MHRA issues GCP inspection metrics
The UK’s Medicines and Healthcare products Regulatory Agency (MHRA) has published metrics relating to the activities of its GCP Inspectorate for the period 1 April 2010 – 31 March 2011. The report provides an overview of the number and types of inspections performed over the 12-month period. It describes all the critical inspection findings and summarises the major and other findings for commercial sponsors, contract research organisations, non-commercial sponsors, Phase I units and investigator sites. Find out more on page 2 ►

Understanding European referral procedures
The risk-benefit profile of a new medicine evolves over time. European legislation allows the European Commission, EU Member States and marketing authorisation holders to initiate a referral procedure in the event of concerns about the safety of an authorised medicine. In response, the European Medicines Agency must conduct a scientific assessment of the medicine and make a recommendation for a harmonised position to be adopted across the EU. See page 5 ►

EMA and FDA strengthen pharmacovigilance collaboration
The European Medicines Agency (EMA) and the FDA have announced regular collaborative meetings to provide a forum for a more systematic and focused exchange of information on the safety of medicines. The increased interaction will allow them to work swiftly in this critical area and to coordinate communication activities. Read more on page 6 ►

Launch of UK Early Access to Medicines Scheme
A new Early Access to Medicines Scheme (EAMS) aims to give patients with life-threatening or seriously debilitating conditions access to unauthorised medicines when there is an unmet medical need. The UK’s Medicines and Healthcare products Regulatory Agency (MHRA) announced EAMS on 14 March 2014. Under the scheme – which begins taking applications from companies in early April 2014 – the MHRA will give a scientific opinion on a new medicine or indication that has demonstrated a positive risk-benefit balance. EAMS underwent consultation in 2012 and is a voluntary scheme. Source: <http://bit.ly/NdkyCo>

HMA releases data on Voluntary Harmonisation Procedure
The EU Heads of Medicines Agencies (HMA) has published metrics on the Voluntary Harmonisation Procedure (VHP). Launched initially as a pilot scheme, the VHP allows sponsors to obtain a coordinated assessment of an application for a multinational clinical trial in the EU before seeking national approval. Once a positive VHP opinion has been given, individual national competent authorities will generally give clinical trial authorisation within 10 days. Learn more about how the procedure has been used on page 4 ►

GCP lessons: lack of financial disclosure information
The FDA regulations require sponsors to submit complete and accurate financial certification or disclosure statements from investigators. A recent FDA inspection found that a sponsor had failed to obtain financial information from 122 sub-investigators across four oncology trials. The findings also highlight how a company’s financial disclosure responsibilities differ when acting as a clinical trial sponsor and when filing a new drug application. Discover why this is important on page 7 ►
MHRA issues GCP inspection metrics


The GCP Inspectorate is responsible for assessing the compliance of organisations with UK and EU legislation relating to the conduct of clinical trials on investigational medicinal products (IMPs). By publishing annual metrics – albeit rather belatedly – the Inspectorate identifies where inspectors have observed non-compliance with GCP in the past, and hopefully prompts stakeholders to review their procedures and operations accordingly.

During the 12-month period a total of 161 GCP inspections (categorised as routine systems, study-specific, triggered and additional site inspections) were undertaken by the Inspectorate. Similar numbers of inspections were performed of non-commercial sponsors (35), investigator sites (34) and commercial sponsors (30). Fifteen triggered inspections were performed as a result of information received by the Inspectorate (eg. in response to a serious breach report). Further details of the inspection findings are provided below for each type of inspected organisation.

Commercial sponsors
Thirty commercial sponsors were inspected, with three triggered inspections. One critical finding was identified relating to subject confidentiality, where serious adverse event reports and drug accountability logs containing subject names were found in the Trial Master File. Moreover, the sponsor did not have a formal procedure for managing such information if inadvertently received.

The majority (22; 73.3%) of inspected sponsors had at least one major and/or critical finding. The mean (maximum) number of major findings per inspection was two (eight); the mean (maximum) number of other findings per inspection was 6.5 (11). The most frequent major and other inspection findings are summarised in Table 1.

Contract research organisations
Twenty-three contract research organisations (CROs) were inspected, with four triggered inspections. One CRO had two critical findings:
• the first related to subject confidentiality, where the CRO transferred source data documents (eg. assessment forms, consent forms and logs) containing subject names to the sponsor; it is unclear whether this was the same sponsor with the critical finding described above
• the second critical finding related to IMP manufacture without an appropriate licence.

