

FDA focuses on medical devices

The FDA has underlined its commitment to the regulation of medical devices by releasing several new draft guidelines and guidance documents on the following: new approaches to speeding up the early-stage development of medical devices; the conditions under which medical device studies may begin more quickly; how to demonstrate that a new device is substantially equivalent to an existing one; and the steps being taken to increase the number of women taking part in device studies. See [page 2](#) ▶

Trials legislation updated in Slovakia

The Slovakian State Institute for Drug Control has issued new clinical trials legislation. The new rules came into effect on 1 December 2011 and, as there is no transition period, apply immediately to all new and ongoing trials conducted in Slovakia. Some of the new requirements relate to the subjects' private health insurance arrangements. Prior to the start of a trial, the sponsor must submit a copy of the clinical trial authorisation issued by the competent authority to each subject's health insurance company and a list of the subjects insured by the particular health insurance company. The investigator should report serious adverse events and unexpected serious adverse reactions to the sponsor and the subject's health insurance company. The definition of a non-interventional clinical trial has been extended and now includes a responsible person called a "guarantee". Such trials should be approved by health insurance companies if the medicinal product has been registered for less than 2 years, and the protocol and final report should be published on the National Centre of Health Information website. For source see [page 7](#) ▶

MHRA seeks input on implementing the Pharmacovigilance Directive

In order to strengthen public health, EU Directive 2010/84/EU makes substantial changes to current pharmacovigilance practice. The requirements of the Directive must enter national Member State legislation by July 2012. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has already begun the necessary consultation process. Find out more on [page 3](#) ▶

Preventing falsified products from entering the supply chain

Falsified medicines represent a significant threat to patient safety but preventing them from entering the supply chain is a challenge. By 2014, the European Commission (EC) will require every pack of authorised medicine to carry a unique identifier within its outer packaging; among other benefits, this will allow verification that the product is authentic. The EC's Concept Paper on the options for introducing this safety feature is outlined on [page 5](#) ▶

GCP lessons: inspectors in Singapore find fault with IP management

Recent GCP inspections in Singapore have found deficiencies in the repackaging of investigational product (IP). The findings highlight why it is important to understand the principles of Good Manufacturing Practice as well as GCP. More on [page 7](#) ▶

Why every computer system validation is unique

Sponsors expect off-the-shelf computer systems to offer efficiencies compared with in-house purpose-built systems. However, sponsors cannot rely on them to be properly validated: time and money are needed to develop complex computer system validation packages. See [page 8](#) ▶

FDA focuses on medical devices

The FDA has underlined its commitment to the regulation of medical devices with the release of several new draft guidelines and guidance documents.

In November 2011, the FDA issued draft guidance aimed at fostering the early-stage development of medical devices. The guidance details new approaches towards feasibility studies undertaken to help resolve final design issues before the device is ready for a large clinical trial.

Under the draft guidance (entitled ‘Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, including Certain First in Human Studies’), early feasibility studies could start earlier in the device development process than previously allowed and certain device modifications would be permitted without FDA approval.

The FDA has sought nine companies to pilot the new approaches. Participants will be sponsors that focus on the type of innovative, early-stage development technologies most likely to benefit from the efficiencies of the programme. Enrolment was due to begin on 12 December 2011 for a 180-day period, and the agency will use findings from the pilot scheme to inform the final guidance.

Understanding trial approvals

On the same day, the FDA issued guidance that describes the agency’s process for approving applications from sponsors of clinical trials involving medical devices. Jeffrey Shuren, Director of the FDA’s Center for Devices and Radiological Health, commented that the “guidance documents give sponsors and FDA device reviewers more flexibility to start investigational studies sooner while maintaining appropriate human subject protections, and they propose efficient ways to support product or study design changes once the study begins.”

