



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

### Guidance note

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## 1. Introduction

- 1.1. If the United Kingdom (UK) leaves the European Union (EU) without a negotiated withdrawal agreement in place (“exit day”), the Human Medicines Regulations 2012 (HMR) (statutory instrument 2012 No. 1916, as amended) will be further amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (“the EU Exit Regulations”), 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.
- 1.2. Regulation 205B (Guidance in respect of good pharmacovigilance practice and post authorisation efficacy studies) of the HMR, as inserted by regulation 169 of the EU Exit Regulations, states that the guidance issued by the Commission<sup>1</sup> 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.
- 1.3. GVP are a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU. GVP apply to MAHs, the European Medicines Agency (“the Agency”) and medicines regulatory authorities in EU Member States. They cover medicines authorised centrally via the EMA as well as medicines authorised at national level.
- 1.4. This document sets out the licensing authority’s determination as to the provisions of the Commission’s GVP guidance that are to 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 exit day.
- 1.5. The EU legislation referenced throughout this document is outlined in full below:
  - Regulation (EC) No. 726/2004 as amended prior to exit day, 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 prior to exit day, 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).
- 1.6. 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

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<sup>1</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

Commission's GVP guidance that applied on exit day and future revisions and development of the GVP shall be duly considered by the licensing authority.

## 2. Overview of the modifications to the EU GVP

- 2.1 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, from exit day, it will continue to apply in the UK.
- 2.2 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 are to be read subject to modification. In practice, this means the following:
  - Throughout the GVP applicable EU legal requirements are referenced and this guidance note seeks to outline the equivalent legal requirements in the UK. The minimum requirements of pharmacovigilance systems and quality systems are set out in HMR Part 11 (Pharmacovigilance) and Schedule 12A (Further provision as to the performance of pharmacovigilance activities).
  - 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.
  - 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 EMA and the Pharmacovigilance Risk Assessment Committee (PRAC).
  - 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.
  - 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 requirements apply).
- 2.3 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".
- 2.4 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.

### 3. Modules covering major pharmacovigilance processes

#### 3.1. GVP Module I – Pharmacovigilance systems and their quality systems

##### 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 “Following exit day, the legal requirement for quality systems is included in HMR Part 11 and the minimum requirements of these quality systems are set out in HMR Schedule 12A. Where reference is made to legal provisions in the IR throughout this module, UK MAHs should note that equivalent legal provisions are described in HMR Schedule 12A.”

##### I.B.11.1. Additional quality system documentation by marketing authorisation holders

- [Paragraph 1] This is modified to “In addition to the quality system documentation in accordance with I.B.11., marketing authorisation holders must document:
  - the organisational structure for the performance of pharmacovigilance activities in the pharmacovigilance system master file (PSMF) (see Module II) [HMR Schedule 12A paragraph 2(e)(i)(aa)];
  - job descriptions defining the duties of the managerial and supervisory staff [HMR Schedule 12A paragraph 10(3)];
  - an organisational chart defining the hierarchical relationships of managerial and supervisory staff [HMR Schedule 12A paragraph 10(3)];
  - instructions on critical processes (see I.B.11.3.) in the PSMF (see Module II); and
  - their record management system in the PSMF (see Module II) [HMR Schedule 12A paragraph 2(e)(ii)].”

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

- [Paragraph 1] The legal requirement for the MAH to have permanently and continuously at its disposal a QPPV that resides and operates in the UK is described in HMR regulation 182(2)(a). The requirements and guidance in this section concerning the responsibilities of the MAH in relation to the QPPV continue to apply to the QPPV that resides and operates in the UK.
- Paragraph 6, in relation to the nomination of a pharmacovigilance contact person at national level, no longer applies to the licensing authority and UK MAHs.

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

- The requirements and guidance in this section concerning the qualifications of the QPPV continue to apply to the QPPV that resides and operates in the UK.

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

- [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 in the UK [HMR regulation 182(2)(a)]. Back-up procedures in the case of absence of the UK QPPV must be in place [HMR Schedule 12A paragraph 2(a)(iv)] 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 that resides and operates in the UK. 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;
  - 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 single 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

- [Paragraph 1] This is modified to “In applying the requirements set out in I.B.9.1. in the UK, the marketing authorisation holder must put in place the following additional specific quality system processes for ensuring:
  - the submission of adverse reaction data to the licensing authority within the legal timelines [HMR Schedule 12A paragraph 11(1)(c)];
  - the retention of minimum elements of the PSMF (see HMR Schedule 12A paragraph 2 and Module II) as long as the system described in the PSMF exists and for at least further 5 years after it has been formally terminated by the marketing authorisation holder [HMR Schedule 12A paragraph 12(4)];
  - the retention of pharmacovigilance data and documents relating to individual authorised medicinal products as long as the marketing authorisation exists and for at least further 10 years after the marketing authorisation has ceased to exist [HMR Schedule 12A paragraph 12(5)];
  - 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 web-portal and on the basis of a continuous monitoring by the marketing authorisation holder of information published on that web-portal [HMR Schedule 12A paragraph 11(1)(f)].”
- Paragraph 2 no longer applies to UK MAHs.

#### 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

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

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

- The general principles in this section continue to apply to the licensing authority, with the exception of the text in paragraphs 1, 4, 5, 6 and 8. This redundant text is in relation to

products authorised through the mutual recognition or decentralised procedure and centrally authorised products, and in relation to the sharing of pharmacovigilance data between competent authorities in the Member States, the European Commission and the European Medicines Agency.

#### I.C.2.2. Role of the European Commission

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

#### 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 no longer applies to the licensing authority and UK MAHs.

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

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

##### 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 no longer applies to the licensing authority and UK MAHs.

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

- 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:

- assessing and processing pharmacovigilance data in accordance with the timelines provided by legislation [HMR Schedule 12A paragraph 15(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)] (see Module XV);
- 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)];
- 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)].

- 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.

#### 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 and UK MAHs.

#### I.C.3. Data protection in the EU

- 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 (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 and the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) (No. 2) Regulations 2019).

From exit day, organisations based in the UK will need to comply with this version of the GDPR (known as the UK GDPR) when processing personal data, in addition to the requirements of the Data Protection Act 2018 (which is amended by the Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations 2019)."

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

- The general 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 the transitional provision introduced in The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019, there is a temporary exemption as to the location of the QPPV. This temporary exemption regarding the location of the QPPV will allow the EU/EEA QPPV who, immediately before exit day, resided and operated in an EEA State, to assume responsibility for UK authorised products until a QPPV who resides and operates in the UK can be established. The transitional period means the period of 21 months beginning with exit day.”