The majority (17; 73.9%) of inspected CROs had at least one major and/or critical finding. The mean (maximum) number of major findings per inspection was two (five); the mean (maximum) number of other findings per inspection was 5.5 (nine). The most common major and other inspection findings are summarised in Table 2.

Non-commercial organisations
Thirty-five non-commercial organisations were inspected, with four triggered inspections. Three non-commercial organisations had at least one critical finding.

Table 1. Most frequent findings from inspections of commercial sponsors (2010–2011).

<table>
<thead>
<tr>
<th>Major inspection finding (% of total)</th>
<th>Other inspection finding (% of total)</th>
</tr>
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<tbody>
<tr>
<td>Quality systems (14.5%)</td>
<td>IMP management/pharmacy (9%)</td>
</tr>
<tr>
<td>Pharmacovigilance (9%)</td>
<td>Record-keeping/essential documents (9%)</td>
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<tr>
<td>Record-keeping/essential documents (9%)</td>
<td>Contracts and agreements (8%)</td>
</tr>
<tr>
<td>Clinical trial authorisation (7%)</td>
<td>Quality systems (8%)</td>
</tr>
<tr>
<td>Contracts and agreements (7%)</td>
<td>Training (8%)</td>
</tr>
<tr>
<td>IMP management/pharmacy (7%)</td>
<td>Medical writing (7%)</td>
</tr>
<tr>
<td>Medical oversight (7%)</td>
<td>Pharmacovigilance (7%)</td>
</tr>
</tbody>
</table>
Table 2. Most frequent findings from inspections of CROs (2010–2011).

<table>
<thead>
<tr>
<th>Major inspection finding (% of total)</th>
<th>Other inspection finding (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality systems (20%)</td>
<td>Contracts and agreements (11%)</td>
</tr>
<tr>
<td>Pharmacovigilance (11%)</td>
<td>Quality systems (9.5%)</td>
</tr>
<tr>
<td>Data management (9%)</td>
<td>Project/trial management (8.5%)</td>
</tr>
<tr>
<td>Computer systems validation (7%)</td>
<td>Quality assurance (8%)</td>
</tr>
<tr>
<td>IMP management/pharmacy (7%)</td>
<td>Record-keeping/essential documents (7.5%)</td>
</tr>
<tr>
<td>Protocol compliance (7%)</td>
<td></td>
</tr>
<tr>
<td>Statistics (7%)</td>
<td></td>
</tr>
</tbody>
</table>

Finding each; for two of these this was at a second follow-up inspection, after previous critical findings had been referred to the MHRA Inspection Action Group. Details of these findings are given in the metrics report and primarily relate to clinical trial oversight by the inspected organisation.

Almost all (34; 97.1%) inspected non-commercial organisations had at least one major and/or critical finding. The mean (maximum) number of major findings per inspection was four (10); the mean (maximum) number of other findings per inspection was 7.5 (13). Major findings covered the lack of specific systems and processes within the organisation to manage trial aspects, including

- the non-submission of annual study reports
- failure to address remarks on MHRA clinical trial authorisations
- failure to gain MHRA approval for substantial amendments or to submit end of trial notifications and serious breach reports
- the inadequate control of the IMP, including failure to ensure that double-blind trials remained blinded
- a poor informed consent processes, including a minor being included in a trial without the consent of a person with parental responsibility
- an inability to verify the trial and its conduct due to failure to maintain essential documents.

Commercial Phase I units

Sixteen inspections were undertaken at commercial Phase I units/clinical research units, 14 of which were also inspections for the MHRA voluntary Phase I accreditation scheme. No critical findings were reported. Three (18.8%) units had one major finding each, relating to

- dose escalation
- IMP management/pharmacy
- protocol compliance.

The most common other inspection findings (percentage of the total number) related to dose escalation (9.5%), quality systems (9.5%), contracts and agreements (8.5%), facilities and equipment (6%) and project/trial management (6%).

Investigator sites

A total of 34 investigator sites in the UK were inspected, with three triggered inspections. All were associated with a sponsor inspection and therefore the focus of the inspection was on site oversight by the sponsor/CRO.

