USA updates its proposed new clinical trial legislation

Updated draft legislation that aims to take drug discovery and development to a new level has been published in the USA. After months of revisions, the new bill now details a range of streamlined policies aimed at ensuring that innovative new therapies in areas of critical need reach patients more quickly. The revised bill recommends significant additional funding for the National Institutes of Health. However, despite requiring the FDA to take on a range of new responsibilities relating to clinical trials, no additional funding is foreseen for the regulatory body.

More on page 2 ▶

New analysis confirms impact of EMA scientific advice

The European Medicines Agency (EMA) has been offering sponsors scientific advice on clinical development plans since 1996. Such advice aims to support the development of effective and safe new medicines that meet the needs of patients, while also preventing the performance of trials that are unlikely to lead to marketing authorisations. A recent analysis of marketing authorisation applications has shown the clear benefits of seeking and following the agency's scientific advice. Details on page 3 ▶

Clinical trial misconduct goes unmentioned in published literature

Given the current demand for the results of all clinical trials to be made publicly available, it would be reasonable to assume that adverse inspection findings from clinical trial sites, sponsors or investigational review boards would be mentioned in any subsequent publications. Surprisingly, however, there is no clear method by which violations of the legislation/GCP – which have led regulators to discount data from evaluations of marketing authorisation applications – are highlighted in either clinical trial registries or peer-reviewed publications. Learn more on page 6 ▶

GCP lessons: falsified signatures lead to investigator disqualification proceedings

International Conference on Harmonisation GCP allows for an investigator to assign some of their duties relating to investigational product accountability at the trial site to an appropriate pharmacist or other individual. The individual chosen, however, remains under the supervision of the investigator. When an unqualified study coordinator falsified signatures on 129 prescriptions for study drugs, it was therefore the investigator who received a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain from the FDA, on the basis that the investigator’s lack of oversight had placed trial subjects at unnecessary risk. See page 7 ▶

EMA defends its approach to confidential commercial information

The European Medicines Agency (EMA) has once again defended its position to the European Ombudsman on the redaction of commercially confidential information in documents subject to an access request. However, it is not just the Ombudsman who wants the EMA to re-evaluate its approach: the German Institute for Quality and Efficiency in Health Care (IQWiG) believes that the agency’s broad definition of commercially confidential information effectively means that it cannot maintain a publicly accessible database of comprehensive data from clinical studies. IQWiG also highlights the potential for the EMA’s current policy to be influenced by financial considerations. See page 4 ▶
USA updates its proposed new clinical trial legislation

The USA has taken the next step towards legislative changes that will speed up patient access to new drugs and overhaul the FDA oversight of clinical trials.

On 28 April 2015, the US House Energy and Commerce Committee released an updated version of its proposed legislation under the 21st Century Cures Initiative. As reported in Issue 358 of Advisor, the Discussion Draft is the product of months of negotiation towards new legislation on drug discovery and development.

Over the last year, the Committee has engaged in a public conversation with patients, innovators, providers, regulators, consumers and researchers about the steps that can be taken to bridge the gap between advances in science and medicine and how those therapies are regulated. The resulting Discussion Draft contains numerous policies to strengthen the development of new treatments and cures, and improve the transition from discovery to development and development to delivery. It includes provisions to

- incorporate the patient perspective into the drug development process
- foster the development, qualification and utilisation of biomarkers
- modernise clinical trials.

Furthermore, given the unique challenges for specific types of therapies, the Discussion Draft includes provisions to facilitate the development of new antibiotics, and a placeholder for providing incentives for re-purposing drugs for serious and life-threatening diseases and disorders. It also includes a section to provide clarity for developers of software products used in health management and medical care.

New focus

The new draft bill contains an entire section on precision medicine that was not in the original draft, and directs the FDA to establish guidance on the definition of a “precision drug”, a product targeted to treat patients with a specific genotype of a disease. The guidance would need “to assist sponsors in the development of such a drug, including clinical studies”.

However, the latest draft is almost half the length of the previous one and, inevitably, several of the more ambitious recommendations have been removed. In particular, while the previous version provided for 15-year market exclusivity from generic competition for drugs for unmet medical needs, this is no longer part of the bill.

