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Guidance

Good manufacturing practice and good distribution practice

Comply with good manufacturing practice (GMP) and good distribution practice (GDP), and prepare for an inspection.

From:
Medicines and Healthcare products Regulatory Agency (/government/organisations/medicines-and-healthcare-products-regulatory-agency) and Department of Health and Social Care (/government/organisations/department-of-health-and-social-care)

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Information on new arrangements for inspections (https://www.gov.uk/government/news/new-arrangements-for-mhra-good-practice-gxp-inspections-due-to-coronavirus-covid-19--2) during the coronavirus (COVID-19) outbreak. Exceptional good distribution practice (GDP) flexibilities for medicines during the coronavirus (COVID-19) outbreak (https://www.gov.uk/guidance/exceptional-good-distribution-practice-gdp-flexibilities-for-medicines-during-the-coronavirus-covid-19-outbreak)

Overview

Good manufacturing practice (GMP) is the minimum standard that a medicines manufacturer must meet in their production processes. Products must:

- be of consistent high quality
- be appropriate to their intended use
- meet the requirements of the marketing authorisation (MA) or product specification

Good distribution practice (GDP) requires that medicines are obtained from the licensed supply chain and are consistently stored, transported and handled under suitable conditions, as required by the MA or product specification.

Organisations that may have to comply with good manufacturing practice (GMP) and/or good distribution practice (GDP) include:

- manufacturer licence holders
- wholesale dealer licence holders
- blood establishment authorisation holders
- non-UK sites employed by UK MA holders

The Medicines and Healthcare products Regulatory Agency (MHRA) carries out inspections to check if manufacturing and distribution sites comply with GMP or GDP. You will be inspected when you apply for a manufacturer or wholesaler dealer licence and then periodically based on risk assessments. Overseas manufacturing sites are also inspected

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If an organisation manufactures or distributes both human and veterinary medicines, MHRA may carry out an inspection of both areas on behalf of the Veterinary Medicines Directorate (http://www.vmd.defra.gov.uk/).

MHRA and the European Medicines Agency (EMA) have published guidance on GMP and GDP.

- Volume 4 of the rules governing medicinal products in the EU (https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en)
- EU GDP guidelines (https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF)
- Orange Guide: Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2022 (https://www.pharmpress.com/product/9780857114396/orangeguide)
- Green Guide: Rules and Guidance for Pharmaceutical Distributors 2022 (https://www.pharmpress.com/product/9780857114419/rules-and-guidance-for-pharmaceutical-distributors-2022-the-mhra-green-guide)
- Guidance for UK manufacturer's licence and manufacturer's authorisation holders (for investigational medicinal products) – on the use of stand alone contract laboratories (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/482018/Guidance_for_mnfs_on_QC_labs_LG_Dec_15_version__doc.pdf) (PDF, 185 KB, 3 pages) - on the use of stand alone contract laboratories

Types of inspection

Inspections under the risk-based compliance programme

Every manufacturer and wholesaler has a risk rating or score and we prioritise inspections for those with the highest ratings or scores. You will be told about these inspections in advance, although under the short-notice inspection programme we may send little or no notification. At the inspection, GMP and/or GDP inspectors examine the systems used to manufacture and/or distribute medicines.

Your GMP rating is based on:

- your compliance report
- internal information about previous inspection history
- organisational changes

You can't appeal against your rating.

An increase in risk will be peer reviewed by a GMP operations manager, a member of the compliance management team (CMT) or a GMP expert inspector before being

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You will be given a full copy of the reasons for your risk rating once the inspection has closed.

For GDP inspections your risk score is based on what activities take place on site and the number and type of deficiencies observed. This indicates the likely date of your next inspection and this information is included on the inspection report.

Inspections may sometimes be carried out with other MHRA inspections, such as with good clinical practice (https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials) or good pharmacovigilance practice (https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp).