One site had one critical finding relating to poor packaging and labelling of the IMP, and provision of the IMP at strengths higher than those required to be given to subjects. As a result, a subject mistakenly took an overdose of IMP and died. The trial sponsor who was responsible for IMP packaging and labelling...
had identified that there was a potential IMP issue via pharmacovigilance signals, but had failed to take prompt action to prevent the subject’s death.

The majority (25; 73.5%) of inspected sites had at least one major and/or critical finding. The mean (maximum) number of major findings per inspection was one (five); the mean (maximum) number of other findings per inspection was five (nine). The most common major and other inspection findings are summarised in Table 3 (on page 3).


Heads of Medicines Agencies releases data on Voluntary Harmonisation Procedure

The EU Heads of Medicines Agencies (HMA) has reported on how the Voluntary Harmonisation Procedure (VHP) has been used over the past 5 years.

In 2004 the HMA established the Clinical Trials Facilitation Group to co-ordinate the implementation of the EU Clinical Trials Directive (2001/20/EC) across EU Member States. Since then, the Group has acted as a forum within which to agree the common principles and processes to be applied throughout the European medicines regulatory network. It has also promoted the harmonisation of clinical trial assessment decisions and administrative processes across national competent authorities.

Multinational clinical trials represent about 25% of the total number of clinical trials performed in the EU and since 2009 the VHP has been key to their harmonisation. The VHP began as a pilot project, and it remains as a voluntary procedure through which sponsors can obtain the coordinated assessment of an application for a multinational clinical trial in the EU prior to seeking national approval.

Under the VHP, a single application is evaluated collectively by the competent authorities of the Member States where the clinical trial will take place; scientific questions on the protocol and the investigational medicinal product are clarified together and the assessment step should take no more than 60 days. The scientific content of an application with a positive VHP opinion may not be changed when submitted to the national competent authorities, although it may be adapted to meet national requirements, and clinical trial authorisation by each competent authority will generally be given within 10 days.

In June 2013 a new modified VHP Guideline (Version 3.1) was released, reflecting experience with the VHP from 2009 to 2012. The procedure was modified in order to streamline the assessment, with the following key improvements:

- the introduction of a second round for the inclusion of new Member States after a positive VHP opinion
- provision for subsequent substantial amendments to be handled by the VHP
- clarification of the rules on fees and for conditions after a VHP or substantial amendment submission
- provision for the harmonised scientific assessment to start immediately after the submission of a single application.

VHP submissions

As of June 2013, all EU national competent authorities (other than Poland, Slovakia and Lithuania) had joined the VHP, although not all authorities had actually taken part at that time. At the start of this year the HMA published a variety of metrics derived from experience with the VHP up to January 2014.
As shown in Table 1, the number of VHP submissions has increased annually for both clinical trial applications and substantial amendments, with almost 20% of all multinational clinical trials in Europe undergoing the VHP before being submitted to national competent authorities in 2013. Overall, 90% of submissions were made by commercial sponsors.

Table 1. Number of VHP submissions by year.

<table>
<thead>
<tr>
<th>Year</th>
<th>Clinical trial applications</th>
<th>Substantial amendments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>2010</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>2011</td>
<td>85</td>
<td>38</td>
</tr>
<tr>
<td>2012</td>
<td>124</td>
<td>129</td>
</tr>
<tr>
<td>2013</td>
<td>166</td>
<td>225</td>
</tr>
<tr>
<td>Total</td>
<td>416</td>
<td>397</td>
</tr>
</tbody>
</table>

Up to the end of 2013, 78.7% of VHPs had a positive outcome, with only 5.0% not being approved. The remaining applications were either open (8.2%), subject to divergent opinions (3.1%) or withdrawn by the applicant (5.0%).

A total of 130 sponsors have used the VHP, with 43% of submissions coming from outside the EU. Notably, the USA has made almost three times as many submissions (160) as any other country. Unsurprisingly, over the period of evaluation the VHP has been used most commonly for Phase II and III trials (see Table 2). On average, six Member States are involved in each VHP.

Finally, for the period under evaluation, the mean duration of a VHP submission (excluding open, withdrawn and accelerated VHPs but including the additional time required for submissions with grounds for non-acceptance) was 53.1 days (minimum 0 days, maximum 75 days).


Understanding European referral procedures

The European Medicines Agency (EMA) may initiate a referral procedure in order to resolve concerns over the safety or benefit-risk balance of a medicine or class of medicines.

