SCHEDULES

[F1SCHEDULE 12A

Regulation 205A

Further provision as to the performance of pharmacovigilance activities

Textual Amendments

F1 Sch. 12A inserted (31.12.2020) by The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (S.I. 2019/775), reg. 1, **Sch. 6** (as amended by S.I. 2019/1385, reg. 1, **Sch. 1 para. 9** and S.I. 2020/1488, reg. 1, **Sch. 2 para. 192**); 2020 c. 1, **Sch. 5 para. 1(1)**

PART 1

Pharmacovigilance system master file

Structure of the pharmacovigilance system master file

1.—(1) The information in the pharmacovigilance system master file must be accurate and reflect the pharmacovigilance system in place.

(2) The holder may, where appropriate, use separate pharmacovigilance systems for different categories of medicinal products and if it does so, each such system must be described in a separate pharmacovigilance system master file.

(3) All medicinal products for which the holder obtained a UKMA(GB) in accordance with these Regulations must be covered by a pharmacovigilance system master file.

Content of the pharmacovigilance system master file

2. The pharmacovigilance system master file must, as a minimum, contain—

(a) the following information relating to the qualified person responsible for pharmacovigilance—

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

(ii) a summary curriculum vitae of the qualified person responsible for pharmacovigilance,

(iii) contact details of the qualified person for pharmacovigilance,

(iv) details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance, and

(v) responsibilities and contact details of the nominated person (where a person is nominated under regulation 182(2A));

(b) a description of the organisational structure of the holder, including the list of each site where one or more of the following pharmacovigilance activities are undertaken—

(i) individual case safety report collection and evaluation,

(ii) safety database case entry,

(iii) periodic safety update report production,

(iv) signal detection and analysis,

(v) risk management plan management,

(vi) pre and post-authorisation study management, and

(vii) management of safety variations to the terms of a UK marketing authorisation;

(c) a description of the location of, functionality of 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;

(d) a description of data handling and recording and of the process used for each of the following pharmacovigilance activities—

(i) the continuous monitoring of the risk-benefit balance of each medicinal product, the result of that monitoring and the decision-making process for taking appropriate measures,

(ii) operation of each risk management system and of the monitoring of the outcome of risk minimisation measures,

(iii) collection, assessment and reporting of individual case safety reports,

(iv) drafting and submission of periodic safety update reports, and

(v) procedures for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to healthcare professionals and the general public;

(e) a description of the quality system for the performance of pharmacovigilance activities, including—

(i) a description of—

(aa) the organisational structure for the performance of pharmacovigilance activities,

(bb) a summary description of the training concept, including a reference to the location of training files and qualifications records, and

(cc) instructions on critical processes,

(ii) a description of the record management system referred to in paragraph 12, including the location of the documents used for pharmacovigilance activities,

(iii) a description of the system for monitoring the performance of the pharmacovigilance system; and

(f) where applicable, a description of the activities or services subcontracted by the holder.

Content of the Annex to the pharmacovigilance system master file

3. The pharmacovigilance system master file must have an Annex containing the following documents—

(a) a list of medicinal products covered by the pharmacovigilance system master file, including the name of each medicinal product, the international non-proprietary name

(INN) of each active substance and the countries other than the United Kingdom in which the products covered are authorised to be marketed;

(b) a list of written policies and procedures for the purpose of complying with Part 11 of these Regulations;

(c) the list of any sub-contracts falling within paragraph 6(1);

(d) a list of the tasks that have been delegated by the qualified person for pharmacovigilance;

(e) a list of all scheduled and completed audits;

(f) where applicable, a list of the performance indicators that support the quality system for pharmacovigilance specified in paragraph 2(e);

(g) where applicable, a list of other pharmacovigilance system master files held by the same holder; and

(h) a logbook containing a record of any alteration of the content of the pharmacovigilance system master file made within the preceding 5 year period, except any alteration of the content that is specified in of paragraph 2(a)(ii) to (iv) or this paragraph.

Maintenance of the pharmacovigilance system master file

4.—(1) The holder must keep the pharmacovigilance system master file up to date and, where necessary, revise it to take account of experience gained, and of technical and scientific progress.

(2) The pharmacovigilance system master file and its Annex must be subject to version control and, in particular, must indicate the date when it was last updated by the holder.