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

#### 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 HMR Schedule 12A. The detailed requirements provided by the Schedule are further supported by the guidance in this GVP Module.”
- Paragraph 3 no longer applies to the licensing authority and UK MAHs.
- [Paragraph 4] This is modified to “The PSMF must be located at the single point in the UK from which the reports of suspected adverse reactions referred to in HMR regulation 187(4) are accessible [HMR Schedule 12A paragraph 7(1)(a)]. This differs from the EU concept where the EU PSMF must be located either at the site where the main pharmacovigilance activities are performed or at the site in the EU where the qualified person responsible for pharmacovigilance operates.”

#### II.B. Structures and processes

- Throughout this section, “EU” is replaced with “UK”. The sentence “Following European Economic Area (EEA) agreements, the QPPV may also reside and operate in Norway, Iceland or Liechtenstein” no longer applies to UK MAHs.

##### 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 is ordinarily resident<sup>2</sup>, and operates, in the UK;
  - 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 location where the PSMF for the medicinal product is kept or, if kept in electronic form, from which it can be accessed, which in either case, must be in the UK.”

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<sup>2</sup> <https://www.gov.uk/government/publications/assessing-ordinary-residence-nationality-policy-guidance>

- [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 located at the single point in the UK from which the reports of suspected adverse reactions referred to in HMR regulation 187(4) are accessible [HMR Schedule 12A paragraph 7(1)(a)].”
- [Paragraph 2] This is modified to “At the time of marketing authorisation application, the applicant should submit electronically the PSMF location information using the agreed format, and subsequently include in the application the 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.”
- [Paragraph 3] This is modified to “Marketing authorisation holders must continue to 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), name and contact details (telephone and fax numbers, postal address and email addresses) and PSMF location information [based on HMR Schedule 10A(1) and Schedule 12A paragraph 4(4)]. Upon a change in the QPPV or location of the PSMF information, the licensing authority must be notified by the marketing authorisation holder via submission of a minor variation of type IA<sub>IN</sub><sup>3</sup> 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 [based on HMR Schedule 12A paragraph 4(4)].”
- Paragraph 5 no longer applies to UK MAHs.

#### 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)]. 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 HMR.”
- [Paragraph 1, bullet point 5] This is modified to “Submission of summary information to the licensing authority cannot contain multiple locations for a single PSMF. The address of the location of the PSMF provided to fulfil the requirement of HMR Schedule 8 paragraph 12 should be an office address which reflects the single point in the UK from

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<sup>3</sup> <https://www.gov.uk/guidance/medicines-apply-for-a-variation-to-your-marketing-authorisation>

which all reports of suspected adverse reactions to the product are accessible [HMR regulation 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.”

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

- [Paragraph 1] The is modified to “The PSMF must contain at least all of the documents listed in 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 UK 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] and/or via submission of a minor variation of type IA<sub>IN</sub> to the licensing authority.”
- [Paragraph 2] This is modified to “The information relating to the QPPV for UK authorised products provided in the PSMF [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; and
  - details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance.”
- [Paragraph 2, bullet point 5] For the avoidance of doubt, the requirement to include information on the responsibilities of a nominated national contact person for pharmacovigilance in the UK PSMF no longer applies to UK MAHs.

##### 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 [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 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 [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 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 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 regarding the quality of ICSR reporting, PSURs or other submissions;
  - An overview of the timeliness of PSUR reporting to the licensing authority (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 covered by the PSMF including the name of the medicinal product and the international non-proprietary name of the active substance(s) [HMR Schedule 12A paragraph 3(a)];

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

- the authorisation number(s);
- the presence on the market in the UK (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 inclusion in the list described in HMR regulation 202A). 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 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 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 [HMR Schedule 12A paragraph 3(d)];
- A list of all completed audits, for a period of five years, and a list of audit schedules [HMR Schedule 12A paragraph 3(e)];
- Where applicable, a list of performance indicators in accordance with HMR Schedule 12A paragraph 9(1) [HMR Schedule 12A paragraph 3(f)];
- Where applicable, a list of other UK PSMFs held by the same marketing authorisation holder [HMR Schedule 12A paragraph 3(g)];

This list should include the 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 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.6.1. 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.”

#### II.C.1.1. Marketing authorisation holders and applicants

- [Paragraph 3] This is modified to “The applicant/marketing authorisation holder is responsible for establishing the PSMF in the UK (at any marketing authorisation holder or contractual partner site, including the site of a contractor or marketing partner) and for registering the master file location with the licensing authority in the marketing authorisation application. 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 and the PSMF location details. 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 and UK MAHs.

#### 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 [HMR Schedule 12A paragraphs 4(1) and 7(2)]. It must also be permanently available for inspection at the site where it is kept [HMR Schedule 12A paragraph 7(1)(b)] (the stated location), irrespective of whether the inspection has been notified in advance or is unannounced.”

#### II.C.3. Transparency

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

### 3.3. GVP Module III – Pharmacovigilance inspections

#### III.A. Introduction

- [Paragraph 2] The legal basis for pharmacovigilance inspections 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) or 61 (conditions of a UK marketing authorisation: new obligations post-authorisation).
- Paragraphs 4, 5, 7, 9 and 10 regarding the supervisory authority for pharmacovigilance, the sharing of information between national competent authorities and the Agency concerning inspection planning, conduct or outcomes, cooperation between national competent authorities and the European Medicines Agency, and information sharing between inspectors and the Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Medicinal Products for Human Use (CHMP), no longer apply to the licensing authority.
- [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 and 210A].”

#### III.B.4.1. Routine pharmacovigilance inspections

- [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, including by the Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019, S.I. 2019 No. 744) and HMR regulation 188 respectively.

### III.B.5. Inspection process

- [Paragraph 1] The Union procedures on pharmacovigilance inspections<sup>4</sup> 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, the Commission or the competent authorities of the Member States no longer applies to the licensing authority.
- [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 and Schedule 12A are outlined in HMR regulations 209 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 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.”

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<sup>4</sup> <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/compliance/pharmacovigilance-inspections/pharmacovigilance-inspection-procedures-human>

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

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

#### III.C.1. Sharing of information

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

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

##### III.C.2.1. General Role of the Agency

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

##### III.C.2.2. Role of the PRAC

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

##### III.C.2.3. Role of the CHMP

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

#### III.C.3. Role of the European Commission

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

#### III.C.4.1. General Considerations

- The general principles continue to apply to the licensing authority, with the exception of the guidance on information sharing and inspection coordination with national competent authorities in the EU Member States [paragraphs 5 to 7].

