

Notes for applicants and holders of a Manufacturer's Licence

MHRA Guidance Note 5



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1 Introduction

- 1.1 This Guidance Note has been published to assist applicants and holders of a Manufacturer's Licence (MIA) or Manufacturer's "Specials" Licence (MS) and outline the key obligations for maintaining the licence.¹ For more in-depth guidance, please refer to the Rules and Guidance for Pharmaceutical Manufacturers and Distributors ("The Orange Guide") available from Pharmaceutical Press:
<http://www.pharmpress.com/product/9780857111029/orangeguide>
- 1.2 MHRA is responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe. MHRA's primary aim is to safeguard public health through a system of regulation. Pharmaceutical manufacturers and distributors operating in the UK marketplace are subject to a system of licensing and inspection, which ensures that licensed medicinal products conform to internationally agreed standards, and that those medicines are manufactured, stored and distributed in compliance with the required regulatory standards.
- 1.3 Before a medicine can be marketed or sold in the UK, a number of licences are required. The companies that are involved in all stages of the manufacture and distribution of the product need to have the relevant licence for the activity in question (Manufacturer's and/or Wholesale Dealer's Licences).
- 1.4 UK legislation in respect of medicinal products is in accordance with European Community Directives 2001/83/EC and 2003/94/EC. These products must, unless exempt, have marketing authorisations before they are placed on the market, and the manufacturer or importer (where import is from a third country) must hold an appropriate manufacturing authorisation. In the UK, this manufacturing authorisation is a "Manufacturer's Licence" (MIA), which is a requirement under regulation 17 of the Human Medicines Regulations 2012 [SI 2012/1916]. The single market extends additionally to members of the European Economic Area, i.e. Member States of the European Community plus Norway, Iceland and Liechtenstein.
- 1.5 The regulation of medicines on the UK market is undertaken by MHRA in accordance with the Human Medicines Regulations 2012.
- 1.6 For the manufacture or assembly of unlicensed medicinal products which are exempt from marketing authorisation requirements ("specials") the appropriate authorisation is a Manufacturer's "Specials" Licence. For guidance on the particular conditions relating to Manufacturer's "Specials" Licences please refer to MHRA Guidance Note 14.
- 1.7 The manufacture and distribution of veterinary medicinal products for animal use is subject to separate legislation. Further advice should be sought from the Veterinary Medicines Directorate (VMD) of DEFRA.

¹ This Guidance Note provides guidance on the law covering the manufacture, assembly and importation of medicinal products. The words "must" or "may" have been used to indicate legal requirements and the words "should" or "could" have been used to indicate guidance or recommendations.

- 1.8 The Licensing Authority, for the purposes of the Human Medicines Regulation 2012 and this Guidance Note refers to the UK Ministers² designated by the Regulations, acting either alone or jointly. MHRA is the Government body set up to discharge the responsibilities of the Licensing Authority, under powers delegated by those Ministers.

2 “Manufacturer’s Licence” and “import from a third country”

- 2.1 A Manufacturer’s Licence (MIA) may be granted for the manufacture and assembly of medicinal products, or just for assembly. The Manufacturer’s Licence also covers the activity of import from a third country. The Manufacturer’s Licence may be granted for the following activities:

Manufacture - in relation to a medicinal product, includes any process carried out in the course of making the product, but does not include dissolving or dispersing the product in, or diluting or mixing it with, some other substance used as a vehicle for the purpose of administering it;

A Manufacturer’s Licence is required for both total and partial manufacture, the various processes of dividing up, packaging or presentation and for import from a third country. However, such a licence is not required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, **solely** for retail supply, by or under the supervision of a pharmacist in a registered pharmacy or hospital.

And/or

Assembly - in relation to a medicinal product, means enclosing the product (with or without other medicinal products of the same description) in a container which is labelled before the product is sold or supplied, or, where the product is already enclosed in the container in which it is to be sold or supplied, labelling the container before the product is sold or supplied.

The over-labelling of medicinal products is an assembly activity and is therefore licensable.

Import from a third country - means import from any country other than an EEA State.

Export to a third country - a Manufacturer’s Licence is required for the manufacture of medicinal products intended for export to a third country.

Batch certification - in relation to medicinal products, concerns the activities conducted by a Qualified Person, in determining that a batch of a finished medicinal product is certified within the EEA before release for sale or supply in

² The Secretary of State and the Minister for Health, Social Services and Public Safety.

accordance with the requirements of the marketing authorisation. MHRA may issue a Manufacturer's Licence solely for the purpose of batch certification to authorise the holder to certify and release batches of products for which they hold the marketing authorisation, where the medicinal product has been manufactured by a contract manufacturer. The QP named on the Manufacturer's Licence granted solely for the purpose of batch certification may either take responsibility for all manufacturing stages conducted by the contract manufacturer or may take account of the confirmation of the batch by the contract manufacturer's QP.

- 2.2 A Manufacturer's Licence holder may store and distribute any medicinal product manufactured or assembled pursuant to their licence, without the need for an additional Wholesale Dealer's Licence. However certain obligations must be complied with - see Section 4.