(3) Any deviations from the pharmacovigilance procedures, their impact and their management must be documented in the pharmacovigilance system master file until resolved.

Form of the documents contained in the pharmacovigilance system master file

5.—(1) The pharmacovigilance system master file documents must be complete and legible.

(2) Subject to sub-paragraph (1), in the pharmacovigilance system master file—

(a) where appropriate, information may be provided in the form of charts or flow diagrams;

(b) all documents must be indexed and archived so as to ensure their accurate and ready retrieval throughout the period for record-keeping; and

(c) the particulars and documents may be presented in modules in accordance with the system delineated in detail in the guidance on good pharmacovigilance practices which applies by virtue of regulation 205B.

(3) The pharmacovigilance system master file may be stored in electronic form provided that the media used for storage remain readable over time, and a clearly arranged printed copy can be made available for audits and inspections.

Subcontracting

6.—(1) The holder may subcontract certain activities of the pharmacovigilance system to third parties, but if it does so it must nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.

(2) The holder must draw up a list of the existing subcontracts between it and the third parties referred to in sub-paragraph (1), specifying each product and each country concerned.

Availability and location of the pharmacovigilance system master file

7.—(2) The holder must ensure that the qualified person and nominated person (where a person is nominated under regulation 182(2A)) for pharmacovigilance have permanent access to the pharmacovigilance system master file.

(3) For the purposes of regulation 182(2)(b), the licensing authority may limit its request to specific parts or modules of the pharmacovigilance system master file and the holder is to bear the costs of submitting the copy of the pharmacovigilance system master file.

(4) The licensing authority may request the holder to submit a copy of the logbook referred to in paragraph 3(h) at regular intervals.

PART 2

Minimum requirements for the quality systems for the performance of pharmacovigilance activities by the licensing authority and holders

Quality system

8.—(1) Any holder, and the licensing authority, must establish and use a quality system that is adequate and effective for the performance of their pharmacovigilance activities.

(2) The quality system must cover organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management.

(3) The quality system must be based on all of the following activities—

(a) quality planning: establishing structures and planning integrated and consistent processes;

(b) quality adherence, namely carrying out tasks and responsibilities in accordance with quality requirements;

(c) quality control and assurance, namely monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; and

(d) quality improvements, namely correcting and improving the structures and processes where necessary.

(4) All elements, requirements and provisions adopted for the quality system must be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.

(5) All persons involved in the procedures and processes of the quality systems established by the licensing authority for the performance of pharmacovigilance activities shall be responsible for the good functioning of those quality systems, and must ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system.

Performance indicators

9.—(1) The holder and the licensing authority may use performance indicators to continuously monitor the good performance of pharmacovigilance activities.

(2) The licensing authority may publish a list of performance indicators.

PART 3

Minimum requirements for the quality systems for the performance of pharmacovigilance activities by holders

Management of human resources

10.—(1) The holder must have sufficient competent and appropriately qualified and trained personnel available for the performance of pharmacovigilance activities.

(2) For the purposes of sub-paragraph (1), the holder must—

(a) ensure that the qualified person responsible for pharmacovigilance has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities; and

(b) where the qualified person has not completed basic medical training in accordance with Article 24 of Directive 2005/36/EC of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications, ensure that the qualified person responsible for pharmacovigilance is assisted by a medically trained person, with such assistance being duly documented.

(3) The duties of the managerial and supervisory staff, including the qualified person responsible for pharmacovigilance, must be defined in job descriptions and their hierarchical relationships must be defined in an organisational chart.

(4) The holder must ensure that the qualified person responsible for pharmacovigilance has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the holder.

(5) All personnel involved in the performance of pharmacovigilance activities must receive initial and continued training in relation to their role and responsibilities, and the holder must keep training plans and records for documenting, maintaining and developing the competences of personnel and make them available for audit or inspection.

(6) The holder must provide appropriate instructions on the processes to be used in case of urgency, including business continuity.

Compliance management

11.—(1) Specific quality system procedures and processes must be in place in order to ensure the following—

(a) the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the holder;

(b) the scientific evaluation by the holder of all information on the risks of medicinal products, as referred to in regulation 182(4)(a);

(c) the submission of accurate and verifiable data on serious and non-serious adverse reactions to the licensing authority within the time limits provided for in regulation 188(1)(a) or (b);

(d) the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions;

(e) effective communication by the holder with the licensing authority, including communication on—

(i) new risks or changed risks,

(ii) the pharmacovigilance system master file,

(iii) risk management systems,

(iv) risk minimisation measures,

(v) periodic safety update reports,

(vi) corrective and preventive actions, and

(vii) post-authorisation studies;

(f) the update of product information by the 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 holder of information published on that web-portal; and

(g) appropriate communication by the holder of relevant safety information to healthcare professionals and patients.