Adequate funding?

The Discussion Draft provides the National Institutes of Health (NIH) with a robust, steady stream of funding starting in 2016. Specifically, the draft recommends that the NIH receives US$10 billion in extra funding over 5 years.

However, although the revised bill lays out new responsibilities for the FDA, it does not make any corresponding budget proposals for the agency. For example, the FDA will be required to prepare 15 new guidance documents relating to clinical trials and drug development, and to establish a structured framework that will allow more patient feedback to be incorporated into regulatory decision-making. Guidance will also be needed on how to evaluate the patient’s perspective on the desired benefits and tolerable risks associated with new treatments.

Given the lack of additional funding, a number of stakeholders have raised concerns that the new requirements could divert resources away from the FDA’s primary task of evaluating drug safety. Janet Woodcock, Director of the Center for Drug Evaluation and Research, has indicated that the FDA’s advisory meetings with drug developers might be one of the first services to be cut if the agency is required to take on new congressionally mandated responsibilities.

Source: <http://1.usa.gov/1zpsVCB>
New analysis confirms impact of EMA scientific advice

The adoption of the European Medicines Agency's (EMA’s) scientific advice on trial design leads to higher success rates, shorter overall assessment times and fewer major objections.

An analysis published online in *Nature Reviews Drug Discovery* on 17 April 2015 has shown that companies that changed their clinical development plans in accordance with recommendations from the EMA are more likely to be granted a marketing authorisation.

When the EMA gives advice to a company on the appropriate tests and studies to be undertaken during the development of a medicine, this is known as scientific advice. The provision was initiated in 1996 as a tool to improve communication between sponsors and regulators during drug development. Scientific advice is designed to facilitate the development and availability of high-quality effective and acceptably safe medicines for the benefit of patients. It also aims to support sponsors in providing adequate data for benefit-risk assessments by the EMA’s Committee for Medicinal Products for Human Use (CHMP) at the time of a marketing authorisation application. Scientific advice also protects patients from participating in clinical trials that are unlikely to lead to the approval of new medicines.

**Analysis findings**

According to an analysis of marketing authorisation application outcomes between 2008 and 2012 conducted by the EMA and its Scientific Advice Working Party, the majority of clinical development plans submitted to the EMA for scientific advice prior to a marketing authorisation application were not suitable for future benefit-risk assessment. However, where the company subsequently amended its clinical development plan in line with guidance received from the agency, it was more likely to be granted a marketing authorisation.

A detailed analysis of marketing authorisation applications received by the EMA that received an opinion between 2008 and 2012, and of the scientific advice provided to the applicants, shows that

- 79 out of 118 (67%) programmes submitted for scientific advice had a poor clinical trial design that was inadequate for generating data for assessing the benefit-risk of the medicine
- submitting an acceptable trial design at the time of scientific advice – or changing a previously deficient trial design to conform with the scientific advice recommendations – increased the likelihood of a positive outcome, with success rates of 84% and 86%, respectively, compared with only 41% when a deficient clinical trial design was not adapted according to scientific advice recommendations
- compliance with scientific advice on clinical trial design was associated with a reduction in major objections raised by the CHMP during the assessment of the application, and an average 61-day-shorter assessment procedure, meaning that these medicines may be available to patients earlier.

**Stronger industry applications**

Medicines may fail to obtain a marketing authorisation due to deficiencies in trial design and the inability to demonstrate that the medicine’s benefits outweigh the risks. This not only deprives patients of new medicines but means that subjects may participate in clinical trials that are incapable of generating data for regulatory assessment.

Scientific advice offers an opportunity to initiate a scientific dialogue on all aspects of a medicine’s development, including clinical trial design. Scientific advice should be sought sufficiently early in the development of a medicine to ensure that...
EMA defends its approach to confidential commercial information

The German Institute for Quality and Efficiency in Health Care (IQWiG) has questioned whether the European Medicines Agency’s (EMA’s) efforts to establish a publicly accessible database containing comprehensive data from clinical studies meets its objectives.