#### III.C.4.2. Role of the Supervisory Authority

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

#### III.C.4.3. Inspection Programmes

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

#### 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.”

### 3.4. GVP Module IV – Pharmacovigilance audits (Rev 1)

#### IV.A. Introduction

- [Paragraph 1] This is modified to “The legal requirement for the licensing authority and UK MAHs 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 and Schedule 12A paragraphs 13(1) and 17(1).”
- [Paragraph 3] This is modified to “The minimum requirements of the pharmacovigilance systems and the quality system are set out in HMR Schedule 12A (Further provision as to the performance of pharmacovigilance activities). Risk-based audits of the pharmacovigilance system should cover all relevant activities required as per the HMR. 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 and 13 for marketing authorisation holders and paragraphs 8, 14, 15, 16 and 17 for the licensing authority].”

#### 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)]. The dates and results of audits and follow-up audits must be documented [HMR Schedule 12A paragraph 13(3)].”

#### IV.C.1.1.1. The qualified person responsible for pharmacovigilance in the EU (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 in the UK, irrespective of where the audit was conducted.

#### 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)]. The dates and results of audits and follow-up audits must be documented [HMR Schedule 12A paragraph 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

- This section no longer applies to the licensing authority.

#### IV.C.4. Transparency

- This section no longer applies to the licensing authority.

### 3.5. GVP Module V – Risk management systems (Rev 2)

#### 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<sup>5</sup>.
- [Paragraph 7] This is modified to “The following articles provide the main references in relation to the legal basis for risk management in the UK, but additional articles may also be relevant:
  - HMR Schedule 8 paragraphs 12 and 13, regulations 59(2)(6), 61(1)(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).”
- The following text is added to the end of this section “The licensing authority will continue to accept EU versions of the RMP. Consequently, two scenarios are envisaged by the licensing authority:
  - Where a MAH has an EU version of the RMP that it wishes to submit to the licensing authority, this document should conform to the format and content requirements

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<sup>5</sup> <https://www.ema.europa.eu/en>

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 in a UK-specific annex.

- Where a MAH does not have an EU version of the RMP, the UK 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 guidance note (Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders)."

#### 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).

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

- [Paragraph 1] The reference to IR Annex I is replaced with HMR Schedule 12A paragraph 25.
- [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<sup>6</sup>; this guidance continues to apply to UK MAHs."
- [Paragraph 3] The reference to DIR Art 8(3) is replaced with HMR Schedule 8 paragraph 13(b).
- [Paragraph 4] The reference to 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), is replaced with HMR regulation 59(4D)(4E).
- [Paragraph 5] The reference to IR Art 30(2) is replaced with HMR Schedule 12A paragraph 22(2).
- [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.

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<sup>6</sup> <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans>

- [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” replaced with “UK”.

##### V.B.5.1.2. Advanced therapy medicinal products

- The reference to Regulation (EC) No 1394/2007 is replaced with HMR regulation 2A(1).

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

- [Paragraph 1] Reference to “EU” replaced with “UK”.
- [Paragraph 2] Reference to “EU” replaced with “UK”.

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

- [Paragraph 1] Reference to “EU” replaced with “UK”.
- [Paragraph 4] Reference to “EU” 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 201 and the format and content of such non-interventional PASS should be as described in HMR Schedule 12A paragraphs 28 to 32 and 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 |
| <b>Imposed PASS</b>        | “Interventional”   | 1                         | Mandatory and subject to penalties | No                 | No                      |
|                            | Non-interventional |                           |                                    | Yes                | Yes                     |
| <b>Specific obligation</b> | “Interventional”   | 2                         | Mandatory and subject to penalties | No                 | No                      |
|                            | Non-interventional |                           |                                    | Yes                | Yes                     |
| <b>Required</b>            | “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 EU 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 required in the EU should continue to be included in the pharmacovigilance plan in the RMP for UK authorised products. 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)].”
- [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”.
- 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, 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<sup>7</sup>.

#### 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.

#### 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 regulation 52, i.e. ‘hybrid’”.
- [Paragraph 1] The reference to DIR Art 10(3) is replaced with HMR regulation 52.

#### 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 regulation 53, 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”.
- [Paragraph 1] The text in relation to centrally authorised products no longer applies to the licensing authority and UK MAHs. The national system for submission of a risk management plan to the licensing authority should be followed<sup>8</sup>.

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<sup>7</sup> <http://www.hma.eu/464.html>

<sup>8</sup> <https://www.gov.uk/guidance/making-submissions-to-the-mhra-in-a-no-deal-scenario>

#### V.C.2.1. Risk management plan updates

- Under ‘RMP updates with the PSUR’, paragraphs 2 and 3 no longer apply to the licensing authority and UK MAHs.

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

- Paragraphs 1 and 3 no longer apply to the licensing authority and UK MAHs.
- [Paragraph 2] This is modified to “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)]”.

#### 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)(d)].”
- Paragraphs 2 and 3 no longer apply to the licensing authority.

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

#### 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 HMR Schedule 12A Parts 5 and 6 apply to the licensing authority and UK MAHs.”

#### VI.B.1.1.2. Literature reports

- [Paragraph 6] The text regarding the monitoring of the scientific and medical literature by the European Medicines Agency no longer applies to the licensing authority and UK MAHs.

#### VI.C. Operation of the EU network

- [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 devices containing medicinal products, 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 Medical Devices Regulations 2002 (MDR), as amended), that single product must be governed by the pharmacovigilance requirements provided in the HMR. The relevant essential requirements, as set out in regulation 9 of the MDR, must 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 must be governed by the MDR, without prejudice to the provisions of the HMR with regard to the medicinal product. This means that the device must be CE marked as a medical device and follow the requirements for medical device vigilance given in the MDR. As detailed in the Guidelines on a Medical Devices Vigilance System<sup>9</sup>, 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 the MDR.”

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

- 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.

<sup>9</sup> <https://ec.europa.eu/docsroom/documents/32305/attachments/1/translations>

- [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.”
- [Paragraph 7] This is modified to “The rules for the submission of valid ICSRs to the licensing authority’s 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.<sup>10</sup>”

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<sup>10</sup> <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medication-errors>

- [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(4)] (see VI.C.6.2.4. and GVP Module I for guidance on ICSRs data quality).”

#### 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 reference is replaced with HMR regulation 187(1).
- [Paragraph 3] In this paragraph “EudraVigilance database” is replaced with “licensing authority’s database”.
- [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 “EU” is replaced with “UK”.