A referral may be initiated by either the European Commission (EC), an EU Member State or a company that markets a particular medicine, for one of the reasons outlined below. Once begun, the referral requires the EMA to conduct a scientific assessment of the medicine (or class of medicines) on behalf of the EU; in effect, the medicine (or class) is ‘referred’ to the agency so that it can make a recommendation for a harmonised position to be adopted across the EU. Once completed, the EC usually issues a decision to all Member States reflecting the measures to take to implement the agency’s recommendation:

- safety-related referrals are assessed by the Pharmacovigilance Risk Assessment Committee and then by either the Committee for Medicinal Products for Human Use (CHMP) or, for nationally authorised medicines, by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human
- all other referrals on human medicines are assessed by the CHMP only.
Types of referral

All referrals are described in current legislative texts that govern how medicines are authorised and monitored in the EU.

• Article 13 referrals are triggered for a medicine that has been authorised by mutual recognition or via the decentralised procedure when there is a disagreement between Member States on a variation.

• Article 20 procedures are triggered for medicines that have been authorised via the centralised procedure where there are manufacturing or safety issues.

• Article 29 paediatric referrals may be triggered by a marketing authorisation holder when applying for a new indication, a new pharmaceutical form or a new route of administration for use in children for a product authorised under Directive 2001/83/EC.

• Article 29(4) referrals are triggered when there is a disagreement between Member States on a medicine being evaluated during a mutual recognition or decentralised procedure, on the grounds of a potential serious risk to public health.

• Article 30 referrals are triggered when Member States have adopted different decisions over the years for certain medicines (eg. different indications or contraindications) and there is a need for harmonisation across the EU.

• Article 31 referrals are triggered when the interests of the Community are involved, following concerns relating to the quality, safety or efficacy of a medicine or class of medicines.

• Article 107i procedures are triggered when a Member State or the EC considers that urgent action is necessary because of a safety issue (eg. consideration of the suspension or revocation of a marketing authorisation; the prohibition of supply of a medicine; or major changes to the marketing authorisation such as the removal of indications, reduction of the recommended dose or new contraindications). The procedure also applies where there is a safety issue with a class of medicines.

In December 2013, the EMA announced that – from 20 January 2014 – all correspondence related to the start of a referral procedure, as well as all subsequent documents provided to marketing authorisation holders and applicants during the referral procedure, will be sent electronically (via e-mail and/or Eudralink only).

New guidance

To support stakeholders, particularly marketing authorisation holders, on 20 January 2014 the EMA published a Questions & Answers guidance document addressing a number of questions relating to the handling of Article 31 pharmacovigilance referral procedures (ie. on the procedures that apply when the referral results from the evaluation of data from pharmacovigilance activities for authorised products). The guidance provides an overview of the practical and operational aspects to be considered in the handling of Article 31 pharmacovigilance referral procedures, and should be read in conjunction with Directive 2001/83/EC.

the new cluster will provide a forum for a more systematic and focused exchange of information on the safety of medicines.

The EMA and the FDA have previously established clusters to discuss issues related to several topics, from biosimilar medicines, blood-based products and cancer treatments to orphan and paediatric medicines. Given the truly global nature of these topics, representatives from the regulatory agencies of Canada (Health Canada) and Japan (the Japanese Pharmaceuticals and Medical Devices Agency) are also involved in some of the clusters.

“In an increasingly globalised pharmaceutical market, collaboration between medicines’ regulators is essential,” explained the EMA’s Executive Director Guido Rasi in a statement made on 19 February 2014. “Medicines’ regulators are inter-dependent: any action taken in one territory has repercussions on the rest of the world. International cooperation is a key area of work for the Agency.”

As part of the new cluster, discussions on any pharmacovigilance issue will now take place between the agencies on a monthly basis by teleconference. This increased degree of interaction will allow the agencies to work swiftly in the area of the safety of medicines and to coordinate communication activities. Representatives from Health Canada and the Japanese Pharmaceuticals and Medical Devices Agency will participate in the meetings as observers.

Source: <http://bit.ly/1m9JuWF>

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GCP lessons

Lack of financial disclosure information

FDA regulations require sponsors of clinical trials to obtain sufficient financial information from investigators to allow them to submit complete and accurate certification or disclosure statements. A recent FDA inspection found that a US sponsor had failed to obtain financial information for each of the 122 sub-investigators participating in four different Phase II oncology trials.