IQWiG was established in 2004 and produces independent evidence-based reports on the benefits and harms of medical interventions. Its comments on the transparency elements of the EMA’s database specifications highlight apparent flaws in the EMA’s proposals relating to confidential commercial information and in meeting patients’ needs. Although IQWiG’s remarks came after the deadline for comments on the database specifications, they may reignite the debate, particularly on what constitutes confidential commercial information and the process by which it could be redacted.

Narrower definition

IQWiG notes that in 2014 the EU Parliament made it clear that clinical study data should not generally be considered commercially confidential and should not ordinarily be exempt from publication in the EU database. IQWiG suggests that for the EMA database to fulfil its aims there needs to be a “precise and narrow” definition of what constitutes commercially confidential information. Moreover, allowing trial sponsors to take part in the decision as to what constitutes confidential commercial data is contrary to the intent of the EU regulation and the aim of achieving transparency in clinical research.

IQWiG also considers that the non-publication of trial data – or long publication delays – is inconsistent with the ethical principles of the Declaration of Helsinki. According to IQWiG, the primary consideration should be ensuring the swift and complete publication of trial data and associated documents, so that the needs of the broadest population of patients – particularly the need for a thorough assessment of treatment options – are met as efficiently as possible. The comments also highlight how the EMA’s proposal provides for financial considerations to override the needs of patients: if, for example, the publication of trial data could affect the acquisition of further third-party funds, sponsors may be permitted to redact information.

IQWiG believes that the non-publication of specific trial data should be an exception, which requires individual and precise justification, and calls on the EMA to “meticulously evaluate” each case.

EMA explains its redaction rules

Meanwhile, the EMA has continued its ongoing dialogue with the European Ombudsman on this topic in an effort to explain its response to an access to documents request.

In October 2014, the European Ombudsman, Emily O’Reilly, made a written request to the agency asking the then Executive Director, Guido Rasi, to explain why certain information had been redacted in response to an access to documents request for three clinical study reports from November 2012. The access request led to a court case against the agency brought by the marketing authorisation holder of one of the drugs in question, who sought to prevent the EMA from releasing the information under its access to documents policy. The legal proceedings were withdrawn by the marketing authorisation holder after the EMA agreed to a limited number of redactions in line with its rules.

On 10 February 2015, the EMA published a detailed response to the European Ombudsman’s questions, again explaining how the agency had applied the rules on access to documents in this case, focusing on three key themes.

• The EMA considers that clinical study reports are not confidential, but recognises that some very limited information within a clinical study report may be considered commercially confidential (eg. commercial development plans that have not yet been disclosed). It notes that in these cases the information may be redacted before the report is released.

• The redaction of information in a clinical study report is a dynamic process that evolves over time. Information that was once considered confidential may no longer be confidential some time later, depending on the ongoing development of the medicine and the availability of public information on any commercial development plans.

• The EMA applies its technical and scientific competence in the assessment of claims of confidentiality made by pharmaceutical companies and in the redaction of clinical study reports. By relying on the competence of its assessors, there is inevitably an element of discretionary analysis, but this is still governed by both the general transparency principles and those of fair and equal treatment of all requestors.

The letter goes on to reiterate that the redactions made by the EMA within the three clinical study reports were consistent with the access to documents policy that was in place at the time, and which the Ombudsman had previously publicly supported. Then – before detailing its specific decisions on individual redactions – the letter highlights what the EMA has done to ensure it meets its transparency and openness obligations, including:

• making data on adverse drug reactions publicly available in the EudraVigilance database
• the publication of the agenda and meetings of the agency’s scientific committees
• the publication of records of declarations of interest from experts involved in EMA decision-making
• the creation of a multidisciplinary team of agency personnel dedicated to dealing with daily requests for information and access to documents.

In 2014 the EMA dealt with 416 access to documents requests and released 1816 documents, amounting to 167,309 pages.


FDA posts guidance on acceptance of device studies from outside the USA

On 21 April 2015, the FDA released new draft guidance entitled ‘Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States’. The guidance updates the FDA’s requirements for the acceptability of data from clinical studies conducted outside the USA. It describes the special considerations that apply when using such data, and provides recommendations to help sponsors ensure that their data are adequate under the applicable FDA standards to support the approval or clearance of a device in the USA. The FDA believes that clarifying its position will minimise the risk of additional or duplicate US studies, will further efforts to harmonise global clinical trial standards, and will promote public health and innovation. Comments on the draft guidance are invited by 20 July 2015 for consideration by the FDA, before work begins on the final version.

