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MHRA reports critical inspection findings relating to Trial Master File

The Trial Master File (TMF) comprises the essential documents that allow the conduct of a clinical trial to be reconstructed and evaluated. Both the development of suitable electronic TMF platforms and the transition from paper to electronic TMF systems are challenging. In the Medicines and Healthcare products Regulatory Agency's (MHRA's) latest annual GCP inspection metrics report, both of the critical inspection findings identified at sponsor organisations were related to the TMF, and included the observation that the TMF was not readily available to the inspectors, directly accessible and complete. More details on page 2 ▶

Cooperation between regulators and health technology assessment bodies creates synergies

Since the initiative began in 2010, the collaboration between the European Medicines Agency and the European network for Health Technology Assessment has brought added value during the development and lifecycle of drugs. It is expected that this will lead to real benefits for the future, from avoiding the duplication of work to optimising the timing and planning of the separate phases of pharmaceutical product development, assessment and management. Details are provided in a new report on the collaboration's 3-year work plan. See page 4 ▶

GCP lessons: lawyer's response to FDA warning letter fails to impress

Following an inspection last summer, the FDA has taken another US investigator to task for deviating from his investigational plans. The resulting warning letter reveals how a lawyer made a written response to the FDA on behalf of the investigator, who did not agree with all of the findings. More on page 7 ▶

Latest on EU Trial Master File guidance

Gabriele Schwarz, Head of the German GCP Inspectorate, has asked us to clarify that EU Trial Master File guidance is expected to be released soon for public consultation.

EMA to assess impact of critical inspection findings on drug authorisations

The European Medicines Agency (EMA) has started a review of medicines where studies were conducted at the Alkem Laboratories site in Taloja, India. This follows a GCP inspection of the site that raised concerns about the possible "intentional misrepresentation" of study data used to support the marketing authorisation applications for some medicines in the EU. The inspection was carried out jointly by the German and Dutch authorities in March 2015 in the context of a routine evaluation of applications for nationally authorised medicines. Further information on page 3 ▶

New ways to tackle counterfeit medicines

The threat of counterfeit medicines – which range from being useless to being fatal – is a growing global phenomenon, with estimates suggesting that up to 10% of drugs in the global supply chain are fake. Efforts to curb counterfeiting are being hampered by the lack of a consistent global approach as counterfeits become increasingly more sophisticated. See page 5 ▶

MHRA reports critical inspection findings relating to Trial Master File

The Medicines and Healthcare products Regulatory Agency (MHRA) has issued a GCP inspection metrics report for the 12 months from 1 April 2014 to 31 March 2105.

In the UK, the GCP Inspectorate is responsible for assessing the compliance of organisations with UK and EU legislation on the conduct of clinical trials on investigational medicinal products (IMPs). It undertakes inspections of sponsor organisations, contract research organisations (CROs), non-commercial organisations, investigational trial sites, clinical laboratories and GCP archives.

A total of 95 inspections were performed by the MHRA GCP Inspectorate over the 12 months to 31 March 2015, notably fewer than in previous years. The 95 inspections were characterised as follows:

- investigator sites – 22
- non-UK/European Medicines Agency (EMA) inspections – 19
- non-commercial sponsors – 14
- commercial sponsors – 11
- Phase I units –10
- laboratories conducting clinical trial sample analysis –10
- CROs –9.

Fifteen triggered inspections were performed, 13 of which were non-UK/EMA inspections, with the other two involving non-commercial sponsors.

Commercial sponsors

The metrics report indicates that of the 11 inspections of commercial sponsors, two (18.2%) had one critical finding and all 11 (100%) had at least one major and/or critical finding. In total there were two critical findings, 33 major findings and 85 other findings.

The two critical findings were identified at two global pharmaceutical companies. In both cases an initial verbal critical finding was given on the failure of the organisation's Trial Master File (TMF) to be the basis for inspection, ie. to be readily available, directly accessible and complete, as per the requirements of Statutory Instrument 2004/1031 Regulation 31A. In April 2014, the MHRA GCP Inspectorate updated its definition of a critical finding to include failures in the provision of the TMF, as such failures prevent inspectors from carrying out their statutory duty in assessing compliance with the applicable legislation. Similar issues were found in previous years with other organisations, but at that time were not graded as critical.