(2) Where a holder has subcontracted some of its pharmacovigilance tasks, it must retain responsibility for ensuring that an effective quality system is applied in relation to those tasks.

Record management and data retention

12.—(1) A holder must record all pharmacovigilance information and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information.

(2) A holder must put in place a record management system for all documents used for pharmacovigilance activities that ensures—

(a) the retrievability of those documents; and

(b) the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

(3) A holder must establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

(4) A holder must arrange for the elements referred to in sub-paragraph (2) to be kept for at least five years, beginning with the day after the system as described in the pharmacovigilance system master file has been formally terminated by the holder.

(5) Pharmacovigilance data and documents relating to individual authorised medicinal products must be retained as long as the product is authorised and for at least 10 years, beginning with the date on which the UKMA(GB) ceased to exist.

Audit

13.—(1) Risk-based audits of the quality system must be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in paragraphs 8, 10, 11 and 12, and to determine its effectiveness.

(2) The audits referred to in sub-paragraph (1) must be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited.

(3) Following a risk-based audit—

(a) any corrective action, including a follow-up audit of deficiencies, must be taken where necessary;

(b) a report on the results of the audit must be drawn up for each audit and follow-up audit;

(c) the audit report must be sent to the management responsible for the matters audited; and

(d) the dates and results of audits and follow-up audits must be documented in accordance with regulation 184(1)(b).

PART 4

Minimum requirements for the quality systems for the performance of pharmacovigilance activities by the licensing authority

Management of human resources

14.—(1) The licensing authority must have sufficient competent and appropriately qualified and trained personnel available for the performance of pharmacovigilance activities: the organisational structures and the distribution of tasks and responsibilities must be clear and, to the extent necessary, accessible.

(2) Named contact points in the licensing authority for pharmacovigilance activities must be established.

(3) The licensing authority must ensure that—

(a) all of its personnel involved in the performance of pharmacovigilance activities receive initial and continued training;

(b) it keeps training plans and records for documenting, maintaining and developing the competences of personnel; and

(c) such plans and records are available for audit.

(4) The licensing authority must ensure that it provides to its personnel performing pharmacovigilance activities appropriate instructions on the processes to be used in case of urgency, including business continuity.

Compliance management

15. The licensing authority must establish specific procedures and processes in order to achieve the following objectives—

(a) ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted;

(b) ensuring the assessment of pharmacovigilance data and its processing within the timelines provided for in Part 11 of these Regulations;

(c) ensuring independence in the performance of pharmacovigilance activities;

(d) 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; and

(e) conducting inspections, including pre-authorisation inspections.

Record management and data retention

16.—(1) The licensing authority must—

(a) record all pharmacovigilance information, and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information; and

(b) put in place a record management system for all documents used for pharmacovigilance activities that ensures—

(i) the retrievability of those documents, and

(ii) the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

(2) The licensing authority must arrange for the essential documents describing their pharmacovigilance system to be kept for at least five years, such period beginning with the day after the system has been formally terminated.

(3) Pharmacovigilance data and documents relating to individual authorised medicinal products must be retained by the licensing authority for as long as the product is authorised and for at least 10 years, such period beginning with the day after the UKMA(GB) has expired.

Audit

17.—(1) Risk-based audits of the quality system must be performed by the licensing authority at regular intervals to ensure that the quality system complies with the requirements set out in paragraphs 8, 14, 15 and 16, and to ensure its effectiveness.

(2) Following a risk-based audit—

(a) any corrective action, including a follow-up audit of deficiencies, must be taken where necessary;

(b) a report on the results of the audit must be drawn up for each audit and follow-up audit;

(c) the audit report must be sent to the management responsible for the matters audited; and

(d) the dates and results of audits and follow-up audits must be documented.

PART 5

Use of terminology, formats and standards

Use of internationally agreed terminology, formats and standards

18. The licensing authority may publish a list of which of the internationally agreed—

(a) terminology; and

(b) 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.