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

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

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

- [Paragraph 1] “EudraVigilance database” is replaced with “licensing authority’s database”.
- [Paragraph 1, sub-paragraph c.] This is modified to “which is based on an analysis from the licensing authority’s database within the UK. 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 products assessed under the mutual recognition, decentralised or centralised procedures 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 as follows “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] “EudraVigilance database” is replaced with “licensing authority’s database”.
- [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 in the UK”.
- [Paragraph 2] This is modified to “According to HMR regulation 188(1),
  - serious valid ICSRs must be submitted by the marketing authorisation holder to the licensing authority 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 within 90 days from the date of receipt of the reports.”

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

- The title of this section is modified to “Submission modalities of ICSRs in the UK”.
- [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 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]. 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.”
- [Paragraph 3] This is modified to “In line with the provisions set out in HMR regulation 188(1), 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.

**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.<sup>11</sup>

**b. Non-Serious ICSRs**

- The marketing authorisation holder must submit all non-serious ICSRs that occur in the UK to the licensing authority.
  - 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.”
- Paragraphs 5, 6, 7 and 8 no longer apply to the licensing authority and UK MAHs.

**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(R2) 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”.
- Paragraph 1 no longer applies to the licensing authority and UK MAHs.
- [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.”

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<sup>11</sup> <https://www.gov.uk/guidance/send-and-receive-information-on-adverse-drug-reactions-adrs>

#### 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)]. 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<sup>12</sup>.”
- [Paragraph 3] This is modified to “Technical tools (ICSR Submissions) have been made available by the licensing authority 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) | <ul style="list-style-type: none"><li>• 'MHRAUK' in the data element M.1.6 'Message receiver identifier' (ICH M2).</li></ul>                                 |
| ICH-E2B(R3) | <ul style="list-style-type: none"><li>• 'MHRAUK' in the data elements N.1.4 'Batch Receiver Identifier' and 'N.2.r.3 Message Receiver Identifier'.</li></ul> |

<sup>12</sup> <https://www.gov.uk/guidance/making-submissions-to-the-mhra-in-a-no-deal-scenario>

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) | <ul style="list-style-type: none"> <li>• Data element A.1.4 'Type of report': <ul style="list-style-type: none"> <li>— spontaneous report;</li> <li>— other;</li> <li>— not available to sender (unknown); or</li> <li>— report from study.</li> </ul> </li> <li>• 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: <ul style="list-style-type: none"> <li>— individual patient use, e.g. compassionate use or named-patient basis; or</li> <li>— other studies, e.g. pharmacoepidemiology, pharmacoconomics, intensive monitoring, post-authorisation study.</li> </ul> </li> </ul> |
| ICH-E2B(R3) | <ul style="list-style-type: none"> <li>• Data element C.1.3 'Type of report': <ul style="list-style-type: none"> <li>— spontaneous report;</li> <li>— other;</li> <li>— not available to sender (unknown); or</li> <li>— report from study.</li> </ul> </li> <li>• 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: <ul style="list-style-type: none"> <li>— individual patient use, e.g. compassionate use or named-patient basis; or</li> <li>— other studies, e.g. pharmacoepidemiology, pharmacoconomics, intensive monitoring, post-authorisation study.</li> </ul> </li> </ul>   |

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) | <ul style="list-style-type: none"> <li>• 'MHRAUK' in the data element M.1.6 'Message receiver identifier' (ICH M2).</li> </ul>                                 |
| ICH-E2B(R3) | <ul style="list-style-type: none"> <li>• 'MHRAUK' in the data elements N.1.4 'Batch Receiver Identifier' and 'N.2.r.3 Message Receiver Identifier'.</li> </ul> |

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

| Reference   | E2B(R2)/(R3) requirements  |
|-------------|--|
| ICH-E2B(R2) | <ul style="list-style-type: none"> <li>• Data element A.1.4 ‘Type of report’: <ul style="list-style-type: none"> <li>— report from study.</li> </ul> </li> <li>• 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: <ul style="list-style-type: none"> <li>— clinical trials.</li> </ul> </li> </ul> |
| ICH-E2B(R3) | <ul style="list-style-type: none"> <li>• Data element C.1.3 ‘Type of report’: <ul style="list-style-type: none"> <li>— report from study.</li> </ul> </li> <li>• 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: <ul style="list-style-type: none"> <li>— clinical trials.”</li> </ul> </li> </ul>  |

#### VI.C.6.2.1. EudraVigilance Database Modules

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

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

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

##### 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 UK MAHs.

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

- Throughout this section, references to sub-paragraphs in IR Article 28 are replaced with the equivalent sub-paragraph in HMR Schedule 12A paragraph 20.

#### VI.C.6.2.2.7. Follow-up information

- [Paragraph 4] “EudraVigilance database” is replaced with “licensing authority’s database”.

#### VI.C.6.2.2.8. Amendment of cases

- [Paragraph 1] “EudraVigilance database” is replaced with “licensing authority’s database”.

#### 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 exit day and the latest version is to be nullified on or after exit day,

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] Data protection requirements in the UK are described in 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 and the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) (No. 2) Regulations 2019. From exit day, organisations based in the UK will need to comply with this version of the GDPR (known as the UK GDPR) when processing personal data, in addition to the requirements of the Data Protection Act 2018 (which is also amended by the Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations 2019).
- [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] This is modified to “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 no longer applies to the licensing authority and UK MAHs.

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

- [Paragraph 3] This is modified to “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). The same applies to cases of adverse reactions originating from clinical trials if they are suspected to be related to a medicinal product other than the IMP and do not result from a possible interaction with the IMP.”

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

- [Paragraph 1] This is modified to “The licensing authority’s database should contain all cases of suspected adverse reactions that are reportable according to the HMR to support pharmacovigilance activities. This applies to all medicinal products authorised in the UK independent of their authorisation procedure.”
- Paragraphs 2, 4 and 5, regarding the EudraVigilance database and the European Medicines Agency’s role in promoting the quality and integrity of submitted data, no longer apply to the licensing authority and UK MAHs.
- [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 within the 15 or 90-day time frame [HMR Schedule 12A paragraph 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)];
  - the detection of duplicates of suspected adverse reactions reports in collaboration with the licensing authority [HMR regulation 188(1)(e)].”
- [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 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)].”
- Paragraphs 9, 10, 11, 12 and 13 no longer apply to the licensing authority and UK MAHs.
- [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”.

