.I.C.2. Reporting of reactions and emerging safety issues

- [Paragraph 1] The communication of signals from EudraVigilance by marketing authorisation holders continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

- Paragraphs 3 and 4 are modified to “When a batch-related issue or a quality defect is suspected for a UK authorised vaccine, the marketing authorisation holder should notify the licensing authority via signalmanagement@mhra.gov.uk (for all UK authorised products) and, additionally, the Agency via qdefect@ema.europa.eu (for products authorised in respect of Northern Ireland) (see GVP Module IX). Activities at the level of the licensing authority may include interactions with the Agency, competent authorities of the Member States, the WHO and other regulatory agencies.”

P.I.C.4. Signal management

- [Paragraph 1] This is modified to “Where a signal is based on a single report of a serious adverse event following vaccination, the signal should be validated by the signal identifier (see GVP Module IX and P.I.B.4.). Where the report does not meet the criteria for signal validation, it should be tracked by the signal identifier and special attention should be paid to any follow-up information or other cases of the same adverse event. Signals, from any source, that meet the definition of emerging safety issues should be notified to the Agency (for products authorised in respect of Northern Ireland) and to the licensing authority (for all UK authorised products) in accordance with the modified version of GVP Module IX that applies to UK MAHs.”

- [Paragraph 2] The text in relation to the periodicity for the monitoring of data from EudraVigilance continues to apply to UK MAHs for products authorised in respect of Northern Ireland.

P.I.C.5. Safety communication about vaccines in the EU

- This section no longer applies to the licensing authority and UK MAHs.

P.I.C.6. Transparency of pharmacovigilance for vaccines in the EU

- The title of this section is modified to “Transparency of pharmacovigilance for vaccines in the UK”.

– This section is modified to “The public summary of the RMP is to be made publicly available by the licensing authority [HMR regulation 203(2)(d)]. It should be written in lay language and considerations should be given to the target audience, which might be different for a vaccine than for a usual medicinal product (e.g. general population *vs.* informed patient groups).”

P.I.C.7. Vaccines intended for markets outside the EU

– This section no longer applies to the licensing authority and UK MAHs.

Product- or Population-Specific Considerations II – Biological medicinal products

Summary of the key modifications to GVP Chapter PII – Biological medicinal products

Updated requirements relating to additional monitoring for biological medicinal products are outlined.

There is reference to the MHRA Guideline for licensing of biosimilar products, which will be available in due course.

Throughout the Chapter, references to “competent authority(ies)” can be replaced with “licensing authority”.

P.II.A. Introduction

– [Paragraph 4] This is modified to “A biosimilar is a biological medicinal product that contains a version of the active substance of a reference product which has been authorised for at least 8 years in the UK or the EEA, and which has shown similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise (see Guideline on Similar Biological Medicinal Products[21] and MHRA Guideline for licensing of biosimilar products, once available).”

– Paragraphs 9 and 10 are omitted.

P.II.A.1.1. Immunogenicity

– [Paragraph 7] The first sentence is modified to “For biosimilars in particular, initial marketing authorisation is based on demonstrated and accepted biosimilarity in accordance with the comprehensive comparability exercise (see MHRA Guideline for licensing of biosimilar products, once available).”

P.II.A.1.4. Product traceability

– [Paragraph 4] The first sentence is modified to “It should be noted that prescribing practice and product interchangeability, and particularly switching and substitution

[21] See http://www.ema.europa.eu

between biologicals, are beyond the scope of this Chapter (see MHRA Guideline for licensing of biosimilar products, once available)."

P.II.B.1. Risk management system

- [Paragraph 1] This is modified to "All marketing authorisation applications submitted in the UK after 21 July 2012 should contain a risk management plan (RMP) that must be approved by the licensing authority prior to the granting of the marketing authorisation. The submission of an RMP, or an update thereof, is also normally required for medicinal products for which the initial application was submitted before the above date if there is a significant change in the marketing authorisation, including a new manufacturing process of a biotechnology-derived medicinal product [HMR regulation 183(2)] (see GVP Module V)."

P.II.B.2. Management and reporting of adverse reactions

- The legal basis for the licensing authority to ensure that all appropriate measures are taken to identify clearly any biological prescribed, dispensed or sold in the UK which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product and the batch number, is included in HMR regulation 178(e).

P.II.B.4. Signal management

- The following text is added to the end of this section "When a batch-related issue is suspected for a UK authorised biological/biosimilar product, the marketing authorisation holder should notify the licensing authority via signalmanagement@mhra.gov.uk (for all UK authorised products) and, additionally, the Agency via gdefect@ema.europa.eu (for products authorised in respect of Northern Ireland) (see GVP Module IX). Activities at the level of the licensing authority may include interactions with the Agency, competent authorities of the Member States, the WHO and other regulatory agencies."

P.II.B.5. Additional monitoring

- This is modified to "Biologicals authorised in respect of Great Britain only after 1 January 2011 must be included in the UK list of medicinal products that are subject to additional monitoring [HMR regulation 202A(2)(b)]. They must be removed from the list under the mandatory scope five years after the UK reference date unless the period of additional monitoring is extended [HMR regulation 202A(5)]. Biologicals authorised in respect of Northern Ireland after 1 January 2011 must be included in the list of medicinal products that are subject to additional monitoring referred to in Article 23 of Regulation (EC) No 726/2004. They must be removed from the list under the mandatory scope five years after the EU reference date referred to in Article 107c(5) of Directive 2001/83/EC."