3 How to apply for a licence

- 3.1 Application forms for a Manufacturer's Licence (MIA) or for a Manufacturer's "Specials" Licence (MS) are available from MHRA's website: <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Informationforlicenceapplicants/Licenceapplicationforms/Wholesaledealerslicencesapplicationforms/index.htm>
- 3.2 An application for a Manufacturer's Licence (MIA) or for a Manufacturer's "Specials" Licence (MS) should be accompanied by a Site Master File (SMF). This should contain specific and factual information about the production and/or control of the pharmaceutical operations to be carried out. Guidance on what information should be included in the SMF and a worked example for reference purposes can be obtained on request from the good manufacturing practice Inspectorate.
- 3.3 The Licensing Authority will only issue a Manufacturer's Licence or Manufacturer's "Specials" Licence when it is satisfied, following an inspection of the site, that the information contained in the application is accurate and in compliance with the requirements of the legislation.
- 3.4 When appropriate, the Licensing Authority may refuse to grant the licence or may grant a licence otherwise than as applied for. In such cases the Licensing Authority will notify the applicant of its proposals. The notification will set out the reasons for its proposals and give the applicant a period of not less than 28 days to respond.
- 3.5 Once granted, any changes to the information shown on the licence must be submitted to the Licensing Authority for prior approval. This should be done by submitting a variation application. Variation application forms can be found at the link above.

4 Manufacturers' and importers' obligations

- 4.1 The holder of a Manufacturer's Licence must comply with certain conditions in relation to the manufacture, assembly and importation of medicinal products. These conditions are set out in regulations 37- 41 of the Human Medicines Regulations 2012 ("the Regulations") and include compliance with the principles and guidelines of good manufacturing practice. See Section 5.
- 4.2 In addition, where the Manufacturer's Licence holder distributes the medicinal product manufactured or assembled in accordance with the Manufacturer's Licence they must comply with the conditions set out in regulations 43 – 45 of the Regulations. These include compliance with the EU Guidelines on Good Distribution Practice (GDP) of Medicinal Products for Human Use (2013/C 343/01):
<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF>
- 4.3 See Appendix 1 for a description of the conditions and provisions of the licence.

5 Compliance with good manufacturing practice (GMP)

- 5.1 GMP is defined as "*the part of Quality Assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use.*" The principles and guidelines for GMP are set out in Directive 2003/94/EC and Directive 2001/83/EC. Compliance with these principles and guidelines is mandatory within the European Economic Area. The EU guide to good manufacturing practice provides interpretation of the principles and guidelines and these in turn are supplemented by a series of annexes which modify or augment the detailed guidelines for certain types of product, or provide more specific guidance on a particular topic: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
- 5.2 Manufacturers, assemblers and importers of licensed medicinal products must demonstrate compliance with the European Commission's 'Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products' and future updates. This also applies to 'specials' and unlicensed medicinal products for export to a third country in accordance with The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations [SI 2003/1680]. See MHRA's interim guidance on minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use available from MHRA's website: <http://www.mhra.gov.uk/Howweregulate/Medicines/Importingandexportingmedicines/TSERegulations/index.htm>
- 5.3 Both the principles and the detailed guidelines of EU GMP are set out in the MHRA publication *Rules and Guidance for Pharmaceutical Manufacturers and Distributors* usually known as "The Orange Guide." This is available from Pharmaceutical Press. <http://www.pharmpress.com/product/9780857111029/orangeguide>

5.4 To comply with GMP, holders of a Manufacturer's Licence (MIA) must:

- establish and implement an effective pharmaceutical quality assurance system;
- have competent and appropriately qualified personnel, sufficient in number to achieve the pharmaceutical quality objective(s);
- define the duties of managerial and supervisory staff responsible for implementing and operating GMP in their job descriptions;
- give personnel sufficient authority and training to meet the pharmaceutical quality objective(s);
- institute and maintain hygiene programmes relating to health, hygiene and clothing;
- provide and maintain premises and equipment appropriate to the intended operations;
- have system(s) of documentation covering all the processes and specifications covering the various operations. Batch documentation must be retained at least one year after the expiry date of the batch to which it relates;
- provide and maintain an independent quality control department, under the authority of the person nominated as responsible for overall quality control;
- retain records and samples of starting materials and finished products for the required periods;
- ensure that any work contracted out is the subject of a written contract;
- maintain an effective system whereby complaints are reviewed and products may be recalled;
- carry out a programme of regular self-inspection.

GMP for starting materials

- 5.5 Community requirements³ oblige holders of a Manufacturer's Licence to use as starting materials only active substances that have been manufactured in accordance with GMP.
- 5.6 This includes both total and partial manufacture of the active substance as well as any repackaging or re-labelling activities carried out by a distributor or broker. Herbal ingredients used as active substances for traditional herbal medicinal products as defined in Directive 2004/24/EC will also be required to comply with the new requirements.
- 5.7 The Human Medicines Regulation 2012 gives powers to the Licensing Authority to carry out inspections at the premises of manufacturers of such materials, the marketing authorisation (MA) holder and any laboratories employed by the MA holder. These inspections which are conducted by the competent authority, may be unannounced and may be carried out at the request of an active substance manufacturer, another Member State, the Commission, or the European Medicines Agency (EMA). The competent authority is empowered to inspect premises, take samples and examine documents.