Before investigators can proceed with a clinical study involving a medical device that poses significant risks to human subjects, the FDA must approve an investigational device exemption (IDE). The draft guidance ‘FDA Decisions for Investigational Device Exemption Clinical Investigations’ provides

clarification on the regulatory implications of the decisions that the FDA may give based on the review of an IDE, and provides a general explanation of the reasons for those decisions. In an effort to promote the timely initiation of clinical investigations in a manner that protects study subjects, the FDA has developed methods to allow a clinical investigation of a device to begin under certain circumstances, even if there are outstanding issues relating to the IDE submission. The following mechanisms are described in the guidance:

- “approval with conditions”, where the FDA might allow patients to enrol in a study while issues are being resolved (eg. data analysis methods that can be resolved prior to gathering the data or minor divergences from study endpoints or study design assumptions)
- “staged approval”, where the FDA might allow studies to begin with a smaller group of subjects while companies gather additional data, prior to larger general enrolment
- “future considerations”, where issues or recommendations that the FDA believes the sponsor should consider in preparation for a marketing application/future clinical investigation are communicated in an approval, approval with conditions or disapproval letter. This is intended to provide helpful advice to sponsors on important elements of the future application that the IDE may not specifically address.

Comments on the draft guidance have been invited by 18 February 2012.

Approval of low-risk devices

On 27 December 2011, the FDA unveiled draft guidance on how it reviews applications for low-risk medical devices, inviting comments by 26 April 2012. The guidance focuses on pre-marketing notification (510(k)) submissions made to the FDA to demonstrate that a new device is “substantially

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equivalent” to a device that is already legally marketed in the USA. The document is designed to provide guidance to the industry and FDA staff about current review practices for 510(k) submissions, in particular to identify, explain and clarify each of the critical decision points in the process used by the FDA to determine substantial equivalence.

The guidance also addresses two alternative approaches to the traditional 510(k) submission process: the special 510(k) and the abbreviated 510(k) programmes.

The draft guidance notes that a new device does not need to be absolutely identical to the approved device for it to be found substantially equivalent. Rather, there is a flexible approach to determining substantial equivalence to accommodate evolving technology, while maintaining predictability and consistency to promote confidence among device developers, practitioners and patients.

Representation of women

On 19 December 2011, the FDA proposed draft guidelines intended to improve the representation of women in medical device clinical studies, by outlining recommendations for both study design and conduct that may enhance the enrolment of women.

Comments have been invited within a 90-day period.

An earlier report by the US Government Accountability Office on FDA-reviewed drug studies found that, while women represented 52% of study subjects, 30% of study documents did not report outcomes by sex and nearly 40% did not report enrolment demographics. Furthermore, a 2009 study of cardiovascular device pre-marketing applications showed that pivotal studies that reported gender enrolled only 34% women.

The draft guidance addresses the evaluation of sex differences, data analysis and reporting in both pre- and post-marketing device clinical studies. It also covers issues relating to statistical analyses of sex differences and how to report gender-specific information in summaries and labelling for approved devices.

Source: The draft guidance documents are available as follows - early-phase development, <www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm277670.htm>; FDA decisions for IDEs, <www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm277669.htm>; 510(k) submissions and substantial equivalence, <www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf>; evaluating sex differences, <www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283453.htm>.

MHRA seeks input on implementing the Pharmacovigilance Directive

The Medicines and Healthcare products Regulatory Agency (MHRA) has launched a consultation on the proposed regulations that will transpose the Pharmacovigilance Directive into UK law.

EU Directive 2010/84/EU makes substantial changes to the existing pharmacovigilance requirements in order to strengthen public health protection and these must enter national legislation by 21 July 2012. In the UK, the MHRA has therefore released a consultation document and is inviting comments from stakeholders by 28 February 2012.

In addition to providing clear responsibilities, roles and obligations for key parties, the revised

legislation has several aims, notably to

- rationalise EU decision-making on drug safety issues
- strengthen medicines safety transparency and communication
- strengthen companies' pharmacovigilance systems, allowing them to improve their systems constantly while reducing the administrative burden
- ensure the proactive and proportionate

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collection of high-quality safety data through risk management systems and structured data collection from post-authorisation safety studies, and rationalised single case and periodic reporting of suspected adverse drug reactions (ADRs)

- involve stakeholders in pharmacovigilance (eg. through direct patient reporting of suspected ADRs and the inclusion of patients and healthcare professionals in decision making)
- simplify the EU pharmacovigilance procedures, with consequent efficiency gains for the industry and regulators.

To transpose the EU requirements into UK law, the MHRA will revise Part 11 of the draft consolidated medicines regulations, which are also the subject of an ongoing consultation. Full details of the parallel consultation, which closed on 17 January 2012, are available on the MHRA website. In some cases the new Directive and regulation will affect consolidation text outside Part 11. However, following completion of the consultation, the two texts will be aligned within The Human Medicines Regulations 2012.