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

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

## 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. For reports received by marketing authorisation holders, these steps are modified to the submission of initial ICSRs (steps 3.1 and 12.1) and follow-up ICSRs (step 6.1) to the licensing authority's database.
- [Figure VI.3 and Table VI.3] Steps referring to submission of initial ICSRs (step 2) and follow-up ICSRs (step 13.1) to EudraVigilance are modified to the submission to the licensing authority's database. 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, with the exception of references to the European Medicines Agency's monitoring of selected medical literature for suspected adverse reactions to medicinal products containing certain active substances.

### 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), upon request of the licensing authority, 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](mailto: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)) no longer applies to the licensing authority and UK MAHs.

- Table VI.6. (Process description - ICSRs submission in EU by competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs)) is renamed to “Process description - ICSRs submission in UK by marketing authorisation holders (MAHs)” and is modified as follows:

| No. | Step                                | Description  | Responsible Organisation |
|-----|-------------------------------------|--|--------------------------|
| 1   | Start.                              | <b>Receipt by the MAH of a report of suspected adverse reaction related to a medicinal product (ADR report). Go to step 2.</b>   | 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.?<br><br>If no, follow-up on the ICSR as described in VI.App.1.1.<br><br>If yes, go to step 3.  | MAH                      |
| 3   | Is ICSR serious?                    | Is the ICSR serious?<br><br>If No go to step 3.1.<br><br>If Yes, go to step 4.   | MAH                      |
| 3.1 | Is ICSR from UK?                    | Is the ICSR from UK?<br><br>If No go to step 3.2.<br><br>If Yes, go to step 4.   | MAH                      |
| 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.<br><br>See guidance in the licensing authority's Business Continuity Plan <sup>13</sup> in case of system failure in safety message generation, submission, receipt, processing and rerouting. | MAH                      |

<sup>13</sup> <https://www.gov.uk/guidance/making-submissions-to-the-mhra-in-a-no-deal-scenario>

| No. | Step  | Description   | Responsible Organisation |
|-----|---|---|--------------------------|
| 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).              | <p>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 &amp; ICSR(s) therein are correct.</p> <p>The acknowledgement message is sent to the sender (Go to step 7).</p> <ul style="list-style-type: none"> <li>- All messages will receive an E2B(R2) acknowledgement.</li> <li>- A correct ICSR will have an E2B(R2) ACK code 01 (ACK_B.1.8).</li> <li>- An ICSR not correct will have an E2B(R2) ACK code 02 (ACK_B.1.8).</li> <li>- A message will receive a transmission acknowledgement code 03 (ACK_A.1.6) if the message is not correctly formatted.</li> </ul> | Licensing authority      |
| 7   | ACK message sent.                                   | <p>The acknowledgement message created in step 6 is transmitted to the sender no later than 2 business days following the receipt of the ICSR.</p> <p>Go to step 11 for the licensing authority's next step.</p> <p>Go to step 8 for MAH's next step.</p>   | Licensing authority      |
| 8   | Receive ACK message.                                | <p>Receive the ACK message.</p> <p>Associate it with the relevant ICSR and check that it was considered valid. Go to step 9.</p>  | MAH                      |
| 9   | Is ICSR ACK positive?                               | <p>Is a positive acknowledgement code received for the ICSR?</p> <p>If yes, go to step 9.1.</p> <p>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</p>  | MAH                      |

| No.  | Step  | Description   | Responsible Organisation |
|------|---|---|--------------------------|
|      |   | <p>first information was received. Go to step 10 to correct the ICSR.</p> <p>Neither an ICSR nor 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.</p>   |                          |
| 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.                      | <p>Resubmit the corrected ICSR to the licensing authority’s database.</p> <p>Go back to step 5 for the receipt of the corrected ICSR in the licensing authority’s database.</p>   | 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?                        | <p>Did the technical validation of the ICSR in step 6 create a positive ACK code?</p> <p>If no, perform no further processing on this version of the ICSR and go to step 12.1</p> <p>If Yes, go to step 13.</p>   | Licensing authority      |
| 12.1 | Await corrected case.                         | <p>The sender should correct every ICSR with an error ACK and retransmit it within the appropriate regulatory timelines.</p> <p>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.</p> | Licensing authority      |

| No. | Step | Description   | Responsible Organisation |
|-----|------|---|--------------------------|
|     |      | 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.  |                          |
| 13  | End. | <p>The ICSR is now stored in the licensing authority's database.</p> <p>It is available for signal detection and data quality analyses following duplicate detection and recoding.</p> <p>See guidance in the licensing authority's Business Continuity Plan in case of system failure in safety message generation, submission, receipt, processing and rerouting.</p> | 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:

| Marketing authorisation procedure | Origin | Adverse reaction type | Destination           | Time frame |
|-----------------------------------|--------|-----------------------|-----------------------|------------|
| • Purely national                 | UK     | All serious           | • Licensing authority | 15 days    |
|                                   |        | All non-serious       | • Licensing authority | 90 days    |
|                                   | 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 no longer applies to the licensing authority and UK MAHs.

## VI. Appendix 7 Duplicate detection and management of ICSRs

- This appendix no longer applies to the licensing authority and UK MAHs. Duplicate management of suspected adverse reaction reports applicable to the licensing authority and UK MAHs is described in the modifications to GVP Module VI Addendum I.

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

#### 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, regulation 188(1)(e).
- [Paragraph 3] The following text is added to the end of this paragraph “Data protection requirements in the UK are described in 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 and the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) (No. 2) Regulations 2019. From exit day, organisations based in the UK will need to comply with this version of the GDPR (known as the UK GDPR) when processing personal data, in addition to the requirements of the Data Protection Act 2018 (which is also amended by the Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations 2019).”

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

- The title of this section is amended to “What to do if possible duplicates in the licensing authority’s database have been detected”.
- This section is modified to:
  - “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](mailto: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:

- The following table is inserted at the end of this section:

**Table VI. Add I.2.** 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.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 exit day and the latest version is to be sent on or after exit day, then you should send it to the licensing authority.”
- [Table VI. Add I.4. Step 9] The third sentence is modified as follows “If the original case was sent to EudraVigilance before exit day and the latest version is to be sent on or after exit day, then you should send it to the licensing authority.”

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

#### VII.A. Introduction

- [Paragraph 2] The legal requirements for submission of periodic safety update reports (PSUR) are established in The Human Medicines Regulations 2012 (HMR).
- [Paragraph 3] This is modified to “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] This is modified to “Further details and guidance for the submission of PSURs in the UK, including the list of UK and Union reference dates and frequency of submission are provided in VII.C.. Details related to the quality system are provided in VII.C.6. and the publication of PSUR-related documents in VII.C.7. as transparency provisions.”