Source: <http://1.usa.gov/1I4pDX1>
Clinical trial misconduct goes unmentioned in published literature

A recent analysis has revealed that violations of the FDA regulations and GCP non-compliance are not being acknowledged in the peer-reviewed literature.

An article in the Journal of the American Medical Association (JAMA) Internal Medicine has highlighted that even when FDA inspectors identify significant GCP non-compliance in a clinical trial, the flaws may not be acknowledged when the data are subsequently reported in clinical trial publications.

Almost every issue of Advisor includes examples of GCP non-compliance and deviations from the federal regulations, and every year the FDA issues dozens of warning letters to investigators, sponsors and institutional review boards (IRBs). However, according to the article by Charles Seife from the Arthur L. Carter Institute of Journalism at New York University, USA, the FDA has no systematic process for communicating such findings to the wider scientific community. As a result, data from affected trials may be reported in peer-reviewed journals without noting the FDA findings.

In order to evaluate this issue further, Seife identified published clinical trials where an FDA inspection in the period 1998–2013 had resulted in an inspection classification of Official Action Indicated (OAI). He then described these violations and aimed to determine whether they had been acknowledged in the peer-reviewed literature. To this end, inspection documents available from the FDA – including warning letters to investigators, Notices of Disqualification Proceedings and Opportunity to Explain, Notices of Opportunity for a Hearing and disbarment decisions – were cross-referenced with the corresponding clinical trial publications and an evaluation made of whether the publications acknowledged the FDA findings.

Fifty-seven published clinical trials were identified for which an FDA site inspection had found significant evidence of a violation of the federal regulations or GCP non-compliance. These were categorised as follows:

- 42 (74%) trials had protocol violations or deviations from the investigational plan
- 35 (61%) trials had inadequate or inaccurate record-keeping
- 30 (53%) trials failed to protect the safety, rights and welfare of patients and/or had issues with IRB oversight or informed consent
- in 22 (39%) trials the FDA had identified data falsification or the submission of false information
- 20 (35%) trials had violations that were not otherwise categorised, including treating patients who were not in a clinical trial with an investigational medicinal product, delegating tasks to unauthorised individuals or failure to supervise the trial appropriately
- 14 (25%) trials had problems with adverse event reporting.

Despite the seriousness of the findings – including violations with an impact on both data integrity and subject protection – only three (4%) of the 78 publications mentioned the objectionable conditions or practices found during the inspection. Furthermore, no corrections, retractions, expressions of concern or other comments acknowledging the key issues identified by the inspection were subsequently published.

Data validity

Although the article notes several limitations of the study and its data, there is still a clear issue if data discounted from evaluations of marketing authorisation applications, because of concerns over data integrity or subject protection, can still be reported as scientifically valid in peer-reviewed journals and elsewhere.
The article proposes several ways to prevent data from clinical trials being published without the disclosure of any adverse inspection findings. It notes that the FDA (and presumably other national and regional regulatory agencies) has legal responsibilities when it identifies scientific misconduct during an inspection, although it recognises that the agency must protect confidential commercial information. More open communication between the FDA and journal editors is one option, as is using clinical trial registries to highlight trials where a site has an OAI inspection classification.

Seife also recommends that the FDA makes publicly available a list of all OAI-rated inspections of trial sites, with links to “relevant, unredacted, inspection-related documents”. For their part, Seife suggests that authors should disclose any adverse findings that affect the data they are aiming to publish, akin to the way in which authors declare conflicts of interests.

Source: <http://bit.ly/1vABx7C>

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**GCP lessons**

**Falsified signatures lead to investigator disqualification proceedings**

On 12 January 2015, the FDA issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) to a US investigator in response to inspection findings.

The investigator had participated in three clinical trials evaluating the use of a recombinant parathyroid hormone in adult patients. The inspection was performed under the FDA's Bioresearch Monitoring Program and revealed repeated or deliberate violations of the federal regulations governing the proper conduct of clinical studies involving investigational products (IPs). The violations were so significant that the FDA moved immediately to initiate an administrative proceeding to determine whether the investigator should be disqualified from performing clinical trials in the future.