³ Article 46(f) of Council Directive 2001/83/EC

- 5.8 A report will be provided to the manufacturer or MA holder who has undergone the inspection and, where relevant, a certificate of GMP compliance issued. Certificates will be entered on a central Community database, as will any failures in compliance.
- 5.9 In order to ensure the reliability of the supply chain and to respond to the increasing threat of falsified medicines entering the supply chain, Community medicines legislation has been further amended by Directive 2011/62/EU which requires that the particulars and documents required for a marketing authorisation now include a written confirmation that the finished product manufacturer has verified that the active substance is manufactured according to EU GMP (*The QP Declaration*).
- 5.10 Community legislation is also amended to provide further obligations on the finished product manufacturer to use only active substances, that have not only been manufactured in accordance with good manufacturing practices for active substances, but which have also been distributed in accordance with good distribution practices for active substances and verify compliance by the manufacturer and distributors of active substances with good manufacturing practice and good distribution practices by conducting audits at the manufacturing and distribution sites of the manufacturer and distributors of active substances.
- 5.11 The holder of the Manufacturing Licence has to verify such compliance either themselves or, through an entity acting on their behalf under a contract.
- 5.12 The primary means by which EU regulatory authorities will supervise compliance with the requirement for active substances to be manufactured in accordance with GMP will be through review of audit reports during inspections of manufacturing authorisation holders.
- 5.13 Audits of active substance manufacturers should be performed by suitably trained auditors. During inspections the competence of auditors will be assessed and if not deemed appropriate this will be raised as an issue.
- 5.14 The holder of the manufacturing authorisation must also ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is. This shall be ascertained on the basis of a formalised risk assessment in accordance with the applicable guidelines to be adopted by the Commission under Community legislation. Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects.
- 5.15 The holder of the Manufacturer's Licence must ensure that the appropriate good manufacturing practice so ascertained, is applied and document the measures that have been taken.
- 5.16 The new Community requirements also require manufacturers, importers and distributors of active substances to be registered with their competent authority. In the UK this is MHRA.

6 Personnel

The Qualified Person

- 6.1 Articles 41, 46 and 48 of Directive 2001/83/EC require that the holder of a Manufacturer's Licence must appoint at least one Qualified Person (QP), to be named on the licence. The QP's duties are specific and are intended to ensure that every batch of medicinal product has been manufactured and/or assembled and checked in accordance with legal requirements.
- 6.2 A QP has a personal responsibility for ensuring that the required tests and controls are carried out and must sign or certify, for each batch, that the appropriate tests have been carried out and that it complies with the relevant marketing authorisation (MA), Article 126a authorisation, certificate of registration or traditional herbal registration. More than one QP may be named on a Manufacturer's Licence.
- 6.3 Articles 49 and 50 of Directive 2001/83/EC prescribe the qualifications for appointment as a QP. Candidates for appointment as QPs must meet specific educational and vocational requirements. Candidates in the UK are usually expected to be members of the Royal Pharmaceutical Society, the Royal Society of Chemistry, the Society of Biology or the Pharmaceutical Society of Northern Ireland, and these professional bodies jointly undertake assessment of the candidate's eligibility on behalf of the Licensing Authority.
- 6.4 Non-UK candidates wishing to be named on a UK Manufacturer's Licence who have been named as a QP on a manufacturer's authorisation in another Member State, must be resident in the UK. At the time of application, they will need to provide a letter from the competent authority of the relevant EU Member State confirming that the person has been nominated as a QP under their provisions and has been named on a manufacturer's authorisation in that Member State.
- 6.5 The QP's tasks can be summarised as follows:
- for medicinal products manufactured and/or assembled within the European Union, a QP must ensure that each batch has been manufactured and checked in compliance with the Human Medicines Regulations 2012 and in accordance with the requirements of the marketing authorisation.
 - in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the European Union a QP must ensure that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation. The QP must certify in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 51 of Directive 2001/83/EC.

- 6.6 Further guidance on the professional duties and responsibilities of a QP is given in the Code of Conduct issued by the professional bodies.

Production Manager

- 6.7 An applicant for a Manufacturer's Licence should have a suitably qualified Production Manager or Head of the Production Department. The Production Manager is responsible for:
- ensuring that products are produced and stored according to the appropriate documentation so that they reach the appropriate standards of quality;
 - approving the instructions relating to production operations and ensuring their strict implementation;
 - ensuring that the production records are evaluated and signed by an authorised person before they are sent to the Quality Control (QC) Department;
 - checking the maintenance of their department, premises and equipment;
 - ensuring that the appropriate validations are done;
 - ensuring that the required initial and continuing training of their department personnel is carried out and adapted according to need.