Consultation document

The UK consultation document (MLX374) summarises the current approach towards key pharmacovigilance topics, and how the Directive will change them, under the following headings:

- reporting, recording and managing suspected adverse reactions
- signal detection and analysis
- risk management
- post-authorisation safety and efficacy studies
- robust and timely decision making
- transparency and communication of pharmacovigilance data
- simplifying and streamlining the system
- enforcement of pharmacovigilance provisions
- application and renewal of marketing authorisations.

The consultation document also presents the draft transposition regulations and explains how they were produced by the MHRA. In addition, it tests that the proposed regulations are a full, accurate and workable legislative text and that the draft has not introduced any unintended changes.

While respondents may comment on any part of the proposed regulations, the MHRA seeks specific input on a number of issues. These are detailed within the relevant sections of the consultation document but are also summarised at the end of the document. The first few, which include the following, are fairly general and ask whether

- respondents agree with the approach taken to the transposition of the Pharmacovigilance Directive
- the draft regulations inadvertently introduce any unforeseen changes
- any of the provisions are unclear
- respondents can comply with the requirements of the legislation
- any other benefits and/or costs arise from the proposals.

However, the remaining questions relate to specific aspects of the draft regulations that change the way in which pharmacovigilance systems currently operate. They include the following.

- Should coroners and carers be allowed to continue to participate in the UK's Yellow Card Scheme, which captures reports of suspected ADRs from healthcare professionals, patients, the public and marketing authorisation holders (MAHs)? The EU Directive requires Member States to take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected ADRs. The Yellow Card Scheme is non-statutory and voluntary, and has been operating for over 40 years. However, for the most part it meets the requirements of the Directive.
- Should the frequency of MAH audits be determined on the basis of a documented risk

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assessment? MAHs will be required to audit their pharmacovigilance system regularly. The frequency of audit will be determined via a documented risk assessment by the MAH, taking into account factors such as the extent of any changes to the pharmacovigilance system, findings from previous audits/compliance checks, findings from regulatory inspections, etc.

- Do you agree with the introduction of an infringement notice process? EU law requires the MHRA to ensure that effective, proportionate and dissuasive penalties are applied to MAHs for non-compliance with pharmacovigilance obligations. The MHRA prefers to engage in educational and advisory activities to ensure compliance; however, when serious and persistent non-compliance is seen, the MHRA has other options, including re-inspection, non-statutory warning letters and meetings with senior company representatives. If these options fail to bring a MAH into compliance, and if there have been serious breaches, the only current legislative option is criminal prosecution. However, this

may not be appropriate, proportionate, timely or effective. The MHRA therefore proposes a more flexible approach whereby an infringement notice is served on a non-compliant organisation when the enforcement authority has objective grounds for considering that it has contravened Directive 2010/84/EU.

- Do you agree with the two-tier level of penalties proposed and the level of penalty attached to the breach of an obligation, and are the proposed penalties proportionate? The draft regulations do not include a specific penalty for breach of an infringement notice, so there is still a requirement to fulfil the need for effective, proportionate and dissuasive penalties. Two options are proposed: criminal prosecution if the breach is a criminal offence, and/or suspension, revocation or variation of one or more marketing authorisations for other breaches.

The full consultation paper is available at <www.mhra.gov.uk/home/groups/comms-ic/documents/publication/con137708.pdf>. Feedback should be submitted using the form provided on the MHRA website (Annex F).

EC Concept Paper on preventing falsified products from entering the supply chain

The European Commission (EC) is seeking feedback on the options for introducing compulsory safety features for medicinal products.

In November 2011 the EC issued a Concept Paper for public consultation. The paper relates to Directive 2011/62/EU, which amends Directive 2001/83/EC with respect to preventing falsified medicinal products from entering the legal supply chain, and is due to be adopted in 2014. The legislation will introduce compulsory safety features for medicinal products as part of the labelling of the outer packaging. These safety features should enable verification that a medicinal product is authentic, allowing identification of an individual pack of

medicinal product. The features should also enable verification of whether the outer packaging has been tampered with.

The consultation on the Concept Paper aims to gather feedback on the various options that could be followed to achieve these aims; stakeholders' comments are invited by 27 April 2012. The paper highlights five consultation topics:

- the characteristics and technical specifications of the unique identifier
- ways to verify safety features

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- systems where information on safety features will be contained
- medicinal products/categories that do not need the safety features
- procedures for notifying medicinal products that are, and those that are not, at risk of falsification.