PART 6

Transmission of reports of suspected adverse reactions

Individual case safety reports

19. Individual case safety reports must be used for reporting to the licensing authority suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time.

Content of the individual case safety report

20.—(1) Holders must—

(a) ensure that individual case safety reports are as complete as possible; and

(b) communicate the updates of those reports to the licensing authority in an accurate and reliable manner.

(2) In the case of expedited reporting, the individual case safety report must include at least an identifiable reporter, an identifiable patient, one suspected adverse reaction and any medicinal product concerned.

(3) Holders and the licensing authority must record the details necessary for obtaining follow-up information on individual case safety reports and such reports must be adequately documented.

(4) When reporting suspected adverse reactions, holders must provide all available information on each individual case, including—

(a) administrative information, namely—

(i) report type, date and a worldwide unique case identification number as well as unique sender identification and sender type,

(ii) the date on which the report was first received from the source and the date of receipt of the most recent information, using a precise date, and

(iii) other case identifiers and their sources, as well as references to additional available documents held by the sender of the individual case safety report, where applicable;

(b) literature reference in accordance with the 'Vancouver style' as developed by the International Committee of Medical Journal Editors for adverse reactions reported in the worldwide literature, including a comprehensive English summary of the article;

(c) study type, study name and the sponsor's study number or study registration number for reports from studies not covered by the Clinical Trials Regulations;

(d) information on any primary source, namely information identifying the reporter, including country of residence and professional qualifications;

(e) information identifying the patient (and parent in the case of a parent-child report), including age at the time of the onset of the first reaction, age group, gestation period when reaction or event was observed in the foetus, weight, height or gender, last menstrual date and, where relevant, gestation period at time of exposure;

(f) relevant medical history and concurrent conditions;

(g) the name of any medicinal product suspected to be related to the occurrence of the adverse reaction, including interacting medicinal products or, where the name is not known, any active substance and any other characteristics that allow for the identification of a medicinal product, including—

(i) the name of the holder, UK marketing authorisation number, pharmaceutical form and each (parent) route of administration,

(ii) any indication for use in the case, dose administered, start date and end date of administration,

(iii) actions taken with any medicinal product, and

(iv) effect of the dechallenge and rechallenge for suspect medicinal products;

(h) for a biological medicinal product, the batch number;

(i) concomitant medicinal products, identified in accordance with paragraph (g), which are not suspected to be related to the occurrence of the adverse reaction and past-medical drug therapy for the patient (and for the parent), where applicable;

(j) information on any suspected adverse reaction, including—

(i) start date and end date of any suspected adverse reaction or duration,

(ii) seriousness,

(iii) outcome of any suspected adverse reaction at the time of last observation,

(iv) time intervals between suspect medicinal product administration and start of any adverse reaction,

(v) the original reporter's words or short phrases used to describe any reaction, and

(vi) country of occurrence of the suspected adverse reaction;

(k) results of tests and procedures relevant to the investigation of the patient;

(l) in the event of death of the patient, date and reported cause of death, including autopsy-determined causes;

(m) a case narrative, where possible, providing all relevant information for individual cases with the exception of non-serious adverse reactions; and

(n) reasons for nullifying or amending an individual case safety report.

(5) For the purposes of—

(a) sub-paragraph (4)(b), upon request of the licensing authority, the 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;

(b) sub-paragraph (4)(h), a follow-up procedure must be in place to obtain the batch number where it is not indicated in the initial report;

(c) sub-paragraph (4)(m), the information must be presented in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained: any relevant autopsy or post-mortem findings must also be summarised in the narrative.

(6) Suspected adverse reactions must be reported in English.

Format of electronic transmission of suspected adverse reactions

21. Holders must use the formats and terminology specified in the list published under paragraph 18 for the electronic transmission of suspected adverse reactions, if the licensing authority has published a list under that paragraph.

PART 7

Risk management plans

Content of the risk management plan

22.—(1) The risk management plan established by the holder must contain the following elements—

(a) an identification or characterisation of the safety profile of the medicinal product concerned;

(b) an indication of how to characterise further the safety profile of the medicinal product(s) concerned;

(c) a documentation of measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those measures; and

(d) a documentation of post-authorisation obligations that have been imposed as a condition of the UKMA(GB).