Quality Controller

- 6.8 An applicant for a Manufacturer's Licence should have a suitably qualified Quality Controller or Head of Quality Control independent of the Production Department. This person may not act as the Production Manager, but can be named as the QP.
- 6.9 The Quality Controller is responsible for:
- approving or rejecting, as they see fit, starting materials, packaging materials, and intermediate, bulk and finished products;
 - evaluating batch records;
 - ensuring that all necessary testing is carried out;
 - approving specifications, sampling instructions, test methods and other quality control procedures;
 - approving and monitoring contract analysts;
 - ensuring the qualification and maintenance of their department, premises and equipment;
 - ensuring that the appropriate validations are done;
 - ensuring that the required initial and continuing training of their department personnel is carried out and adapted according to need.
- 6.10 The Heads of Production and QC have some shared or jointly exercised responsibilities relating to quality. These may include:
- the authorisation of written procedures and other documents, including amendments;
 - the monitoring and control of the manufacturing environment;
 - plant hygiene;

- process validation;
- training;
- the approval and monitoring of suppliers of materials;
- the approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities;
- the designation and monitoring of storage conditions for materials and products;
- the retention of records;
- the monitoring of compliance with the requirements of good manufacturing practice;
- the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality;
- participation in management reviews of process performance, product quality and of the quality management system and advocating continual improvement;
- ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

7 Import of licensed medicines from third countries

- 7.1 If a licensed medicinal product is imported from a third country (i.e. outside the EEA) the importer must hold a Manufacturer's Licence that authorises import. This provides the authorisation referred to in Article 40 of Directive 2001/83/EC.
- 7.2 A list of the licensed products to be imported must be submitted to the Licensing Authority as part of an application for a Manufacturer's Licence, giving:
- product name;
 - pharmaceutical form;
 - UK marketing authorisation number (PL) or Community marketing authorisation number (EU);
 - country of origin.
- 7.3 The licence holder must:
- have at its disposal a Qualified Person (QP) as defined in Article 48 of Directive 2001/83/EC. The QP must ensure that each production batch has undergone:
 - a full qualitative analysis;
 - a quantitative analysis of at least all the active substances;
 - all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation. The QP must certify in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 51 of Directive 2001/83/EC. These requirements are waived if the batch had entered the territory of another Member State and a QP in that State had performed the responsibilities set out above and there is written evidence to this effect, signed by the QP, or, if there is a Mutual Recognition Agreement (MRA) between the Community and the third country (see below).
 - keep the register or other record available for inspection by the Licensing Authority for five years from the date of certification.

- notify the name and address, qualifications and experience of the QP and of any change of QP.
- not permit the QP to perform their duties when notified in writing by the Licensing Authority that they do not have the required qualifications or experience or are not fulfilling their responsibilities. However, the licence holder and the QP are given the opportunity to make representations.
- ensure that all manufacture and assembly has been carried out in accordance with GMP by a duly authorised manufacturer or assembler.
- keep readily available for examination by the Licensing Authority samples of each batch of finished products for at least one year after the expiry date of the batch concerned, except where earlier destruction of such samples is authorised by the Licensing Authority.
- implement a system for reviewing and recording complaints together with an effective system for recall.
- record and investigate all such complaints and immediately inform the Licensing Authority of any defect that could result in a recall or in an abnormal restriction on sale, supply, or exportation.

7.4 Where a batch of a medicinal product is imported from a third country which has a Mutual Recognition Agreement (MRA) with the Community then full retesting of the batch in the UK is not required. A MRA is the “appropriate arrangement” referred to in Article 51 (2) of Directive 2001/83/EC, which when operational, allows a QP to be relieved of the duty of checking that certain controls have been carried out on each batch in the UK, before certifying it prior to release.

7.5 When a MRA is fully operational, which in some cases will only be after successful completion of a transitional period, a batch certificate from the manufacturer may be accepted in place of retesting. Before certifying the imported batch, the QP should check that this certificate:

- identifies the manufacturer in accordance with the MA;
- identifies the product and batch;
- states the product specifications in accordance with the marketing authorisation;
- gives the test results and shows that these comply with the specification;
- states that the batch was made to a standard equivalent to EU GMP at a facility authorised in that country for that dosage form, and is in compliance with that country’s marketing authorisation;
- is signed by the person responsible for quality;
- identifies that person and is dated.

7.6 A manufacturer’s batch certificate conforming to WHO recommendations and with the additional statement on GMP meets these requirements. The QP should also ensure that the batch appears physically satisfactory and has not been subjected to adverse conditions during transit. The MRAs do not exempt a product from any official batch release procedure which may be a condition of the marketing authorisation, for example, for some immunological and blood products. The current operational status of MRAs is published on the EMA

website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000248.jsp&mid=WC0b01ac058005f8ac