Product-related GMP inspections

MHRA conducts product-related GMP inspections when assessing an application for a UK marketing authorisation (https://www.gov.uk/guidance/apply-for-a-licence-to-market-a-medicine-in-the-uk). This inspection checks if the manufacturer complies with GMP. We tell you about this inspection in advance.

Product-related inspections can also be requested by the European Medicines Agency (EMA):

- Committee for Human Medicinal products (CHMp) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp) during the pre-application of a centralised marketing authorisation application
- Co-ordination group for Mutual Recognition and Decentralised Procedures – human (CMDh) (http://www.hma.eu/cmdh.html).

EMA uses inspectors from EU member states to ensure compliance with GMP principles.

Triggered inspections

MHRA may inspect you if we're informed about possible GMP or GDP breaches by:

- a whistle blower
- other MHRA departments
- another regulatory authority

We may send little or no notification of these inspections in advance.

Complete a compliance report

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You should send completed compliance reports to the email address given by the inspector. Hard copies of compliance reports will not be accepted.

- GDP compliance report (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/615515/CAD_FINAL_DRAFT__002_.doc) (MS Word Document, 251 KB)
- GMP pre-inspection compliance report (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/893996/PreInspection_Compliance_Report_document.doc) (MS Word Document, 404 KB)
- GMP interim compliance report (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/898999/Interim_Compliance_Report_v5.doc) (MS Word Document, 342 KB)
- GMP compliance report and interim update guidance (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/714749/GMP_Compliance_Report_Guidelines_V_7.pdf) (PDF, 104 KB, 7 pages)
- GMP Quality Control Laboratory Pre-Inspection Compliance Report (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/892435/GMP_QC_Testing_Laboratory_Pre_Inspection_Compliance_Form.docx) (MS Word Document, 56.2 KB)
- GMP QC compliance report and interim update guidance (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/881102/GMP_QC_Testing_Laboratory_Compliance_Report_and_Interim_Update-_guidelines_for_completion_and_submission.pdf) (PDF, 156 KB, 6 pages)

The inspection

During an inspection the inspection team will:

- interview relevant personnel
- review documents
- conduct site visits

Site visits may include any facility or process involved in producing, purchasing and distributing medicines, including:

- manufacturing areas
- quality control (QC) laboratories
- stock and stock management
- storage areas
- temperature monitoring
- returns areas

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- transportation arrangements

The inspection team may ask for additional documentation and samples for testing during the inspection. They may also change the focus of the inspection if they suspect serious non-compliance.

At the closing meeting the inspector will provide feedback and discuss any deficiencies with you and agree timelines for corrective actions.

Grading of inspection findings

Deficiencies found during inspections are graded at 3 levels. The definitions below are summaries. For the full definition see page 47 of the EMA compilation of community procedures on inspections and exchange of information (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf)

Critical deficiency

A deficiency which has produced or significantly risks producing a product which is harmful to humans or veterinary patients or which could result in a harmful residue in a food-producing animal.

Any departure from good distribution practice that results in a significant risk to patients. This includes an activity which increases the risk of counterfeit medicines reaching patients.

Major deficiency

A non-critical deficiency which:

- has or may produce a product that doesn't comply with its marketing authorisation
- indicates a major deviation from GMP or GDP or from the terms of the manufacturer licence or wholesale licence
- indicates a failure to carry out satisfactory batch release procedures or (within EU) a failure of the Qualified Person or Responsible Person to fulfil their legal duties
- a combination of several 'other' deficiencies which on their own may not be major but together may represent a major deficiency and should be explained and reported as such

Other

A deficiency which cannot be classified as either critical or major or there is not

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from good manufacturing and distribution practice.

Actions after the inspection

After the inspection closing meeting, you will receive a post inspection letter confirming any deficiencies found.

You must respond to the inspector by email to confirm the proposed corrective actions and dates for when these actions will be completed. The inspector will review your response. If they accept it, you will receive a GMP or GDP certificate with your inspection report. An unacceptable response may lead to compliance escalation if further requests for information are unsatisfactory.