- [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<sup>14</sup>. The timelines for submission described in this paragraph continue to apply to UK MAHs.
- [Paragraph 9] This is modified to “The 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), homeopathic medicinal products (authorised under HMR regulation 103) 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 the licensing authority and UK MAHs.
- The following text is added to the end of this section “The licensing authority will continue to accept EU versions of the PSUR. 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.B.5. Where the licensing authority has made a specific request for information to be included, this information should be provided in a UK-specific regional appendix.”

## 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 HMR Schedule 12A paragraph 27.”
- [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.”

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

- This section and the associated flow chart (Figure VII.2.) no longer apply to the licensing authority and UK MAHs.

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<sup>14</sup> <https://www.gov.uk/guidance/making-submissions-to-the-mhra-in-a-no-deal-scenario>

### 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, 6 monthly PSUR submission should be continued following initial placing on the market in the UK 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 “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(6)].”
- [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 “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 EMA under Article 107c(7) of the 2001 Directive is deemed to be the UK reference date [HMR regulation 193(6A)].”

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

- [Paragraph 1, bullet point 2] The text in relation to the role of the PRAC no longer applies to the licensing authority and UK MAHs.
- [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, traditional herbal and homeopathic 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).”

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

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

- The following text is added to the end of this section “Marketing authorisation holders 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”.
- [Paragraph 1] 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 the medicinal product [HMR regulation 195]. This includes PSURs for medicinal products subject to different marketing authorisations, containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holder and for which the frequency and dates of submission of PSURs have been harmonised in the list of UK or EU reference dates.”
- Paragraphs 2, 3, 4 and 8 no longer apply to the licensing authority and UK MAHs.

- [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. Any decisions or recommendations published on the European medicines web-portal following the EU single assessment of the same active substance or combination of active substances will be considered by the licensing authority. Furthermore, marketing authorisation holders are reminded of their obligation to keep their marketing authorisation up to date in accordance with HMR regulation 76.”
- [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.”

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

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

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

- This section (incorporating sub-sections VII.C.4.2.1., VII.C.4.2.2., VII.C.4.2.3. and VII.C.4.2.4.) no longer applies to the licensing authority and UK MAHs.

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

- PSURs submitted to the licensing authority should include the EU regional appendix. Any UK-specific information and/ or conclusions should be included in a separate UK regional appendix.

#### 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 [HMR regulation 76].”
- [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.”

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

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

#### 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.”
- Paragraphs 3, 4, 5 and 6 no longer apply to the licensing authority and UK MAHs.

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

- The title of this section is modified to “Publication of PSUR-related documents on the national medicines web-portal”.
- [Paragraph 1] This is modified to “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 text is inserted after paragraph 1 “The following should be made publicly available by means of the national medicines web-portal:
  - final PSUR assessment conclusions.”
- Paragraphs 2, 3 and 4, no longer apply to the licensing authority and UK MAHs.

#### VII.C.8. Renewal of marketing authorisations

- 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.

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

#### 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 201 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 does not apply to non-interventional PASS conducted in the UK pursuant to an obligation imposed by the licensing authority, or to non-interventional PASS required in the risk management plan agreed in the UK or conducted voluntarily in the UK. This is without prejudice to the requirements for the registration of PASS conducted in the EU where the study is also conducted in the UK.

### VIII.B.3. Study protocol

- [Paragraph 2] This is modified to “For non-interventional PASS imposed as an obligation, the draft study protocol must be submitted by the MAH to the licensing authority [HMR regulation 199(2)].”
- [Paragraph 3] This is modified to “For non-interventional PASS conducted voluntarily, the licensing authority may require the MAH to submit the protocol to the licensing authority [HMR regulation 198(2)].”
- [Paragraph 5] The role of the pharmacovigilance contact person at national level no longer applies to UK MAHs.

#### 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]. 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 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 licensing authority any new information that arises at any point during the study which might influence the evaluation of the risk-benefit balance for that product [HMR 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 via email ([SignalManagement@mhra.gov.uk](mailto:SignalManagement@mhra.gov.uk)). 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 licensing authority [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.” GVP Module VIII Addendum I no longer applies to the licensing authority and UK MAHs.

### 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 of the guidance [HMR Schedule 12A paragraph 32] and must be submitted within 12 months of the end of data collection. 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 2 no longer applies to the licensing authority and UK MAHs.
- [Paragraph 4, bullet point 2] This is modified to “**Abstract:** stand-alone summary in the format presented below [HMR Schedule 12A paragraph 31].”

### 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 and the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) (No. 2) Regulations 2019). From exit day, organisations based in the UK will need to comply with this version of the GDPR (known as the UK GDPR) when processing personal data, in addition to the requirements of the Data Protection Act 2018 (which is amended by the Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations 2019).”

### 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].” The role of the PRAC no longer applies to the imposition of PASS under this regulation.

### 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 licensing authority during a post-authorisation regulatory procedure, for example, an extension or a variation to a marketing authorisation, a renewal procedure or a PSUR procedure. 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].” The role of the PRAC no longer applies to the imposition of PASS under this regulation.

### 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 or a national competent authority, as applicable, 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. 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].” The role of the PRAC no longer applies to the imposition of PASS under this regulation.

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

- This section is modified to “If safety concerns apply to more than one medicinal product, the licensing authority must encourage the UK marketing authorisation holders concerned to conduct a joint PASS [HMR regulation 61(6)(a)]. 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 can 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 “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.”

#### 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 201, Schedule 12A paragraphs 28 to 32 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 “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 for review [HMR regulation 199(2)] as appropriate. 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 “The study may commence only when the written endorsement from the licensing authority has been issued.”
- [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 [HMR regulation 200(2)] (see VIII.A.1. for the definition of a substantial amendment).”
- [Paragraph 6] This is modified to “Upon completion of the study, 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)(3)].”
- Paragraphs 7 and 8 no longer apply 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 licensing authority”.
- [Paragraph 1] This is modified to “Within 60 days from submission of the draft protocol, the licensing authority 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(3)].”
- [Paragraph 2] This is modified to “If the study proves to be interventional, 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 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 must assess the amendments and inform the marketing authorisation holder of its endorsement or objection [HMR regulation 200(3)]. 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.”
- Paragraphs 3, 5 and 6 no longer apply to the licensing authority.

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

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

### 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 within 12 months of the end of data collection unless a written waiver has been granted [HMR regulation 201(2)(3)].”
- [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(4)].”
- [Paragraph 3] This is modified to “Following the review of the final study report, the licensing authority may recommend variation, suspension or revocation of the marketing authorisation.”
- Paragraphs 4, 5 and 6 do not apply to the licensing authority or UK MAHs.