Unique identifier

In principle, the obligation to provide a unique identifier applies to all medicinal products marketed in the EU, including imported products and marketed products used in clinical studies. The EC recognises that the only way to uniquely identify a pack is to give it a serialisation number, and for this to be an effective authentication tool the number has to be randomised. If a carrier such as a barcode on the outer packaging ‘holds’ the serialisation number, the number on the pack can be checked against its entry in a repositories system to verify its authenticity.

In terms of implementation, there are two options: to leave the choice of technical specification of the unique identifier to individual manufacturers, or to create regulation to harmonise the approach across the EU. The first part of the consultation therefore relates to the benefits and disadvantages of each option. The document then outlines options for creating the unique identifier and asks about the advantages and disadvantages of using the following items:

- the manufacturer product code
- the unique identification number of the pack
- the batch number
- the expiry date.

The pros and cons of the different methods of carrying the serialisation number on the outer packaging (eg. using linear barcodes, 2D-barcodes or radio-frequency identification) are discussed and the EC seeks views on the costs associated with reading devices for the different carriers and for adapting the packaging.

Verifying safety features

The second part of the paper discusses options for “checking-out” products so that the serialisation number is verified before the product enters the supply chain. Three options are proposed:

1. systematic check-out of the serialisation number at the dispensing point
2. as (1) but with additional random verifications by wholesale distributors
3. as (2) but with additional systematic verification by wholesale distributors.

Repositories system

The costs of the system that will hold the information needed to verify the authenticity of a medicinal product will be borne by the manufacturing authorisation holders of those products bearing safety features. Points for consultation on the repositories system include

- handling commercially sensitive information
- the protection of personal data
- repackaging of medicinal products (eg. as may be needed in clinical trials).

White and black lists

Prescription medicinal products may be exempted from having the safety features if the EC places them on a “white list”; non-prescription products will not need the safety features unless they are placed by the EC on a “black list”. The two lists will form an annex to the final legislation and will reflect both the risk of falsified medicines and the risk from falsified medicines (ie. the potential hazard). Important factors for consideration include

- price – cheaper medicines are less likely to be falsified
- sales volume – products marketed in low volumes are less likely to be falsified
- the number and frequency of previous incidents of falsified medicines
- the characteristics of the product that may make it more/less likely to be falsified
- the seriousness of the licensed indication – falsified medicines rarely have the same efficacy as the originals, which may have severe consequences for serious indications.

The paper lists four approaches to identifying medicinal products to go on the black and white lists, and seeks views on which is the most suitable.

Source: <http://ec.europa.eu/health/files/counterf_par_trade/safety_2011-11.pdf>

GCP lessons

Singapore GCP inspections find fault with IP management

In Singapore, the Health Products Regulation Group – under the auspices of the Health Sciences Authority (HSA) – ensures that drugs, innovative therapeutic agents, medical devices and health-related products meet the appropriate standards of safety, quality and efficacy.

Clinical trials on medicinal products must comply with the Medicines Act, the Medicines (Clinical Trials) Regulations and the Singapore Guideline for GCP (SGGCP). Furthermore, all clinical trials on medicinal products conducted in Singapore require a Clinical Trial Certificate from the Centre for Drug Administration at the HSA.

In September 2009, the HSA implemented the GCP Inspection Framework and the first GCP site inspection was performed in Singapore 2 months later. Last June, the Health Products Regulation Group published its first quarterly newsletter, *From the GCP Inspector's Desk*. The newsletter provides a brief update on the latest GCP inspection news and Issue 3 (December 2011) focuses on the repackaging of investigational products (IPs). It notes that

- 40% of the 16 sites inspected in 2011 had been involved in repackaging IP onsite
- of these, 80% had major GCP inspection findings relating to repackaging.

It appears that most sites were unaware that secondary assembly is a form of manufacturing, and that it therefore has to comply with the principles of Good Manufacturing Practice (GMP) and the SGGCP. This requires IP to be manufactured, handled and stored in accordance with GMP and used in accordance with the approved protocol.

There is an important GCP/GMP lesson here for sponsors and investigators. Although the newsletter does not indicate the nature of the repackaging undertaken at the inspected sites, it does explain that it is permissible to repackage IP outside a GMP-certified facility provided that GMP is followed.