**Numerous falsified signatures**

For one of the three inspected trials, the FDA found that both the investigator’s and the sub-investigator’s signatures had been falsified on numerous prescriptions for study drugs. The prescriptions included orders for the IP/placebo as well as for vitamin D metabolite/analogue therapy and magnesium, vitamin D and calcium supplementation. In total, of the 150 prescriptions written for the trial from 2009 to 2011, 129 prescriptions contained falsified signatures, 127 of which were the sub-investigator’s and two of which were the investigator’s.

The NIDPOE indicates that the signatures were falsified by an unqualified study coordinator and notes the significant impact this may have had on subjects’ safety and welfare. The IP was expected to improve calcium homeostasis, thereby reducing the requirements for supplemental calcium and vitamin D metabolites or analogues. Following randomisation, subjects were to have undergone staged reductions in calcium and active vitamin D metabolite/analogue supplementation while maintaining clinically acceptable stable serum calcium. Up-titration of the IP was to reflect changes in serum calcium and phosphate levels as well as the risk of high or low blood calcium levels. Given that the level of supplementation with active vitamin D metabolites/analogues and oral calcium was expected to be highly variable both between and within trial subjects, it was essential for reasons of subject safety that prescriptions were written by qualified medical personnel. The NIDPOE "calls into question whether appropriate clinical judgment was executed”.

Falsified signatures were not limited to prescriptions. The investigator’s signature was also falsified on two Form FDA 1572s, one of which was submitted to the FDA.

**Corrective action**

Following the inspection the investigator agreed that his signature and that of his sub-investigator had been falsified on prescriptions and on one FDA 1572. He submitted a corrective action plan as follows:

- all prescription pads are now held by physicians in their offices in locked drawers, and are accessible to individual physicians only
- all FDA forms will be reviewed and signed by the clinical investigator prior to submission to the FDA and sponsor
- at mandatory weekly meetings the investigator will review items including, but not limited to: subject eligibility and consent; orders for medications and test articles; protocol violations; documentation of study procedures; unanticipated problems and adverse events; and communications with the sponsor, institutional review board and FDA
- the investigator will ensure that training takes place for all study staff, including training on GCP and FDA-regulated research, and protocol-specific training.
However, given the number of falsified signatures, the FDA repeated its stance that the findings raised serious concerns about the adequacy of supervision of trial personnel, and concluded that the investigator’s assurances of future compliance were inadequate.

In view of the violations, and others described in the NIDPOE, the FDA considered that the investigator had repeatedly or deliberately failed to comply with the relevant regulations, had placed trial subjects at unnecessary risk and had jeopardised the integrity of trial data. As a result, the agency proposes to disqualify the investigator – it remains to be seen how the investigator will respond.

Source: <http://1.usa.gov/1HoO7Kr>

French regulator launches pilot for new EU Clinical Trial Regulation

The new European Clinical Trial Regulation will come into effect after 28 May 2016, once the single European portal is fully functional. In the interim, the French National Agency for Medicines and Health Products Safety (ANSM) is implementing a voluntary pilot phase, in conjunction with academic and industrial sponsors and Research Ethics Committees (known as CPPs in France). Thirteen CPPs – one-third of the total – have volunteered to take part in the pilot, during which the Regulation will be applied. This is particularly important as the CPPs will be required to follow the new timelines and work practices.

France is the first European country to launch a pilot in preparation for the EU Clinical Trial Regulation. An information meeting will take place in June and the pilot will begin in September 2015, with the various stakeholders working towards the following:

- sponsors – preparing for new procedures required by the European Regulation; implementing a single submission review calendar; receiving a single ANSM authorisation notification and a single CPP opinion notification; facilitating the procedure for submitting clinical trial authorisation requests
- CPPs – standardising clinical trial management and assessment practices; preparing for the future assessment calendar restrictions defined by the European Regulation; strengthening relationships with the ANSM
- ANSM – preparing for the centralisation of clinical trial authorisation requests; strengthening relationships with CPPs.