If you're being inspected for GMP you should complete an interim assessment if there are changes to your site following your first inspection.

Guidance on responding to a post-inspection letter (https://www.gov.uk/guidance/guidance-on-responding-to-a-gmpgdp-post-inspection-letter)

The daily rate inspection fee includes preparation for, reporting and close-out of the inspection. Inspections with critical findings or other significant non-compliance requiring referral to the GMDP Compliance Management Team and/or Inspection Action Group may require the inspector(s) to spend additional time beyond that covered by the daily rate overseeing the adequacy of the company's Corrective and Preventative Actions (CAPA) and the company's return to compliance. For such inspections, an office-based inspection fee may be charged for this additional time spent by the inspector(s) on such activities (for example, reviewing CAPA plans, impact assessments and periodic CAPA status updates).

Compliance escalation process

If your compliance is found to be poor but has not hit the threshold for regulatory action you may go through the compliance escalation process. The aim of this process is to support companies to achieve compliance before regulatory action becomes necessary.

Once the process has been completed you will be returned to the routine risk-based inspection programme. However you could still be referred for regulatory action if you do not make the necessary improvements.

The process may also be used if the Inspection Action Group has closed their case referral but the company to be monitored until remedial action plans have been completed.

The process may include:

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- making recommendations on close monitoring of compliance improvement work through inspection
- meetings and correspondence with company senior management clearly outlining the consequences of continued non-compliance

Information sheets

Re-inspection of site under Compliance Management (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653121/Re-inspection_of_site_under_Compliance_Management.pdf) (PDF, 29.3 KB, 1 page) Compliance Management - Specials Manufacturers (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653087/Compliance_Management_Specials_manufacturers.pdf) (PDF, 36.1 KB, 1 page) Compliance Management - MIA MIA(IMP) and third country manufacture (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653088/Compliance_Management_MIA_MIA_IMP__and_third_country_manufacture.pdf) (PDF, 37.4 KB, 2 pages) Compliance Management - Contract Laboratory (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653089/Compliance_Management_Contract_Laboratory.pdf) (PDF, 29.4 KB, 1 page) Compliance Management - Active Substance (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653090/Compliance_Management_Active_Substance.pdf) (PDF, 29.6 KB, 1 page) Regulatory action – UK Wholesaler (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/774120/Regulatory_Action_-_UK_Wholesaler-converted.pdf) (PDF, 83.7 KB, 2 pages)

Feedback from GMP inspections

To help you understand the areas where GMP inspectors have found compliance problems during GMP inspections in the UK and overseas, the GMP inspectorate produces a report of common deficiencies from previous GMP inspections (https://www.gov.uk/government/statistics/good-manufacturing-practice-inspection-deficiencies).

The GMP Inspectorate has compiled an anonymised raw data set, so that stakeholders can do their own tailored analysis of our findings specific to their supply chain.

GMP contact form (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1139996/GMP_contact_form.docx) (MS Word Document, 16.1 KB)

Suspension of your licence

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If the inspector finds critical deficiencies or that agreed action plans from previous inspection deficiencies have not been resolved they will contact the Inspection Action Group (IAG). The IAG can refuse or suspend your licence, increase inspection visits or request a meeting with the licence holder.

Information Sheets

Re-inspection of site under Regulatory Action (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653094/Re-inspection_of_site_under_Regulatory_Action.pdf) (PDF, 32.4 KB, 1 page)
Regulatory Action - Specials manufacturers (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653095/Regulatory_Action_Specials_manufacturers.pdf) (PDF, 37.9 KB, 2 pages)
Regulatory Action - MIA MIA(IMP) and Third Country manufacture (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653097/Regulatory_Action_MIA_MIA_IMP__and_Third_Country_manufacture.pdf) (PDF, 39.5 KB, 2 pages) Regulatory Action Contract Laboratory (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653098/Regulatory_Action_Contract_Laboratory.pdf) (PDF, 33.6 KB, 2 pages)
Regulatory Action - Active Substance (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653100/Regulatory_Action_Active_Substance.pdf) (PDF, 34.1 KB, 2 pages) Deficiency data (2018) (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/838906/2018_Deficiency_Data.xlsx) (MS Excel Spreadsheet, 456 KB)