P.II.C.1.1.4. Additional monitoring

- The legal references in this section are updated to HMR regulation 202A(2)(3) for products authorised in respect of Great Britain only and REG Art 23(1)(1a) for products authorised in respect of Northern Ireland.

P.II.C.1.2. Competent authorities in Member States

- The guidance in this section continues to apply to the licensing authority.

P.II.C.1.2.3. Periodic safety update report (PSUR)

- This section is modified to “For the assessment of PSURs for biosimilars, it is critical that the data can be assessed in parallel to the safety data collected for the reference product. In accordance with HMR regulation 193(1), where products that are subject to different authorisations or registrations contain the same active substance or the same combination of active substances, the frequency and dates of submission may be amended and harmonised.”

P.II.C.1.3. European Medicines Agency

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

P.II.C.1.3.1. Pharmacovigilance Risk Assessment Committee

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

P.II.C.2. Safety communication about biologicals in the EU

- This section no longer applies to the licensing authority and UK MAHs.

Product- or Population-Specific Considerations IV – Paediatric population

Summary of the key modifications to GVP Chapter PIV – Paediatric population

The roles and responsibilities in relation to assessing the content of paediatric investigation plans (PIPs) and applications for a full or partial PIP waiver and for study deferrals have changed.

P.IV.A. Introduction

- [Paragraph 3] The legal provisions described in Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC and Regulation (EC) No 726/2004, referred to as the ‘Paediatric Regulation’, continue to apply to products authorised in respect of Northern Ireland. The equivalent legal provisions have been incorporated into the Human Medicines Regulations 2012 (HMR), as amended, and these provisions apply to products authorised in respect of Great Britain only.

- [Paragraph 6] This is modified to “Consequent to these changes, the previous guideline EMEA/CHMP/PhVWP/235910/2005 rev 1 needed to be updated, and revised guidance is now provided in this Product-Specific Considerations Chapter P.IV of the Good Pharmacovigilance Practices (GVP). This guidance should be read in conjunction with Title IV of the Paediatric Regulation and its Article 34, for products authorised in respect of Northern Ireland, and HMR Part 5 (Marketing Authorisations), in particular regulations

50A to 50F, for products authorised in respect of Great Britain only, as well as HMR regulation 59 and Part 11, which apply to all UK authorised products."

P.IV.B.5. Signal management

- [Paragraph 2] The text in relation to monitoring data in the EudraVigilance database continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

P.IV.C.1.2. European Medicines Agency

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

P.IV.C.1.2.1. The Paediatric Committee (PDCO)

- The PDCO continues to have responsibility for assessing the content of paediatric investigation plans (PIPs) and applications for a full or partial PIP waiver and for study deferrals for products authorised in respect of Northern Ireland. The licensing authority will assess the content of PIPs for products authorised in respect of Great Britain only, as well as applications for a full or partial PIP waiver and for study deferrals.

P.IV.C.1.2.2. Interaction between the PDCO and the Pharmacovigilance Risk Assessment Committee (PRAC)

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

P.IV.C.2. The paediatric investigation plan in the EU (PIP)

- The title of this section is modified to "The paediatric investigation plan in the UK (PIP)".

- [Paragraph 1] The legal basis for requiring a PIP when developing a medicine or when a marketing authorisation holder in the UK wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorised and covered by a supplementary protection certificate (SPC) or a patent that qualifies for the granting of a SPC is included in HMR regulations 50A, 50E and 50F, for products authorised in respect of Great Britain only, and Regulation (EC) No 1901/2006, for products authorised in respect of Northern Ireland.

P.IV.C.6. Signal management within the EU regulatory network

- This section continues to apply to the licensing authority and UK MAHs for products authorised in respect of Northern Ireland.

P.IV.C.7. Safety communication in the EU

- The title of this section is modified to "Safety communication in the UK".

- This section is modified to "Children and their families in the UK can be consulted by the marketing authorisation holder as well as by the licensing authority through the

established young person advisory groups for the preparation and revision of safety communication and educational materials for additional RMMs. The Enpr-EMA Working Group on Young Persons Advisory Groups (YPAGs), as well as other UK YPAGs, currently work on resources and on establishing a framework of interaction."

GVP Annex I – Definitions (Rev 4)

- The definitions provided in GVP Annex I continue to apply to the licensing authority and UK MAHs.

GVP Annex II – Templates

- The template cover page of the periodic safety update report (PSUR) continues to apply to UK MAHs.

- The templates in GVP Annex II for 'Direct Healthcare Professional Communication' and 'Communication Plan for Direct Healthcare Professional Communication' continue to apply to UK MAHs.

GVP Annex III – Other pharmacovigilance guidance

The guidance listed in GVP Annex III continues to apply to the licensing authority and UK MAHs.

GVP Annex IV – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for pharmacovigilance

The ICH guidelines continue to apply to the licensing authority and UK MAHs.

GVP Annex V – Abbreviations

The abbreviations provided in GVP Annex V continue to apply to the licensing authority and UK MAHs.