### 3.10. GVP Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev 2)

- GVP Module VIII Addendum I no longer applies to the licensing authority and UK MAHs.

### 3.11. GVP Module IX – Signal management (Rev 1)

#### 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 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.

#### IX.A.1.1. General terminology

- Paragraph 4 under ‘Signal’ no longer applies to the licensing authority and UK MAHs.
- [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 the licensing authority and UK MAHs.

#### 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 no longer applies to UK MAHs.
- [Paragraph 3] This is modified to “Signals detected 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 licensing authority in accordance with the process outlined in IX.C.2..”
- [Paragraph 5] This is modified to “The marketing authorisation holder should collaborate with the licensing authority for the assessment of the signals by providing the additional information requested [HMR regulation 75(4)] (see IX.C.7.).”
- [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 UK web-portal established in accordance with regulation 203(1) [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 “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](mailto:SignalManagement@mhra.gov.uk). 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 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 6] This is modified to “The marketing authorisation holder should collaborate with the licensing authority in the assessment of the emerging safety issue [HMR regulation 75(4)].”
- [Paragraph 8] This is modified to “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 should be done in parallel to the licensing authority ([withdrawcancel@mhra.gov.uk](mailto:withdrawcancel@mhra.gov.uk)) in accordance with the requirements set out in HMR regulation 73(3) and (5A).”
- [Paragraph 9] This is modified to “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 should be notified to the licensing authority ([SignalManagement@mhra.gov.uk](mailto:SignalManagement@mhra.gov.uk)) in accordance with HMR regulation 75(2).”

## IX.C.3. Monitoring of EudraVigilance data

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

### IX.C.3.1. Principles for access

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

### IX.C.3.2. Periodicity of monitoring

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

### IX.C.3.3. Analysis of EudraVigilance data

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

#### 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”.
- [Paragraph 1] This is modified to “Where a marketing authorisation holder detects a new signal from any data source, it must validate it and must forthwith inform the licensing authority.”
- [Paragraph 2] This is modified to “For this purpose, signal validation by the marketing authorisation holder should include a thorough analysis of relevant data available to them (e.g. own database, literature, clinical trials) (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 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 licensing authority in relation to signals.”

##### 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.”

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

- [Paragraph 1] Explanatory note: UK MAHs should consult the list of UK reference dates published by the licensing authority in accordance with HMR regulation 193(7), as well as the list of European Union reference dates and frequency of submission of periodic safety update reports (EURD list), when deciding whether the submission of a separate standalone signal notification to the licensing authority is required.
- 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](mailto:SignalManagement@mhra.gov.uk).”

#### IX.C.4.3. Standalone signal notification

- [Paragraph 1] This is modified to “When a marketing authorisation holder, based on their assessment of a signal detected through any 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 and send it to the licensing authority using the mailbox [SignalManagement@mhra.gov.uk](mailto:SignalManagement@mhra.gov.uk).”

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

- The title of this section is modified to “Signal confirmation, prioritisation and analysis by the licensing authority”.
- [Paragraph 1] This is modified to “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.”
- Paragraphs 2, 3, 4, 6 and 7 no longer apply to the licensing authority and UK MAHs.
- The principles described in paragraph 5 continue to apply to the licensing authority.

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

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

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

- The title of this section is modified to “Recommendations on signals from the licensing authority”.
- [Paragraph 1] The text ‘PRAC recommendations’ is replaced with ‘licensing authority recommendations’. In addition, bullet points 7, 8 and 9 no longer apply to the licensing authority and UK MAHs.
- [Paragraph 2] This is modified to “Recommendations to provide additional data are communicated directly to concerned marketing authorisation holders by the licensing authority.” The text in relation to the role of the PRAC, the Committee for Medicinal Products for Human Use (CHMP) and the Co-ordination Group for Mutual Recognition and Decentralised procedures – Human (CMDh) no longer applies to the licensing authority and UK MAHs.
- Paragraph 3 no longer applies to the licensing authority and UK MAHs.

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

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

## IX.C.9. Transparency

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

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

- These figures no longer apply to the licensing authority and UK MAHs.

## 3.12. 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.

## 3.13. GVP Module X – Additional monitoring

### X.A. Introduction

- [Paragraph 2] The concept of additional monitoring has been transposed into the Human Medicines Regulations 2012 (HMR) as amended, regulation 202A, by virtue of the EU Exit Regulations.
- [Paragraph 3] This is modified to “As defined in HMR regulation 202A(1), the licensing authority must set up, maintain and make public a list of medicinal products 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 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

- [Paragraph 1] This is modified to “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

- [Paragraph 1] This is modified to "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."
- [Paragraph 2] This is modified to "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 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(6)."

#### 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.

### X.C.3.3. National competent authorities

- Bullet points 1, 2 and 4 no longer apply to the licensing authority.

### X.C.3.4. The Pharmacovigilance Risk Assessment Committee (PRAC)

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

## X.C.4. Creation and maintenance of the list

- This section is omitted to reduce repetition.

### X.C.4.1. Process for the creation of the list

- This section is omitted to reduce repetition.

### X.C.4.2. Process for the maintenance of the list

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

#### X.C.4.2.1. Inclusion of medicinal products in the list

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

### X.C.5. Black symbol and explanatory statements

- [Paragraph 1] This is modified to “For medicinal products included in the list, 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 (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 “Pursuant to HMR regulation 203(2)(e), the licensing authority will make publicly available the list of the names and active substances of all medicinal products approved in the UK subject to additional monitoring.”
- Paragraph 2 no longer applies to the licensing authority and UK MAHs.

### 3.14. GVP Module XV – Safety communication (Rev 1)

#### 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(3)]. 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

- The title of this section is modified to “Consistency of communication”.
- The principles of inter-authority communication no longer apply to the licensing authority. The text in this section is modified to “Where the licensing authority takes regulatory action on a particular safety concern, preparation of internal background communication material, such as lines-to-take, should be considered. Lines-to-take are documents prepared by the licensing authority to assist its staff, and those of any co-operating bodies as appropriate under embargo, in responding consistently to external enquiries or communicating a consistent message on a specific issue.”

#### 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) and Schedule 12A paragraph 11(g) apply to marketing authorisation holders. HMR Schedule 12A paragraph 15(d) applies to the licensing authority.”

### XV.C.1. Coordination of safety announcements in the EU

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

#### XV.C.1.1. Process for exchange and coordination of safety announcements

- Paragraphs 1, 2, 3 and 5 no longer apply to the licensing authority. For the avoidance of doubt, 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.