8 Inspection

- 8.1 MHRA GMP Inspectorate carries out regular and repeated inspections of manufacturing sites both in the United Kingdom and in those non-EU countries with which the EU does not have a Mutual Recognition Agreement. All sites named on a Manufacturer's Licence are subject to regular inspections. Each site is inspected every 2-3 years depending on the nature and scale of operation. Inspection enables the Licensing Authority to confirm that licence holders are complying with the conditions of their licence, with the provisions of the Human Medicines Regulation 2012 and with GMP. The ability to demonstrate compliance with the principles of GMP will result in the issuing of a GMP certificate.
- 8.2 Amongst other things, GMP Inspectors are empowered to:
- inspect the premises organised arrangements and procedures used in the manufacture, assembly, testing, storage and distribution of medicinal products;
 - interview key personnel named on licences;
 - take samples;
 - require production and examine any documentation or records relating to the manufacture, assembly, storage and distribution of medicinal products in accordance with the Human Medicines Regulations 2012.
- 8.3 It is a requirement of UK legislation that licence holders shall make their premises available for inspections by the Licensing Authority at any reasonable time.
- 8.4 A fee is charged for these inspections. See Section 10 on fees.
- 8.5 The major stages of the inspection process are:
- the introductory or opening meeting
 - the detailed inspection
 - the summary or closing meeting.
- 8.6 The purpose of the introductory or opening meeting is for the inspector to meet with the appropriate key personnel from the company to discuss the arrangements for the inspection. The inspector would typically confirm the purpose and scope of the inspection, areas to be visited and indicate any documentation which may be required.
- 8.7 The purpose of the site inspection is to determine the degree of conformity of the operations to requirements of good practice and to assess compliance with the terms and conditions of licences issued under the appropriate legislation or with details submitted in support of an application for a licence.
- 8.8 The inspection schedule is therefore determined by the type of inspection planned. The inspection will typically involve visits to operational areas, interviews with key personnel

and documentation review. Any observations, recommendations and deficiencies noted during the inspection would normally be discussed with the company representatives at the time.

- 8.9 During inspections of manufacturing and wholesale operations, samples of starting materials, work in progress and finished products may be taken for testing if an inspector considers that this might assist in the detection of quality deficiencies. Occasionally samples may be taken, when these cannot be obtained from other sources, for routine surveillance purposes.
- 8.10 The purpose of the summary or closing meeting is for the inspector to provide the company with a verbal summary of the inspection findings and to allow the company to correct at this stage any misconceptions. The inspector would typically summarise the definition and classification of deficiencies they propose to report and the company is encouraged to give an undertaking to resolve the deficiencies and to agree a provisional timetable for corrective action. The inspector would also describe the arrangements for the formal notification of the deficiencies to the company (the post-inspection letter) and what is expected as a response.
- 8.11 All deficiencies are classified as critical, major or other. A reference to the relevant sections of the GMP/GDP legislation or Guidelines, will be given for those deficiencies classified as critical or major. The definitions used are as per the EU Community Report format:

Critical deficiency: A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

Major deficiency: A non-critical deficiency:

- That has produced or may produce a product, which does not comply with its marketing authorisation
- or which indicates a major deviation from EU good manufacturing practice
- or (within EU) which indicates a major deviation from the terms of the manufacturing authorisation
- or which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil their legal duties
- or a combination of several 'other' deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Other deficiency: A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice. (A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as major or critical).

Several related major or other deficiencies may be taken together to constitute a critical or major deficiency (respectively) and will be reported as such.

All critical and major deficiencies found will be reported even if remedial action has been taken before the end of the inspection.

- 8.12 The choice of company representatives at the meeting is primarily for the company to decide, but should normally include the senior staff who were present during the inspection, technical management and the QPs.
- 8.13 Following an inspection, the Inspector prepares a summary of their findings, which is sent to the licence applicant asking for proposals to remedy them. There are several standard letters from the Medicines Inspectorate detailing graduated levels of response. In the most serious cases the report is referred to the Licensing Authority for considering more formal action (see Section 9). Where the licence is granted, subsequent inspections are based on a risk assessment. The inspector will use the inspection outputs along with a number of other factors to identify a risk rating for the site which, will in turn, equate to a future inspection frequency.
- 8.14 Where quality control testing is contracted to a third party, the testing site must also be made available for inspection.

9 Regulatory action

- 9.1 The Licensing Authority will take regulatory action where breaches of legislation are identified; this may take the form of adverse licensing action e.g. compulsorily making a variation to an existing licence, suspension or revocation of a licence and/or the instigation of criminal proceedings.
- 9.2 Where poor compliance is identified which does not meet the threshold for consideration of adverse regulatory action, a compliance escalation process may be implemented. The process is managed by the Compliance Management Team (CMT) and directs companies towards a state of compliance, without the need for regulatory action.

10 Fees

- 10.1 The Medicines Act 1971 introduced provisions for the payment of fees for licences, certificates and inspections. The current fees legislation for human medicinal products is contained in The Medicines (Products for Human Use) (Fees) Regulations 2013 (S.I. 2013 No. 532).
- 10.2 Fees are currently payable for the following:
- licence applications.
 - licence variations.
 - inspections.
 - duplicate or multiple GMP Certificates.