In each case, an initial inspection showed that, overall, the presentation of the selected trial TMFs was "grossly inadequate". The TMF was not readily available or accessible and there was some evidence of it being incomplete. Essentially, there was a failure to have a single TMF within the company because multiple electronic systems based on drug/function hierarchy had been combined to create the TMF. Thus there was no single system that was designed to be the electronic TMF (eTMF) with the appropriate functionality. The ability of inspectors to access documents for review and to evaluate whether the TMF was complete was severely hampered as a result. Following the verbal critical findings, the companies were both given the opportunity to present the full TMF for some trials at a subsequent inspection a few months later, so that the inspectors could assess the compliance of the trial.

The TMFs were presented for inspection in paper format at one organisation and primarily in electronic format at the other. The companies demonstrated that a single TMF for a trial could be provided by collating all the documents from the different systems into one place. However, the provision of the TMF in this way for subsequent inspection took considerable time and effort, and the critical finding therefore remained because the TMF could not be regarded as being "readily available".

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The companies were subsequently required to provide quarterly summary updates to the Lead Inspectors on the progress of the development of the eTMF project and the implementation of the new system, to include details of its use once up and running. This will enable a further inspection to be scheduled at an appropriate time to assess the new eTMF for compliance with the legislation.

The most common major inspection findings reported for commercial sponsors were in the areas listed below. Reassuringly there were no major findings relating to subject safety, informed consent or subject confidentiality, and unlike in previous reports there were no major findings relating to contracts and agreements:

- record keeping/essential documents – 19%
- quality systems – 13%
- IMP management/pharmacy – 10%
- quality assurance –10%
- archiving – 6%
- monitoring – 6%
- organisation's oversight of clinical trials – 6%
- pharmacovigilance – 6%.

CROs

Nine CROs had a systems inspection and six of these had a major finding. In total there were 14 major and 75 other inspection findings. The majority of the major inspection findings were reported only once, with just record keeping/essential documents reported three times and case report form data/source data reported twice.

Investigator sites

All 22 investigator site inspections were associated with a related sponsor/CRO inspection. None of the sites had a critical finding but 11 (50.0%) had at least one major finding. In total, there were 22 major and 235 other inspection findings. Major inspection findings most commonly related to IMP management and pharmacy or case report form data/source data, both of which were reported on five occasions.

The awaited European TMF guidance should help to prevent some of these issues!

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

EMA to assess impact of critical inspection findings on drug authorisations

Following critical inspection findings in two bioequivalence studies, the German regulatory agency has asked the European Medicines Agency (EMA) to evaluate whether marketing authorisations of other medicinal products are safe.

In a notification to the EMA dated 24 March 2016, the German Federal Institute of Drugs and Medical Devices (BfArM) reported critical findings observed during a joint inspection of Alkem Laboratories, India, undertaken by BfArM and the Health Care Inspectorate of the Dutch Ministry of Health. The findings in two of the three inspected studies – which were performed in 2013 and 2014 – cast doubt over the validity of data from the site.

- In one trial, an electrocardiogram (ECG) printout was used as source data for two different subjects. As the subject's identifier and date of birth must have been actively changed, the inspection team considered this to be intentional misrepresentation of trial data.
- In a second trial, in at least one case ECGs recorded at consecutive time points and ascribed to two different individuals and were judged by experts as having been recorded from one individual. This too was considered to be intentional misrepresentation of trial data.

The following observations were also noted for

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the same day: wrongly assigned ECGs for blocks of successive subjects, displacement or inversion of ECG leads, wrong subject details (date of birth) on an ECG and inaccurate assessment of an ECG by a physician.

The site subsequently acknowledged that there were severe errors within the ECGs, which they say were recorded by contractual technicians, and acknowledged carelessness and non-compliance with the quality system by these users.

In its notification to the EMA, BfArM highlighted that the intentional misrepresentation of data was neither avoided nor detected by the site's quality management system. Moreover, given that the quality management system was a general system covering all parts of the trial, and that a failure of the system in relation to the ECGs was acknowledged by the site, BfArM considers the system to be highly insufficient, and believes undetected severe failure in other areas of the trial cannot be ruled out.