One critical text for understanding the requirements of GMP is Annex 13 of Volume 4 of the EU GMP guidelines. Using the term investigational medicinal products (IMPs) rather than IP, the text makes it clear that the sponsor always remains responsible for ensuring that any repackaging of IMP is adequately documented and carried out in accordance with GMP; furthermore, while a Qualified Person (QP) may not be required to certify this activity, the sponsor may well want to seek advice from a QP to ensure that it has been performed correctly. The text further notes that

- the packaging and labelling of IMPs are likely to be more complex and prone to error than those for marketed products, particularly for blinded products with identical appearance; the need to guard against mislabelling is therefore critical

- it is permissible to change the use-by date on IMPs by affixing an additional label to the IMP, which should state the new use-by date and repeat the batch number; it may be superimposed on the old use-by date but not on the original batch number
- over-labelling should ideally be performed at an authorised manufacturing site, but may be done at the investigator site by or under the supervision of the clinical trial site pharmacist (or other healthcare professional in accordance with the national regulations); where this is not possible, it may be performed by an appropriately trained clinical trial monitor
- over-labelling should always be performed according to GMP principles, and specific and standard operating procedures, and should be checked by a second person
- details should be noted in the trial documentation and batch records.

Common inspection findings

Serious inspection findings relating to IMP are not uncommon in other parts of the world, but are perhaps more likely in non-commercial trials. For example, GCP inspections by the Medicines and Healthcare products Regulatory Agency have identified critical findings in relation to IMP management/pharmacy as a result of the following:

- lack of/inadequate QP certification
- importation and manufacturing of IMP without the appropriate licence
- use of expired/recalled/non-GMP-manufactured IMP
- poor/ineffective blinding system
- poor IMP accountability
- lack of agreements with IMP suppliers
- uncontrolled site-to-site transfer.

In addition, warning letters issued following FDA inspections often cite deviations from the federal regulations relating to IP, such as failure to maintain adequate records of the disposition of IP (including dates, quantity and use by subjects).

Source: <www.hsa.gov.sg/publish/bsaportal/en/health_products_regulation/clinical_trials/guidelines/gcp_compliance_inspection.html>



Brookwood's Foundation Course in Clinical Research & GCP

Guildford, UK, 6-7 March 2012
 Budapest, Hungary, 8-9 March 2012
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 Visit www.brookwoodacademy.org for details

Trials legislation updated in Slovakia

Source: <www.sukl.sk/en/clinical-trials/instructions/main-changes-in-slovak-drug-law-clinical-trials-human?page_id=2822>

News in brief

Why every computer system validation is unique

Sponsors can no longer rely on computer system validation (CSV) packages produced by system vendors.

For those looking to contain costs by purchasing off-the-shelf computer systems, the need for in-house CSV may be both costly and frustrating. Some would argue that the developer's own validation should be sufficient, although regulatory agencies may not agree. A recent article in *Quality Matters* looks at other possible cost-containment measures and explains why sponsors cannot just cite a single validation package produced by the vendor.

The article relates to preclinical systems, particularly those subject to Good Laboratory Practice; however, it is also relevant to GCP. It notes that, for several reasons, today's technology is less suitable for vendor CSV than ever before. Modern systems offer increasingly greater options for flexibility and customisation than those from 15 years ago. In addition

- they tend to interface with far more other systems and sit within complex networks
- security threats are increasingly sophisticated and numerous
- systems now routinely include electronic records and signatures.

However, it is the way in which computerised systems are now used that renders the vendor's systems development validation insufficient. Key concerns relate to the need for modern systems to

- be highly configurable by the end-user: systems may need to contain multiple normal ranges, high and low endpoints, coding dictionaries, etc; each of these configurations has to be tested to verify correct inclusion, function and display, but they are unique to each end-user and therefore cannot be tested during the vendor's own testing
- undergo further testing once a system has been installed within the end-user's unique organisational technology environment
- comply with a given SOP unique to the end-user company.

In view of the above, the authors suggest focusing on other measures to reduce the cost and time associated with CSV:

- use the same CSV process for all validation projects
- involve personnel from all groups that will use the technology in the validation process
- make the best use of any support available from the vendor
- perform a thorough audit of the system before buying it.

Huss H, McCormack J, Siconolfi R et al. Preclinical computerised system validation cost containment. December 2011. SQA Technical Document 2011-4. Charlottesville, VA: Society of Quality Assurance

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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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