- 10.3 An annual service charge is also payable during the currency of a licence.
- 10.4 A schedule of the current fees is available on MHRA's website:
<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Feespayablefortheregulationofmedicines/index.htm>
- 10.5 When MHRA plans to make changes to the amount or frequency of fees, licence holders are consulted and given the opportunity to comment on MHRA's proposals. Details of consultation letters (known as MLXs) can be found on MHRA's website:
<http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/index.htm>

11 Further information

- 11.1 Extracts from EU and UK medicines legislation and EU guidelines on GMP together with notes on duties of the QP and operation of MHRA's Defective Medicines Report Centre are published in *Rules and Guidance for Pharmaceutical Manufacturers and Distributors* ("The Orange Guide") available from Pharmaceutical Press, <http://www.pharmpress.com/product/9780857111029/orangeguide>
- 11.2 Copies of relevant UK statutory instruments are also available from The Stationery Office, <https://www.tso.co.uk/> and Legislation.gov.uk : <http://www.legislation.gov.uk/>
- 11.3 Copies of the following MHRA Guidance are available on MHRA's website:
- MHRA Guidance Note 5: Notes for applicants and holders of a Manufacturer's Licence
 - MHRA Guidance Note 6: Notes for applicants and holders of a Wholesale Dealer's Licence (WDA(H) or Broker Registration.
 - MHRA Guidance Note 8: A guide to what is a medicinal product
 - MHRA Guidance Note 13: A guidance note on manufacturer's licences authorising a non-orthodox practitioner to mix and assemble unlicensed medicinal products
 - MHRA Guidance Note 14: The supply of unlicensed medicinal products ("specials")
 - MHRA Guidance Note 23: The Blue Guide - Advertising and promotion of medicines in the UK
 - MHRA Guidance Note 25: Best Practice Guidance on the labelling and packaging of medicines

12 Glossary of legislation

European legislation

Council Directive 2001/83/ EC on the Community code relating to medicinal products for human use

Legislation regulates the Licensing and Manufacture of and Wholesale dealing in Medicinal Products within the European Community.

Council Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products

This Directive lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture requires an authorisation.

UK legislation

The Human Medicines Regulations 2012 (SI 2012/1916)

Replaces nearly all UK medicines legislation – most of the Medicines Act 1968 and over 200 statutory instruments. The Regulations set out a comprehensive regime for the authorisation of medicinal products for human use; for the manufacture, import, distribution, sale and supply of those products; for their labelling and advertising; and for pharmacovigilance.

The Human Medicines (Amendment) Regulations 2013 (SI 2013/1855)

The majority of provisions in these amending Regulations introduce new provisions into the 2012 Regulations in relation to brokers, active substances and the sale of medicinal products at a distance in order to implement Directive 2011/62/EU as regards the prevention of the entry into the legal supply chain of falsified medicinal products

The Medicines (Products for Human Use) (Fees) Regulations 2013 (SI 2013/532)

These Regulations make provision for the fees payable under the Medicines Act 1971 in respect of marketing authorisations, licences and certificates relating to medicinal products for human use.

The Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031)

These Regulations implement Directive 2001/20/EC on the approximation of laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations (SI 2003/1680)

Regulates the importation and marketing of unlicensed medicinal products for human use in order to minimise the risk of the transmission of Transmissible Spongiform Encephalopathies via those products.

APPENDIX 1 - A description of the conditions and provisions of a Manufacturer's Licence

The Regulations require that the licence holder shall:

- comply with the principles and guidelines for good manufacturing practice including insofar as they relate to the import of medicinal products;
- only use active starting materials which have been manufactured in accordance with the principles and guidelines for good manufacturing practice for active substances and have been distributed in accordance with the guidelines on good distribution practice for active substances, unless they are for use or used in an exempt medicinal product (special medicinal product);
- verify:
 - that the manufacturer or distributor of an active substance that they have used has complied with the requirements of good manufacturing practice and good distribution practice for active substances by means of an audit performed directly by themselves or by a person acting on their behalf;
 - that unless the active substance is imported from a third country, any manufacturers, importers or distributors supplying them with the active substances are registered with the competent authority of a member State in which they are established.
- ensure the authenticity and quality of the active substance;
- ensure:
 - excipients are suitable for use in a medicinal product by ascertaining what the appropriate good manufacturing practice is;
 - that the ascertained good manufacturing practice is applied;
 - the suitability of the excipient is ascertained on the basis of a formalised risk assessment as described in paragraph 5 of Article 47 of the 2001 Directive and the assessment takes account of the source requirements under other quality systems, intended use of the excipients, and previous instances of quality defects;
 - the authenticity and quality of any excipient used is verified; and
 - the measures taken under this paragraph are documented by the licence holder.
- maintain such staff, premises, equipment and facilities necessary to conduct the manufacture and assembly of medicinal products in accordance with the requirements of their Manufacturer's Licence and the appropriate authorisation of the medicinal product being manufactured;