BfArM believes that action is needed at EU level to assess the potential impact of the reported findings on the benefit-risk balance of other medicinal products authorised by Member States on the basis of trials performed at the inspected site, and on pending procedures based on trials performed there in the 2-year period during which the inspected trials were performed. Specifically, the German regulator has urged the EMA to consider whether any action needs to be taken on marketing authorisations for any of the affected drugs.

According to a press release dated 15 April 2016, the EMA will not comment on the case while the review is ongoing.

Source: <http://bit.ly/1Vp9VgP>

Cooperation between regulators and HTA bodies creates synergies

The European Medicines Agency (EMA) and the European network for Health Technology Assessment (EUnetHTA) have published a report on their joint work plan for November 2012 to December 2015.

The EMA–EUnetHTA collaboration aims to create synergies between regulatory evaluation and health technology assessment (HTA) over the lifecycle of a medicine, so as to improve the efficiency and quality of processes for the benefit of EU public health.

The report – issued on 14 April 2016 – highlights how the collaboration has fostered an approach to the generation of data on medicines (pre- and post-authorisation) that reconciles regulatory and HTA requirements into one clinical development programme. This is expected to improve the usefulness of the regulatory evaluation and the information derived from it for subsequent HTAs. It will also enhance experience and knowledge sharing over the lifespan of a medicine. The key achievements of the collaboration over the past 3 years have included the following:

- joint regulatory/HTA scientific advice/early dialogue for medicines developers to reduce duplication and to streamline and optimise the medicines development process for the benefit of patients. EMA and EUnetHTA participated in each other's pilot projects to explore efficient processes by which regulators and HTA bodies can give medicines developers simultaneous feedback on their development plans. The aim is to bring together data requirements for both benefit-risk (regulatory) and value assessments (HTA) into a

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single development plan, which generates data that satisfy the needs of both bodies.

- improved EMA assessment reports to address the needs of HTA bodies. The EMA and EUnetHTA worked together to change the way in which information on the benefits and risks of a medicine is presented in the European public assessment report, resulting in improvements to the report structure. EMA and EUnetHTA also discussed options for displaying the key effects observed for a medicine in a structured manner, making value judgments in scientific decision making more transparent.
- new approaches to the collection of robust data post-authorisation. A number of initiatives explored methods to generate and collect high-quality data that fulfil the information needs of regulators and HTAs once a medicine is authorised and in use. EMA and EUnetHTA collaborated to foster the development and use of patient registries that can collect data relevant for both organisations.
- facilitating EUnetHTA's pilot projects on the rapid relative effectiveness assessment of pharmaceuticals. EMA and EUnetHTA worked to facilitate a framework to allow the timely provision of information from regulatory benefit-risk assessment reports in the rapid relative effectiveness assessments of medicines.
- discussion on the therapeutic indication for medicines. The recognition of the importance of the wording of the indication as approved by regulators for subsequent HTAs led to discussions that will contribute to the development of principles for optimisation, as well as an exchange of views on how to document the scientific reasoning behind the wording.

The EMA and EUnetHTA will continue their collaboration and further areas for cooperation are outlined in the report, including

- more structured interactions in the context of marketing authorisation applications, such as pre-submission dialogue and exchange at the time of concluding the regulatory assessment
- further improvement of regulatory reports to support later HTAs (eg. the inclusion of patient-reported outcomes)
- collaboration on the development of scientific guidelines for the design of clinical development programmes in specific conditions.

Source: <http://bit.ly/1U1Zmzj>

New ways to tackle counterfeit medicines

New anti-tamper and anti-counterfeit labelling solutions have been designed to address the growing global threat of counterfeit medicines.

Counterfeit pharmaceuticals may be contaminated or may contain the wrong or no active ingredient. Alternatively they may have the right active ingredient but at the wrong dose, and consequently have far-reaching public health implications. Estimates of the extent of the problem vary: it is widely quoted that up to 10% of all medicines in the global supply chain are counterfeit, although there is significant regional variation. The threat from counterfeit medicines has attracted considerable concern from bodies such as the World Health Organization (WHO) as well as from governments, regulators and pharmaceutical companies.

