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MHRA GPvP Inspectorate describes six critical findings in annual report

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) Good Pharmacovigilance Practice (GPvP) Inspectorate completed 37 inspections during the 12 months to 31 March 2017. On average there were six findings per inspection, although critical findings were infrequent. The six critical findings identified were in five areas: signal management; the maintenance of Reference Safety Information; the supervision and oversight of the pharmacovigilance system; non-interventional programmes; and failure to establish a global pharmacovigilance system. Details on page 2 ▶

New Data Protection Regulation for Europe and the UK

The EU General Data Protection Regulation (GDPR) will replace the Data Protection Directive (95/46/EC) with effect from 25 May 2018. In an increasingly data-driven world that is vastly different to that of 1995 when the Directive was established, the GDPR aims to protect EU citizens from privacy and data breaches. While many of the key points in the Regulation are clear, others still need to be decided upon, and there is currently uncertainty on how the new Regulation will affect healthcare and clinical research. Find out more on page 4 ▶

ICH focuses on multiregional clinical trials and paediatric medicines

The International Council for Harmonisation's (ICH's) latest Assembly meeting took place in Geneva, Switzerland, on 11–16 November 2017. Key decisions were made on membership and on the focus for the coming months, highlighting ICH's continued interest in multiregional clinical trials and paediatric research. The next meeting will be in Kobe, Japan, in June 2018. See page 6 ▶

EMA surveys companies on their readiness for Brexit

The European Medicines Agency (EMA) and the European Commission are continuing to provide guidance to pharmaceutical companies as they prepare for the UK's withdrawal from the EU. Their focus is on ensuring that companies are ready to take the necessary steps to ensure an undisrupted supply of their medicines when the UK becomes a third country on 30 March 2019. On 23 January 2018, the EMA announced that it will survey UK-based holders of centralised marketing authorisations for medicines, as well as certain other companies, to gather information on their Brexit preparations. See page 5 ▶

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GCP lessons: poor management of ECGs jeopardises subject safety

Essential documents are those that individually and collectively permit the evaluation of trial conduct and the quality of the data produced. They serve to demonstrate compliance with both GCP and the applicable regulatory requirements. The timely and accurate filing of essential documents at investigator sites is critical to trials and – in the context of a regulatory inspection – helps to confirm the validity of study conduct and the integrity of study data. The inadequate management of essential

MHRA GPvP Inspectorate describes six critical findings in annual report

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) Good Pharmacovigilance Practice (GPvP) Inspectorate reported six critical inspection findings in its latest annual Pharmacovigilance Inspection Metrics Report.

During the 12 months to 31 March 2017, the GPvP Inspectorate conducted 36 inspections of marketing authorisation holders (MAHs) and one of a pharmacovigilance service provider. The 37 inspections examined compliance with EU and national pharmacovigilance regulations and guidelines, and were described as follows:

- 13 inspections of MAHs/organisations that had not previously undergone an MHRA GPvP inspection
- 15 routine re-inspections
- nine inspections triggered by previous critical findings or in response to a specific issue
- 18 inspections performed under the European Medicines Agency's inspection programme for centrally authorised products.

Six critical, 150 major and 84 minor findings were identified (Table 1). The number of critical findings equated to approximately one in every six inspections, somewhat less than in the previous reporting period where there was approximately one critical finding in every three inspections. This reduction could indicate that significant issues identified at previous inspections were found to have been largely resolved on re-inspection, or that there has been a more general positive trend toward compliance. It could also reflect that the inspection programme from April 2016 to March 2017 mainly included routine, rather than targeted, inspections.

The six critical inspection findings are summarised below.

Signal management

Two of the six critical findings related to signal management, and both had previously been reported at an earlier inspection.

In the first case, there was a repeated failure to include all available safety data in signal detection activities, including cumulative individual case safety report (ICSR) data located in the global safety database and non-ICSR literature articles. Further methodological deficiencies were also identified for quantitative signal detection using adverse reaction data derived from ICSRs, and the MAH lacked an appropriate process to track safety signals.

In the second case, the evaluation of a safety signal was incomplete, with the conclusions drawn (and consequent decisions) from the safety evaluation not supported by appropriate scientific or clinical justification. In addition, inadequate document control for safety reviews led to a lack of accurate records on when reviews were conducted, whether appropriate clinical review had taken place and whether reports had been finalised in a timely manner. Other findings highlighted procedural deficiencies in signal management processes.

Table 1. Findings by inspection type (1 April 2016 – 31 March 2017).

Inspection type	Number of inspections	Number of inspection findings[a]		
		Critical	Major	Minor
Routine initial inspection	13	2	54	31
Routine re-inspection	15	2	68	36

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organisations may need to implement as soon as precise details of the new law become clear. In the meantime, while there is uncertainty, it is not anticipated that the law change will have a significant impact on most research studies. The new legislation only addresses some of the requirements relating to the handling of personal data, and other important considerations are not changing.