- maintain such staff, premises, equipment and facilities for the handling, control, storage and distribution of the medicinal products manufactured or assembled in accordance with their Manufacturer's Licence as necessary to maintain the quality of those medicinal products;
- ensure that any arrangements made for the control, storage and distribution of the medicinal products are adequate to maintain the quality of those products;
- not carry out any manufacture or assembly of medicinal products other than in accordance with their Manufacturer's Licence and at the premises specified in the licence;
- not use any premises for the handling, control, storage or distribution of medicinal products other than those named on their Manufacturer's Licence which have been approved by the Licensing Authority for that purpose;
- inform the Licensing Authority before making any material alteration to the premises or facilities used under their Manufacturer's Licence, or in the operations for which they are used;
- inform the Licensing Authority of any proposed changes to any personnel named in their Manufacturer's Licence as responsible for quality control, including the person named as the qualified person;
- permit the Licensing Authority to carry out inspections, take samples or copies of documentation as necessary to enable the Licensing Authority to ascertain whether there are any grounds for suspending, revoking or terminating the Manufacturer's Licence or to verifying any statement contained in an application for a licence;
- ensure that any blood or blood component that they import into the United Kingdom and use as a starting material or raw material in the manufacture of a medicinal product meets equivalent standards of quality and safety to those laid down in Commission Directive 2004/33/EC, implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components;
- ensure that they have at all times at their disposal the services of at least one qualified person who is responsible for carrying out, in relation to the medicinal products being manufactured or assembled, the duties specified in Article 51 of the Directive 2001/83/EC.

Where the Manufacturer's Licence holder distributes the medicinal product manufactured or assembled in accordance with the Manufacturer's Licence they shall:

- comply with the principles of good distribution practice;
- ensure the appropriate and continued supply of the medicinal product that they manufacture or assemble;
- sell only, or offer for sale or supply, the medicinal product in accordance and conformity with a marketing authorisation unless it is an exempt medicinal product or is distributed to another Member State where it can be legally used as an unlicensed medicinal product in the Member State concerned;
- distribute only their medicinal products to a holder of a wholesale dealer's licence relating to those products; a holder of an authorisation granted by the competent authority of another EEA State authorising the supply of those products by way of wholesale dealing; any person who may lawfully sell those products by retail or who

may lawfully supply them in circumstances corresponding to retail sale; or any person who may lawfully administer those products;

- where the medicinal product is supplied to a person for retail sale or supply, the Manufacturer's Licence holder must enclose with the product a document which makes it possible to ascertain the date on which the supply took place; the name and pharmaceutical form of the product supplied; the quantity of product supplied; and the names and addresses of the person or persons from whom the products were supplied.

The Manufacturer's Licence holder must immediately inform the competent authority of a member State and, where applicable, the marketing authorisation holder, of medicinal products which come within the scope of their manufacturing authorisation which the licence holder knows or suspects or has reasonable grounds for knowing or suspecting, to be falsified.

The Standard Provisions are incorporated into all Manufacturer's Licences in the form set out in Schedule 4 of the Human Medicines Regulations 2012, that is, those provisions which may be included in all licences unless an individual licence provides variations to them. They require that the Manufacturer's Licence holder shall:

- place their quality control system referred to in Article 11(1) of Commission Directive 2003/94/EC under the authority of the head of the Quality Control (QC);
- provide information about the products being manufactured or assembled under their Manufacturer's Licence and about the operations being conducted in relation to such manufacture or assembly as may be requested by the licensing authority;
- inform the Licensing Authority of any proposed changes to be made to any personnel named on their licence, responsible for supervising the production operations; in charge of the animals from which are derived any substances used in the production of the medicinal products being manufactured or assembled; or responsible for the culture of any living tissues used in the manufacture of the medicinal products being manufactured or assembled;
- keep readily available for inspection by a person authorised by the Licensing Authority the batch documentation referred to in Article 9(1) of Commission Directive 2003/94/EC, and permit that person to take copies or make extracts from such documentation;
- keep readily available for examination by a person authorised by the licensing authority, samples of each batch of finished medicinal product referred to in Article 11(4) of Commission Directive 2003/94/EC;
- withhold any batch of any medicinal product from sale or export so far as may be reasonably practicable for up to 6 weeks when informed that it does not comply with its licence specifications or with the provisions of the Human Medicines Regulations 2012;
- ensure that any tests for determining conformity with the standards and specifications applying to any particular product used in the manufacture of a medicinal product shall, except so far as the conditions of the product specification for that product otherwise provide, be applied to samples taken from the medicinal product after all manufacturing processes have been completed, or at such earlier stage in the manufacture as may be approved by the licensing authority;

- where the Manufacturer's Licence relates to the assembly of any medicinal product or class of product, and the licence holder supplies that medicinal product at such a stage of assembly that does not fully comply with the provisions of the product specification that relate to labelling, the licence holder shall communicate the particulars of those provisions to the person to whom that product has been so supplied;
- where the Manufacturer's Licence relates to the assembly of a medicinal product; and that medicinal product is not manufactured by the licence holder; and particulars as to the name and address of the manufacturer of, or of the person who imports, that medicinal product have been given by the licence holder to the licensing authority, the licence holder shall forthwith notify the Licensing Authority in writing of any changes in such particulars;
- keep readily available for examination by a person authorised by the Licensing Authority durable records of the details of manufacture of any intermediate products held by them which are for use in the manufacture of biological medicinal products for human use and shall be in such form as to ensure that the Manufacturer's Licence holder has a comprehensive record of all matters that are relevant to an evaluation of the safety, quality and efficacy of any finished biological medicinal product for human use which they manufacture using those intermediate products. The records shall not be destroyed without the consent of the Licensing Authority until the records of the details of manufacture of any finished medicinal products which were or may be manufactured using those intermediate products may be destroyed in accordance with the requirements of these Regulations;
- arrange for animals which are used in the production of any medicinal products, to be housed in premises of such a nature, and be managed in such a manner, as to facilitate compliance with the provisions relating to them in the relevant marketing authorisations;
- take all reasonable precautions and exercise all due diligence to ensure that any information they provide to the Licensing Authority which is relevant to an evaluation of the safety, quality or efficacy of any medicinal product for human use which they manufacture or assemble; or any starting materials or intermediate products that they hold which are for use in the manufacture of medicinal products, is not false or misleading in any material particular.