In 2006, WHO created the International Medical Products Anti-Counterfeiting Taskforce, and it has actively forged international collaboration that seeks global solutions to this worldwide challenge and raises awareness of the dangers of counterfeit medicinal products. More recently WHO has adopted the term "Substandard, spurious, falsely labelled, falsified

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and counterfeit (SSFFC) medical products", and in 2013 it launched the Global Surveillance and Monitoring System for SSFFC medical products with a view to

- providing technical support in emergencies, linking incidents between countries and regions, and issuing WHO medical product alerts
- accumulating a validated body of evidence to more accurately demonstrate the scope and scale of, and harm caused by, SSFFC medicinal products and to identify vulnerabilities, weaknesses and trends.

Anti-counterfeit labelling

Denny Bros, a UK producer of multi-page pharmaceutical labels and printing solutions, has developed a number of anti-counterfeit labelling solutions that it hopes will help to safeguard both pharmaceutical producers and the public. These include the use of

- a two-dimensional security matrix, which enables information to be encoded using either text or numeric data
- microtext, which enables words to be printed at a size almost unnoticeable to the human eye without the help of magnification
- deliberate print "hickies", which may not be identified by the human eye and would therefore not be reproduced in a counterfeit item
- thermochromatic ink that, when exposed to heat, can reveal or hide print features
- unique serial numbers for incorporation into the print to identify and authenticate individual products
- fluorescent ultraviolet (UV) reactive inks to hide text or pictures until uncovered with UV light
- void protection material, which displays text to show that a product has been tampered with
- silver foil coating and bespoke holograms to make an item more difficult to counterfeit.

For those with an interest in ways of combating or preventing drug counterfeiting, an interesting systematic review was published in *BMJ Open* in March 2015.

Source: <http://bit.ly/1TI0tlz>, <http://bit.ly/1qt7Pz3>

EMA issues draft guideline on good pharmacogenomic practice

The International Council for Harmonisation E15 and E16 Guidelines and current EMA guidance describe some principles for the regulatory evaluation of genomic biomarkers, but there is no guideline on good genomic practice. By addressing this gap, the European Medicines Agency's (EMA's) draft guideline on good pharmacogenomic practice should increase the value of information gathered from genomic studies and facilitate the integration of pharmacogenomics into drug development and patient treatment.

Genomic data have become increasingly important in the evaluation of the safety and efficacy of new drugs, and in guiding patient treatment. As a result, information on genomic biomarkers is now being included in drug labels where relevant. The integration of genomic biomarkers into clinical trials, as well as the technology used, should follow certain principles to ensure that the resulting data are appropriate to underpin decision making and patient treatment.

The new guideline lays out the requirements for the choice of appropriate genomic methodologies during the development and lifecycle of a drug, and reviews the problems encountered during previous studies on genetic variation in drug response. To reflect the continuing advances in genomic technologies, the following topics are covered:

- the emerging knowledge of epigenetic alterations and their use as predictors for drug resistance and response
- the importance of rare mutations in drug response and a comparison of different DNA sequencing methods
- the design of randomised controlled trials for analysing the influence of genetic variation on adverse drug reactions and response
- the translation of knowledge of pharmacogenomic biomarkers into the clinic.

The consultation continues until 16 September 2016.

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

GCP lessons

Lawyer's response to FDA warning letter fails to impress

In July/August 2015, the FDA inspected the conduct of two trials performed in New York, USA, by a psychiatrist and presented its findings to the investigator at the end of the inspection. About 2 weeks later, the investigator took the unusual step of asking his lawyer make a written response to the FDA on his behalf.

Poorly maintained case histories

The inspectors found that the investigator had personally hand-printed the name of his sub-investigator on worksheets for medical history, physical examinations and neurological examinations, to indicate that the corresponding study procedures had been conducted by the sub-investigator even though they had been performed by either the investigator or another study employee. These included

- screening medical history for two subjects
- screening physical examinations and screening neurological examinations for all 14 enrolled subjects
- Day 8 brief physical examinations for 11 subjects
- follow-up visit brief physical examinations for eight subjects.

In addition, on 15 other study records the sub-investigator signed as having performed the respective study procedures, even though they had been performed by either the investigator or another study employee:

- screening psychiatric evaluations for all 14 enrolled subjects
- screening suicide risk assessment for one subject.