Source: <https://tinyurl.com/ydeow578>

EMA surveys companies on their readiness for Brexit

The European Medicines Agency (EMA) has launched a survey to gather information on companies' preparations for Brexit and address concerns about the supply of medicines.

The EMA is asking marketing authorisation holders located in the UK – or those with quality control, batch release and/or import manufacturing sites, or a Qualified Person for Pharmacovigilance (QPPV) or Pharmacovigilance System Master File in the UK – about their plans to submit transfers, notifications or variations to their marketing authorisations in the context of the UK's withdrawal from the EU. The aim of the survey is

- to identify companies where there is a need for concerted action to address medicines supply concerns due to Brexit, in order to protect human (and animal) health
- to help the agency and the European Commission (EC) plan resources for areas where the submissions will be processed.

Information from the survey will also be used to inform the next steps in Brexit preparations for the EMA, the EC and the European medicines regulatory network.

UK sites

The survey was sent directly to holders of a centralised marketing authorisation for human (or veterinary) medicines located in the UK, or those with an important part of their site operations in the region. The deadline for returning completed

- 427 have UK-based marketing authorisation holders
- 323 have UK-based QPPVs.

The survey should also prompt companies to start planning for the regulatory steps required for their centrally authorised products to remain on the EU market post-Brexit, minimising disruption to medicines supply and avoiding shortages.

Further surveys may be carried out by the EU national competent authorities for nationally authorised products. Companies should check the EMA's dedicated webpage regularly for guidance on the consequences of Brexit.

Source: <https://tinyurl.com/y85rq849>

News *in brief*

Swissmedic updates approach to biosimilar studies

On 1 January 2018, the Swiss Agency for Therapeutic Products (Swissmedic) issued updated guidance and a Frequently Asked Questions document on the authorisation of biosimilar products.

For a biosimilar to be authorised, the applicant must prove that the candidate biosimilar is sufficiently similar to the reference product in terms of structure, biological activity, efficacy, safety and immunogenicity. Previously, for main studies on the comprehensive comparability with a biosimilar, Swissmedic only accepted data for a reference product authorised in Switzerland or the EU. For supplementary studies, comparator products from Japan were also accepted.

The updated guidance now allows the foreign comparator product for main studies to originate from the USA, while that for supplementary studies can originate from Canada. However, where applicants choose to source comparators from the USA they will need to meet additional regulatory requirements. Specifically, "if the product is obtained from the USA for the comprehensive comparability studies with the biosimilar – including safety and efficacy – three-way bridging between the biosimilar, the EU and the US comparator product must be carried out". In contrast, companies that use EU comparators only need to perform bridging with the Swiss reference product.

Source: <https://tinyurl.com/y9uqq5of>

FDA releases draft guidance to discourage incomplete submissions

The FDA has released draft guidance entitled 'Refuse to File: NDA and BLA Submissions to CDER'. The guidance is designed to clarify the circumstances under which the Center for Drug Evaluation and Research (CDER) may refuse to file a new drug application (NDA), a supplemental NDA (sNDA), a biologics licence application (BLA) or a supplemental BLA (sBLA). The guidance emphasises the importance of submitting a complete application to CDER to minimise the risk of a refuse-to-file action. The FDA will file an NDA (and usually a BLA) within 60 days of receipt or will inform the applicant of the refusal to file, effectively stating that the application meets the threshold (in terms of its completion) to permit a substantive review. However, the

Aim
To provide news and information to allow clinical research and quality assurance professionals, trainers, regulators, academics and members of ethics committees to stay up to date with clinical research and good practice developments.

Scope
Executive summaries of key laws and guidelines relating to clinical research in the ICH regions.

Summaries of relevant articles and information in other publications, press releases and information on the Internet.

Information on:
- changes in regulations, codes of practice, guidelines and new clinical research procedures
- news from important meetings and conferences
- ICH developments and progress
- news, views and opinions about ICH GCP implementation
- solutions to compliance-related problems
- inspection findings and lessons to be learnt
- clinical research methodology, statistical and legal issues
- quality assurance issues and procedures
- self- and independent audit practice
- training courses, jobs and other opportunities.

Sources of information
- We gather news from correspondents and other sources around the world.
- We gather intelligence from those actively involved in the regulatory process.
- We review the major medical, clinical research and QA journals.
- We search the web and regularly visit the websites of the major regulatory authorities in Europe, the USA and Japan, pharmaceutical industry and professional associations, major academic organisations and health associations.
- Sources of information, current at the time of publication, are usually quoted at the end of each article.

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