(2) Medicinal products may, where appropriate be subject to the same risk management plan if they—

(a) contain the same active substance; and

(b) belong to the same holder.

(3) Where a risk management plan refers to post-authorisation studies—

(a) it must indicate whether those studies are initiated, managed or financed by the holder voluntarily, or pursuant to obligations imposed by the licensing authority or an equivalent authority to the licensing authority in another country; and

(b) all post-authorisation obligations must be listed in the summary of the risk management plan referred to in paragraph 23, together with a timeframe for meeting those obligations.

Summary of the risk management plan

23.—(1) The summary of the risk management plan to be made publicly available in accordance with regulation 203(2)(d) (obligations on licensing authority in relation to national medicines web-portal) must include key elements of the risk management plan with a specific focus on risk minimisation activities and, with regard to the safety specification of the medicinal product concerned, important information on potential and identified risks as well as missing information.

(2) Where a risk management plan concerns more than one medicinal product, a separate summary of the risk management plan must be provided by holders for each medicinal product.

Updates of the risk management plan

24.—(1) Subject to sub-paragraph (2), where the holder updates a risk management plan, it must submit the updated risk management plan to the licensing authority.

(2) If the licensing authority agrees, the holder may submit only the modules concerned by the update.

(3) If necessary, the holder must provide the licensing authority with an updated summary of the risk management plan.

(4) Each submission of the risk management plan must—

(a) have a distinct version number; and

(b) be dated.

Format of the risk management plan

25. The risk management plan must be in the following format—

(a) Part I: product overview;

(b) Part II: safety specification consisting of—

(i) Module SI: epidemiology of each indication and each target population,

(ii) Module SII: non-clinical part of the safety specification,

(iii) Module SIII: clinical trial exposure,

(iv) Module SIV: populations not studied in clinical trials,

(v) Module SV: post-authorisation experience,

(vi) Module SVI: additional EU requirements for the safety specification,

(vii) Module SVII: identified and potential risks, and

(viii) Module SVIII: summary of the safety concerns;

(c) Part III: pharmacovigilance plan, including post-authorisation safety studies;

(d) Part IV: plans for post-authorisation efficacy studies;

(e) Part V: risk minimisation measures, including evaluation of the effectiveness of risk minimisation activities;

(f) Part VI: summary of the risk management plan; and

(g) Part VII: annexes.

PART 8

Periodic safety update reports

Content of periodic safety update reports

26.—(1) The periodic safety update report ("PSUR") must—

(a) be based on all available data; and

(b) focus on new information which has emerged since the data lock point of the last PSUR.

(2) The PSUR must provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions.

(3) The estimate of exposure referred to in sub-paragraph (2) must be accompanied by a qualitative and quantitative analysis of actual use, which must indicate, where appropriate, how actual use differs from the indicated use based on all data available to the holder, including the results of observational or drug utilisation studies.

(4) The PSUR must contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk–benefit assessment.

(5) Where any conditions are imposed under regulation 59(4A) (conditions in relation to UK marketing authorisations to which paediatric specific provisions apply) or 59(4D) (conditions in relation to UK marketing authorisations for advanced therapy medicinal products), the PSUR must also include an assessment of the effectiveness of any risk management system, and the results of any studies performed, in order to comply with those conditions.

(6) Subject to sub-paragraph (7), holders are not required to include systematically detailed listings of individual cases, including case narratives, in the PSUR.

(7) Holders must provide case narratives in the relevant risk evaluation section of the PSUR where integral to the scientific analysis of a signal or safety concern in the relevant risk evaluation section.

(8) Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the holder must draw conclusions in the PSUR as to the need for changes or actions, including implications for the approved summary of product characteristics for each product for which the PSUR is submitted.

(9) Unless otherwise agreed with the licensing authority, a single PSUR must be prepared for all medicinal products which—

(a) contain the same active substance; and

(b) are authorised for the same holder,

and sub-paragraph (10) applies to that single PSUR.

(10) Where this sub-paragraph applies—

(a) the PSUR must cover all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures; and

(b) where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen must be presented in a separate section of the PSUR, with any safety concerns addressed accordingly.

(11) Unless otherwise agreed with the licensing authority, if the substance that is the subject of the PSUR is also authorised as a component of a fixed combination medicinal product, the holder must either—

(a) submit a separate PSUR for the combination of active substances authorised for the same holder, with cross-references to each relevant single-substance PSUR; or

(b) provide the combination data within one of the single-substance PSURs.