Following the inspection, the sponsor wrote to the FDA to explain that it considered it unnecessary to obtain financial disclosures from these sub-investigators (all of whom were subjects’ or patients’ local physicians) because there were no financial relationships to disclose. However, the sponsor also described one corrective action relating to the information that it will provide to the agency when it files the new drug application (NDA). The proposed corrective action highlights a critical misunderstanding.

As indicated in the resulting FDA warning letter, a sponsor’s responsibilities as an applicant at the time of an NDA filing differ from its responsibilities as the sponsor of a clinical trial. A sponsor is required to comply with all of the relevant requirements, including the requirement to obtain financial information. The sponsor must therefore collect this information at the investigational new drug application (IND) stage and it must also obtain each sub-investigator’s commitment to update this information promptly if any relevant changes occur during the trial and for 1 year following the completion of the trial.

In February 2013 the FDA issued guidance entitled ‘Financial Disclosure by Clinical Investigators’, which is intended to help clinical investigators, the industry and FDA staff to interpret and comply with the regulations governing financial disclosure by investigators. The guidance explains why financial disclosure data are important and why they need to be collected prior to study initiation.

The financial disclosure process provides the FDA with information on whether, and to what extent, a sponsor has taken steps to minimise the risk of bias. For example, a sponsor might minimise the potential for bias resulting from any financial interests and arrangements through study design (eg. using randomisation and blinding techniques) or by asking someone with no financial interests or arrangements to evaluate the study endpoints.

The FDA considers the financial disclosure information and the methods used by the sponsor to minimise bias during the review of marketing applications, to assess the reliability of the resulting clinical data. Sponsors can work with the FDA to minimise any potential bias. The FDA also strongly encourages sponsors of studies not conducted under an IND/investigational device exemption application to collect financial information prior to study initiation.

Sponsors should appreciate that the agency may refuse to file a marketing application that does not contain the required financial information, or a certification indicating that the applicant has acted with due diligence to obtain the information but was unable to do so, stating a reason.

Source: <http://1.usa.gov/1bbUaA>, <http://1.usa.gov/1jrVLZr>
**EMA identifiers track new medicines**

In February 2014, the European Medicines Agency (EMA) announced the introduction of unique product identifiers (UPIs) to track medicines through the pre-authorisation procedures. With immediate effect, companies that approach the EMA for the first time with a new medicine – regardless of whether the medicine is for an orphan designation, a procedure related to paediatric development or a scientific advice procedure – must complete a registration form to provide simple information on the medicine. This must then be sent to upiregistration@ema.europa.eu in order to receive a UPI. Companies will then need to use this UPI every time they contact the agency about any matter related to the medicine. The assignment of UPIs contributes to the agency’s initiatives to improve the efficiency of its processes as part of its ongoing reorganisation. It will also help to create a unique platform for all pre-authorisation activities. The EMA will assign UPIs to all new medicines, but the new procedure does not apply to medicines for which procedures are already ongoing. In addition, the agency has begun updating guidance documents, such as the Procedure for Orphan Medicinal Product Designation, which are affected by the introduction of UPIs.

*Source: <http://bit.ly/1dHpF3P>*

**IMB guide on adverse reactions**

In January 2014, the Irish Medicines Board (IMB) issued a guide to help marketing authorisation holders and applicants with the implementation and introduction of new requirements for product information for medicinal products authorised in Ireland. The guide includes national recommendations for including information on the status of additional monitoring in materials to be distributed to healthcare professionals and patients. Current EU pharmacovigilance legislation introduces a new framework for enhanced risk proportionate post-authorisation data collection for medicinal products. This includes additional monitoring to characterise the safety profile of newly authorised medicinal products or those requiring further safety data. It also mandates the inclusion of standard text in the product information of authorised medicines, expressly asking healthcare professionals and patients to report suspected adverse reactions in accordance with their national spontaneous reporting system. Medicinal products under additional monitoring are identified across all EU Member States by an inverted black triangle. The guide highlights the need for marketing authorisation holders to regularly check the European list of products under additional monitoring, which is reviewed monthly and maintained on the European Medicines Agency website.

*Source: <http://bit.ly/1n1hoje>*