In the letter submitted by the investigator's lawyer, the investigator indicated that he had indeed performed the procedures noted above and added the sub-investigator's name instead of his own. He noted that the protocol did not specify to whom the responsibility of obtaining medical histories and performing physical and neurological examinations could be delegated, nor did it specify that a licensed psychiatrist had to document the psychiatric evaluations. He also stated that after the study staff collected the information to complete these study records, the investigator and his sub-investigator carefully reviewed and discussed subject eligibility. He further explained that the worksheets were case report forms that had not been provided by the sponsor, and were "merely considered a work in progress" rather than final documents. The FDA responded that while the protocol did not specify to whom the responsibility of these study activities could be delegated, inaccurate information was recorded in numerous records, which falsely attributed the conduct of study procedures to the sub-investigator.

The lawyer also indicated that while the investigator did not agree with the basis for the assertion of the deficiencies observed during the inspection, the responsibility for these deficiencies rested with the investigator's employer not with the investigator. Predictably, the FDA responded by emphasising that, by signing the Statement of the Investigator (Form FDA 1572), the investigator had agreed to take on the responsibilities of a clinical investigator at his site; he was consequently responsible for ensuring that the studies were conducted properly and in compliance with the FDA regulations, both to protect the rights, safety and welfare of study subjects and to ensure the integrity of study data.

Deviations from approved protocol

Several deviations from the protocols were noted by the inspectors and are detailed in the FDA warning letter. The lawyer's response underlines the lack of appreciation of the importance of protocol adherence:

- although participation in another clinical study involving an investigational drug within 30 days or 5 half-lives (whichever was longer) before the current study began and/or during study participation was an exclusion criterion, one subject who completed another study on 20 January 2015 was randomised into this study on 4 February 2015. The lawyer agreed that this had happened, but noted that the subject did not report any adverse events in either study and was closely monitored throughout the course of the inspected study.
- the eligibility of 13 of the 14 subjects enrolled in one protocol was not verified in accordance with the requirements of the protocol.
- for at least three subjects, an assessment that should have been performed 24 hours post-dose at Visit 2 to measure the overall severity of symptoms and to monitor for adverse events was not performed. The lawyer indicated that because the protocol required the assessment to be administered twice within a short period of time (4 and 24 hours post-dose), "the staff and subjects were instructed to rate these timeframes [sic] in their assessments".

Lessons learned

The tone of the warning letter indicates that the FDA was alarmed by the extent of the inspection findings, and by the investigator's apparent lack of understanding of the implications of both failing to prepare and maintain adequate and accurate case histories and deviating from the protocol. The FDA concluded that the investigator's explanation of the findings (via his lawyer) suggests systemic failures in his conduct of the trials, and specifically raises concerns about the validity and integrity of the data captured at the site.

It is unusual for an investigator's lawyer to reply to an FDA warning letter. Unfortunately, the lawyer's letter met with a common response, ie. it was considered inadequate because it did not indicate that the investigator had put a corrective action plan in place to prevent similar violations in the future.

Source: <http://1.usa.gov/1NaAUdn>

News *in brief*

Enhancing clinical evidence by proactively building quality into trials

An article in *Clinical Trials* has highlighted the importance of "quality-by-design" in the planning and conduct of trials. The report – written by authors from within industry, academia and the regulatory authorities – notes that the current approach to clinical drug development is unsustainable and, as a result, our collective ability to generate reliable data to underpin regulatory and prescribing decisions is at risk.

The Clinical Trials Transformation Initiative (CTTI) investigated how to prospectively build quality throughout the design of clinical trials (ie. quality-by-design), so that trials remain feasible to perform and critical errors are prevented. This led to the development of the CTTI quality-by-design principles document, which outlines the factors that are generally relevant to the reliability of trial data and patient safety. These principles were developed further during several workshops, and independent qualitative interviews subsequently explored the potential challenges for implementing a quality-by-design approach to clinical trials. The CTTI project team then developed recommendations and an online resource guide to support the implementation of this approach.

The authors note that the quality-by-design workshops underlined the importance of incorporating the views of representatives from both within and outside an organisation, including, for example, investigators, site staff and trial subjects. The value of focusing oversight on elements of a trial where errors would have a major impact on subject safety or the reliability of data was also highlighted. Applying the CTTI quality-by-design recommendations and principles should enable organisations to

- prioritise the most critical determinants of trial quality
- identify non-essential activities that can be eliminated to streamline trial conduct and oversight
- formulate appropriate plans to define, avoid, mitigate, monitor and address important errors.

Source: <http://bit.ly/1rR7g3E>

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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