Format of periodic safety update reports

27.—(1) Electronic PSURs must be submitted in the following format—

(a) Part I: title page including signature;

(b) Part II: executive summary; and

(c) Part III: table of contents which contains—

(i) introduction,

(ii) worldwide marketing authorisation status,

(iii) actions taken in the reporting interval for safety reasons,

(iv) changes to reference safety information,

(v) estimated exposure and use patterns—

(aa) cumulative subject exposure in clinical trials,

(bb) cumulative and interval patient exposure from marketing experience,

(vi) data in summary tabulations—

(aa) reference information,

(bb) cumulative summary tabulations of serious adverse events in clinical trials,

(cc) cumulative and interval summary tabulations from post-marketing data sources,

(vii) summaries of significant findings from clinical trials during the reporting interval—

(aa) completed clinical trials,

(bb) ongoing clinical trials,

(cc) long-term follow-up,

(dd) other therapeutic use of medicinal product,

(ee) new safety data related to fixed combination therapies,

(viii) findings from non-interventional studies,

(ix) information from other clinical trials and sources,

(x) non-clinical data,

(xi) literature,

(xii) other periodic reports,

(xiii) lack of efficacy in controlled clinical trials,

(xiv) late-breaking information,

(xv) overview on signals: new, ongoing or closed,

(xvi) signal and risk evaluation—

(aa) summaries of safety concerns,

(bb) signal evaluation,

(cc) evaluation of risks and new information,

(dd) characterisation of risks, and

(ee) effectiveness of risk minimisation (if applicable),

(xvii) benefit evaluation—

(aa) important baseline efficacy and effectiveness information,

(bb) newly identified information on efficacy and effectiveness, and

(cc) characterisation of benefits,

(xviii) integrated benefit-risk analysis for authorised indications—

(aa) benefit-risk context: medical need and important alternatives, and

(bb) benefit-risk analysis evaluation,

(xix) conclusions and actions, and

(xx) appendices to the PSUR.

(2) In this paragraph, "signal evaluation" means the process of further evaluating a validated signal taking into account all available evidence, to determine whether there are new risks causally associated with the active substance or medicinal product, or whether known risks have changed, and that process—

(a) may include non-clinical and clinical data; and

(b) must be as comprehensive as possible regarding the sources of information used for that process.

PART 9

Post-authorisation safety studies

Scope and interpretation

28.—(1) This Part applies to non-interventional post-authorisation safety studies initiated, managed or financed by a holder under obligations imposed under regulation 59 or 61 (conditions of UK marketing authorisation).

(2) In this Part—

"start of data collection" means the date on which information on the first study subject is first recorded in the study dataset or, in the case of the secondary use of data, the date on which the data extraction starts; and

"end of data collection" means the date on which the analytical dataset is completely available.

Obligations as to post-authorisation safety studies

29.—(1) The holder must submit in English—

(a) the study protocol; and

(b) the abstract of the final study report and the final study report.

(2) The holder must ensure that—

(a) all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information;

(b) the confidentiality of the records of the study subjects remains protected; and

(c) the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

(3) The licensing authority may publish appropriate templates for the protocol, abstract and final study report.

Format of the study protocol

30. The study protocol for a non-interventional post-authorisation safety studies must be submitted in the following format—

(a) title: informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version;

(b) name of holder;

(c) responsible parties including a list of all collaborating institutions and other relevant study sites.

(d) abstract, which must consist of a stand-alone summary of the study protocol, including the following subsections—

(i) title with subtitles including version and date of the protocol and name and affiliation of the main author,

(ii) rationale and background,

(iii) research question and objectives,

(iv) study design,

(v) population,

(vi) variables,

(vii) data sources,

(viii) study size,

(ix) data analysis, and

(x) milestones;

(e) amendments and updates, namely any substantial amendment and update to the study protocol after the start of data collection, including a justification for the amendment or update, the date of the change, and a reference to the section of the protocol where the change has been made.