Transitional Qualified Persons (QPs) for investigational medicinal products (IMPs)

We are aware there is some concern for UK business and personal careers, over the status of transitional QPs that were recognised under the transitional arrangements provided in SI 2004/1031, when the Clinical Trials Directive was implemented in 2004. Under the Clinical Trials Regulation EU No. 536/2014 Article 61, 2b., QPs will need to fulfil the conditions of qualification set out in Article 49(2) and (3) of Directive 2001/83/EC. The GMDP Inspectorate has worked closely with MHRA's legal advisors to ensure that the original qualification eligibility assessments made between 2004-2006 remain valid, and that transitional QPs can continue to be considered eligible where their qualifications are also supported by at least 2 years practical experience from working in a licenced manufacturing facility.

The GMDP Inspectorate have launched a reassessment process to give transitional QPs for IMP the opportunity to demonstrate how they now meet Article 49(2) & (3) of Directive 2001/83/EC, in line with the requirements of EU Regulation 536/2014 and

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form (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/518913/TQP_Reassessment_form.doc) (MS Word Document, 374 KB). This information will be used to provide a summary of qualifications and work experiences of acting in a transitional QP role to date, and will be added to information provided with the original 2004 – 2006 applications. There is no charge for the application and completed forms should be emailed to gmpinspectorate@mhra.gov.uk for assessment. Following assessment, eligibility certificates will be issued to those meeting the requirements set out in set out in Article 49(2) and (3) of Directive 2001/83/EC.

The reassessment process only applies to applicants who were assessed and acknowledged as transitional QPs under the SI 2004/1031 arrangements, which means transitional QPs that have been named as a QP in a valid application for a manufacturing authorisation for IMPs made prior to 1st May 2006 under the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031). This scheme is not open to any new trainee QPs wanting to specialise in the IMP sector, who would need to apply for eligibility assessment through the Joint Professional Bodies category A assessment route.

Fees for inspection

Fees for GMP and GDP inspections (https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees#inspection-fees).

Contact

For further information on good manufacturing practices, please complete this contact form (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1139996/GMP_contact_form.docx) and email gmpinspectorate@mhra.gov.uk.

If your email relates to a good distribution practice please email gdp.inspectorate@gov.uk.

For further information on the planning of GMP inspections, email inspectionplanning@mhra.gov.uk and for GDP inspections gdpplanning@mhra.gov.uk

GxP inspections from 1 January 2021

From 1 January 2021, the MHRA's GxP risk-based inspection programmes will remain unchanged.

GMP inspection outcomes from EEA regulatory authorities will continue to be

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Inspections performed by existing mutual recognition partners will also continue to be accepted, if they are within the scope of the mutual recognition agreement in place before 1 January 2021.

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Guidance on responding to a GMP/GDP post inspection letter (/guidance/guidance-on-responding-to-a-gmpgdp-post-inspection-letter)

Out-of-specification investigations (/government/publications/out-of-specification-investigations)

Exceptional good distribution practice (GDP) flexibilities for medicines during the coronavirus (COVID-19) outbreak (/guidance/exceptional-good-distribution-practice-gdp-flexibilities-for-medicines-during-the-coronavirus-covid-19-outbreak)

Medicines: apply for a variation to your marketing authorisation (/guidance/medicines-apply-for-a-variation-to-your-marketing-authorisation)

Detailed guidance

Good pharmacovigilance practice (GPvP) (/guidance/good-pharmacovigilance-practice-gpvp)

Good clinical practice for clinical trials (/guidance/good-clinical-practice-for-clinical-trials)

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