The Manufacturer's Licence holder may use a contract laboratory⁴ pursuant to Article 11(2) of Commission Directive 2003/94/EC if operated by a person approved by the licensing authority, i.e. if not on the Manufacturer's Licence a contract laboratory will not be acceptable.

The Standard Provisions require the Manufacturer's Licence holder that imports medicinal products from a state other than an EEA State to:

- provide such information as may be requested by the Licensing Authority concerning the type and quantity of any medicinal products which the licence holder imports.

⁴ A contract lab is required to be named on the Manufacturer's Licence

- withhold the batch of imported product from distribution, so far as reasonably practicable, for up to six weeks when told that the strength, quality or purity of a batch of a medicinal product to which the licence relates has been found not to conform with the specification of the medicinal product in question; or those provisions of the Regulations that are applicable to the medicinal product,
- ensure that any tests for determining conformity with the standards and specifications applying to any ingredient used in the manufacture of a medicinal product must, except so far as the conditions of the product specification for that ingredient otherwise provide, be applied to samples taken from the medicinal product after all manufacturing processes have been completed, or at such earlier stage in the manufacture as may be approved by the licensing authority.
- take all reasonable precautions and exercise due diligence to ensure that any information provided to the Licensing Authority which is relevant to an evaluation of the safety, quality or efficacy of a medicinal product for human use which is imported from a state other than an EEA State, handled, stored or distributed under the licence is not false or misleading in a material particular.

The Standard Provisions also require the holder of a Manufacturer's Licence relating to the manufacture and assembly of exempt advanced therapy medicinal products to ensure that:

- the immediate packaging of an exempt advanced therapy medicinal product is labelled to show the following particulars:
 - the name of the exempt advanced therapy medicinal product;
 - the expiry date in clear terms including the year and month and, if applicable, the day;
 - a description of the active substance, expressed qualitatively and quantitatively;
 - where the product contains cells or tissues of human or animal origin:
 - a statement that the product contains such cells or tissues, and
 - a short description of the cells or tissues and of their specific origin;
 - the pharmaceutical form and the contents by weight, volume or number of doses of the product;
 - a list of excipients, including preservative systems;
 - the method of use, application, administration or implantation and, if appropriate, the route of administration, with space provided for the prescribed dose to be indicated;
 - any special storage precautions;
 - specific precautions relating to the disposal of the unused product or waste derived from the product and, where appropriate, reference to any appropriate collection system;
 - the name and address of the holder of the manufacturer's licence;
 - the Manufacturer's Licence number;
 - the manufacturer's batch number;
 - the unique donation code referred to in Article 8(2) of Directive 2004/23/EC; and
 - where the exempt advanced therapy medicinal product is for autologous use, the unique patient identifier and the words "for autologous use only".

- the package leaflet of the exempt advanced therapy medicinal product shall include the following particulars:
 - the name of the exempt advanced therapy medicinal product;
 - the intended effect of the medicinal product if correctly used, applied, administered or implanted;
 - where the product contains cells or tissues of human or animal origin:
 - a statement that the product contains such cells or tissues, and
 - a short description of the cells or tissues and, where such cells or tissues are of animal origin, their specific origin;
 - where the product contains a medical device or an active implantable medical device, a description of that device and, where that device contains cells or tissues of animal origin, their specific origin;
 - any necessary instructions for use, including:
 - the posology,
 - the method of use, application, administration or implantation and, if appropriate, the route of administration,
 - a description of symptoms of overdose,
 - action to be taken in the event of overdose, including any emergency procedures,
 - action to be taken if one or more doses have been missed, and
 - a recommendation to consult the doctor or pharmacist for any clarification on the use of the product;
 - where adverse reactions are known, a description of those which may occur under recommended conditions of use of the product and, if appropriate, an indication of action to be taken in such a case;
 - an instruction that the patient report any adverse reaction not specified in the package leaflet to the doctor or pharmacist;
 - the expiry date in clear terms and a warning against using the product after that date;
 - any special storage precautions;
 - a description of any visible signs of deterioration;
 - a complete qualitative and quantitative composition;
 - the name and address of the holder of the Manufacturer's Licence; and
 - the date on which the package leaflet was last revised.
- the licence holder must keep data to trace the exempt advanced therapy medicinal through the sourcing, manufacturing, packaging, storage, transport and delivery to the establishment where the product is used, for longer than 30 years.