(f) milestones, namely a table with planned dates for the following milestones—

(i) start of data collection,

(ii) end of data collection,

(iii) any study progress report as referred to in regulation 198(2),

(iv) any interim report of study results, if applicable, and

(v) final report of study results;

(g) rationale and background, namely a description of any safety hazard, the safety profile or the risk management measures that led to the study being imposed as an obligation for a UKMA(GB);

(h) research question and objectives in accordance with the decision of the licensing authority in imposing the study as an obligation;

(i) research methods, namely a description of the research methods, including—

(i) study design,

(ii) setting, namely the study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria: where any sampling from a source population is undertaken, a description of the source population and details of sampling methods must be provided and where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies must be explained,

(iii) variables,

(iv) data sources, namely strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives: where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data must be reported and in the case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators must be described,

(v) study size, namely any projected study size, precision sought for study estimates and any calculation of the study size that can minimally detect a pre-specified risk with a pre-specified interpretative power,

(vi) data management,

(vii) data analysis,

(viii) quality control, and

(ix) limitations of the research methods;

(j) protection of human subjects, namely safeguards in order to comply with national requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies;

(k) management and reporting of adverse events or adverse reactions and other medically important events while the study is being conducted;

(l) plans for disseminating and communicating study results; and

(m) references.

Format of the abstract of the final study report

31. The abstract of the final study report for a non-interventional post-authorisation safety studies must be submitted in the following format—

(a) title, with subtitles including date of the abstract and name and affiliation of main author;

(b) keywords (not more than five keywords indicating the main study characteristics);

(c) rationale and background;

(d) research question and objectives;

(e) study design;

(f) setting;

(g) subjects and study size, including dropouts;

(h) variables and data sources;

(i) results;

(j) discussion (including, where relevant, an evaluation of the impact of study results on the risk–benefit balance of the product);

(k) name of holder; and

(l) names and affiliations of principal investigators.

Format of the final study report

32. The final study report for a non-interventional post-authorisation safety studies must be submitted in the following format—

(a) title, including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of the main author;

(b) abstract, namely a stand-alone summary referred to in paragraph 31;

(c) name and address of the holder;

(d) investigators, namely the names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators, and list of all collaborating primary institutions and other relevant study sites;

(e) milestones, namely the dates for the following milestones—

(i) start of data collection (planned and actual dates),

(ii) end of data collection (planned and actual dates),

(iii) study progress reports,

(iv) interim reports of study results, where applicable,

(v) final report of study results (planned and actual date), and

(vi) any other important milestone applicable to the study, including date of study registration in the electronic study register

(f) rationale and background, namely a description of the safety concerns that led to the study being initiated, and critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill;

(g) research question and objectives;

(h) amendments and updates to the protocol, namely a list of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update;

(i) research methods, namely—

(i) study design: key elements of the study design and rationale for this choice,

(ii) setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection: in the case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale,

(iii) subjects: any source population and eligibility criteria for study subjects. Sources and methods for selection of participants shall be provided, including, where relevant, methods for case ascertainment, as well as number of and reasons for dropouts,

(iv) variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions: diagnostic criteria shall be provided, where applicable,

(v) data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement; if the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data must be reported and in the case of a systematic

review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators,

(vi) bias,

(vii) study size: study size, rationale for any study size calculation and any method for attaining projected study size,

(viii) data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why,

(ix) statistical methods: description of the following items—

(aa) main summary measures,

(bb) all statistical methods applied to the study,

(cc) any methods used to examine subgroups and interactions,

(dd) how missing data were addressed,

(ee) any sensitivity analyses, and

(ff) any amendment to the plan of data analysis included in the study protocol, with rationale for the change, and

(x) quality control: mechanisms to ensure data quality and integrity;

(j) results: comprising the following subsections—

(i) participants, namely numbers of study subjects at each stage of study: in the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage,

(ii) descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data. In the case of a systematic review or meta-analysis, characteristics of each study from which data were extracted,

(iii) outcome data: numbers of study subjects across categories of main outcomes,

(iv) main result: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision and where relevant, estimates of relative risk must be translated into absolute risk for a meaningful time period,

(v) other analyses, and

(vi) adverse events and adverse reactions;

(k) discussion which must include—

(i) key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant, the impact of the results on the risk–benefit balance of the product,

(ii) limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them, sources of potential bias and imprecision, and validation of the events; both the direction and magnitude of potential biases must be discussed,

(iii) interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence, and

(iv) generalisability; and

(l) references.**]**

Changes to legislation:
There are currently no known outstanding effects for the The Human Medicines Regulations 2012, SCHEDULE 12A.