As a complement to the coordination of safety announcements, the licensing authority should interact with concerned stakeholders (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

- [Paragraph 1] This is modified to "There are situations where new safety information is to be published, or has been published, by a party other than the licensing authority or marketing authorisation holder (e.g. scientific journals, learned societies). Where necessary and after evaluation of the information, the licensing authority should consider the appropriateness of preparing a lines-to-take document or a safety announcement to address the information from the third party."
- [Paragraph 2] This is modified to "Furthermore, the licensing authority may become aware of safety announcements to be published by other regulatory authorities outside the UK. Again, the need for national lines-to-take or safety announcements should be considered, taking into account any relevant confidentiality agreements or embargoes on the information."

#### 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 be required to inform the licensing authority [HMR regulation 205(2)]. Informing the licensing authority at the same time as the public (i.e. without advance notice to the licensing authority) 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(3)]."
- [Paragraph 3] The legal basis for informing the licensing authority that a third party intends to issue communications that could potentially impact the risk-benefit balance of a medicinal product authorised in the UK and for sharing the content of the communications with the licensing authority can be found in HMR 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.2.1. Processing of DHPCs

- Paragraphs 2, 4, 5, 6 and 8 do not apply to the licensing authority and UK MAHs. For the avoidance of doubt, 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 (as published on the licensing authority’s website) and the guidance provided in the annotations in the template should be followed as appropriate.

For all relevant UK 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. The marketing authorisation holder should allow a minimum of two working days for comments during the review. However, whenever possible, more time should be allowed. The timing may be adapted according to the urgency of the situation.

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.”

- [Paragraph 10] The flow chart describing the processing of DHPCs in Figure XV.1. no longer applies to the licensing authority and UK MAHs.

### XV.C.2.2. Translation and dissemination of DHPCs

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

## GVP Annex II - Templates

- The templates for Direct Healthcare Professional Communication and the Communication Plan for Direct Healthcare Professional Communication in GVP Annex II no longer apply to UK MAHs. National templates will be made available on the licensing authority's website<sup>15</sup>.

### 3.15. GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)

#### 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 and 52 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

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

##### 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.

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<sup>15</sup> <https://www.gov.uk/government/publications/how-to-draft-a-direct-healthcare-professional-communication>

### XVI.C.1.3. Competent authorities in Member States

- The general principles described in this section continue to apply to the licensing authority.
- [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. In addition, the text in relation to centrally authorised products no longer applies to the licensing authority.
- Paragraphs 4, 6 and 9 no longer apply to the licensing authority.

### 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 regulations 203(2)(b)(c)].”

## 3.16. GVP Module XVI Addendum I – Educational materials

### XVI. Add I.1. Introduction

- [Paragraph 2] The role of the PRAC, the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) is no longer applicable to the development and distribution of educational materials in the UK. This paragraph 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 5 no longer applies to the licensing authority and UK MAHs.

### 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).”

## 4. Chapters on product- or population-specific considerations

### 4.1. Product- or Population-Specific Considerations I – Vaccines for prophylaxis against infectious diseases

#### 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.”

#### P.I.C.1.5. European Medicines Agency

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

#### P.I.C.2. Reporting of reactions and emerging safety issues

- [Paragraph 1] The communication of signals from EudraVigilance by marketing authorisation holders no longer applies to UK MAHs.
- Paragraph 3 no longer applies to the licensing authority and UK MAHs.
- [Paragraph 4] This is modified to “Where a quality defect is suspected, marketing authorisation holders should notify the licensing authority ([SignalManagement@mhra.gov.uk](mailto:SignalManagement@mhra.gov.uk)).”

#### P.I.C.4. Signal management

- [Paragraph 1] The text in relation to the role of the PRAC Rapporteur or Lead Member State in signal validation no longer applies to the licensing authority and UK MAHs.
- [Paragraph 2] The text in relation to the monitoring of data from EudraVigilance no longer applies to the licensing authority and UK MAHs.

#### 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 legal basis for the public summary of the RMP to be made publicly available by the licensing authority is described in HMR regulation 203(2)(d).

#### P.I.C.7. Vaccines intended for markets outside the EU

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

## 4.2. Product- or Population-Specific Considerations II – Biological medicinal products

### P.II.A. Introduction

- Paragraphs 9 and 10 no longer apply to the licensing authority and UK MAHs.

### 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

- Explanatory note: 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.5. Additional monitoring

- Explanatory note: The legal basis for the inclusion of biologicals in, and removal from, the UK list of medicinal products that are subject to additional monitoring is included in HMR regulations 202A(1)(b) and (5) respectively.

### P.II.C.1.1. Marketing authorisation holder and applicant in the EU

- The text “Medicinal products developed by means of one of the biotechnology processes listed in the Annex of Regulation (EC) No 726/2004, or fulfilling any other criteria of the Annex, shall be authorised in the EU through the centralised authorisation procedure” no longer applies to the licensing authority and UK MAHs.

### P.II.C.1.1.2. Reporting of adverse reactions and signal management

- [Paragraph 1] This is modified to “When reporting suspected adverse reactions, marketing authorisation holders must provide all available information on each individual case, including, for biologicals, the name and batch number(s) of the administered product [HMR Schedule 12A paragraph 20(4)(h)].

### 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 no longer applies to the licensing authority and UK MAHs.

##### P.II.C.1.3.1. Pharmacovigilance Risk Assessment Committee

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

#### P.II.C.2. Safety communication about biologicals in the EU

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

### 4.3. Product- or Population-Specific Considerations IV – Paediatric population

#### 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’, have been incorporated into the Human Medicines Regulations 2012 (HMR), with modifications, by virtue of the EU Exit Regulations.
- [Paragraph 6] This is modified to “This guidance should be read in conjunction with the Human Medicines Regulations 2012 Part 5 (Marketing Authorisations), in particular regulations 50A to 50F and 59, and Part 11 (Pharmacovigilance).”

#### P.IV.B.5. Signal management

- [Paragraph 2] The text in relation to monitoring data in the EudraVigilance database no longer applies to the licensing authority and UK MAHs.

#### P.IV.C.1.2. European Medicines Agency

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

##### P.IV.C.1.2.1. The Paediatric Committee (PDCO)

- The role of the PDCO no longer applies to the licensing authority and UK MAHs. The licensing authority will assess the content of paediatric investigation plans (PIP) for a medicinal product, 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 no longer applies to the licensing authority and UK MAHs.

#### 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] Explanatory note: The legal basis for requiring a paediatric investigation plan 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.

#### P.IV.C.6. Signal management within the EU regulatory network

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

### 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’ no longer apply to UK MAHs. National templates will be made available on the licensing authority’s website.

### 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.