CLINICAL RESEARCH

CLINICAL QUALITY ASSURANCE

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FDA releases new annual BIMO inspection metrics

The FDA has updated its annual Bioresearch Monitoring (BIMO) inspection metrics, releasing data for 2009–2018. The BIMO Program monitors all aspects of the conduct and reporting of FDA-regulated research, with a view to assuring the quality and integrity of data supporting new product approvals, and protecting the rights and welfare of research subjects. The newly released cumulative data provide a variety of inspection metrics over a 10-year period, including inspection type and geographic spread, and the number of warning letters issued each year. More on page 2 ▶

Harmonising global regulatory approaches to innovation

Drug development, manufacture, marketing and distribution are truly global enterprises, and efforts to characterise the safety and effectiveness of new drugs are being increasingly conducted in a wide range of countries. Harmonising regulatory pathways across the globe has clear benefits, particularly for innovative products and technologies that may deliver therapeutic benefits to patients with life-threatening and serious diseases. However, the existing regulatory frameworks do not always meet the unique needs of innovative products and new approaches may be needed. See page 5 ▶

UK speeds access to pioneering treatments

New improvements to the UK's Accelerated Access Collaborative (ACC) are intended to ensure that pioneering treatments are fast-tracked into the National Health Service so they can reach patients quicker. The ACC is designed to select the most promising new treatments, tests and medical devices at an early stage, and to steer them through the clinical development and regulatory approval process faster. A new unit will be set up with the objective of reducing the time taken, from 17 to 13 years, for treatments to get from patents to UK patients, focusing on prevalent conditions such as cancer, dementia and diabetes.

UK continues to prepare for the EU Clinical Trial Regulation

The new EU Clinical Trial Regulation will harmonise the electronic submission and assessment process, and will improve collaboration, information sharing and decision making across EU Member States. The Regulation aims to increase the transparency of information on clinical trials and to ensure the highest standards of safety for all trial participants. Authorities in the UK are preparing for the new Regulation while the UK remains an EU Member State. This includes a 'combined ways of working' pilot, which is testing an integrated process for regulatory and research ethics submissions. Details on page 4 ▶

FDA draft guidance on clinical trials in pregnancy and lactation

The FDA has noted that that more thought is needed on how to include human data on drug use in pregnancy and lactation within product labelling, in a way that is accurate and meaningful to prescribers. The lack of robust clinical data does not mean that women are not using medicines during pregnancy: a 2011 study found that at least one prescription medication had been taken by 70% of a sample of pregnant women. The FDA has recently released two draft guidance documents outlining its recommendations on conducting pregnancy safety studies and lactation

FDA releases new annual BIMO inspection metrics

The FDA has released updated inspection metrics for the compliance programmes performed under its Bioresearch Monitoring Program (BIMO). The publication now covers the period 2009–2018.

BIMO is a comprehensive agency-wide programme of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research. Inspections performed under BIMO are conducted by the FDA's Office of Regulatory Affairs, which is the agency's lead office for all field activities. Inspections are overseen by the Office of Scientific Investigations (OSI) and the Office of Study Integrity and Surveillance (OSIS), both of which sit within the FDA's Center for Drug Evaluation and Research.

OSI aims to verify the integrity of efficacy and safety data submitted to the FDA in support of new drug applications, and to assure that the rights and welfare of human research subjects are protected. OSIS performs a similar role but with a focus on inspections of bioavailability/bioequivalence and non-clinical studies.

The newly released cumulative data provide a variety of inspection metrics from fiscal years 2009 to 2018. Below we examine the available data for the period 2014–2018; we will take a closer look at the data for 2018 in a later article.

Overview

Table 1 summarises the number of inspections overseen by OSI/OSIS each year for the period 2014–2018. There was a notable increase in the total number of inspections from 2016 to 2017, including a 20% increase in the number of inspections at investigator sites. However, the total number has since plateaued, as has the number of bioequivalence inspections, which had increased significantly each year from 2014 to 2017.

Global reach

The FDA is responsible for protecting public health in the USA but extends BIMO to overseas locations. Table 2 summarises the annual number of inspections overseen by OSI/OSIS within and outside the USA for 2014–2018, highlighting the differences for inspections of investigators and sponsors.

The past 2 years have seen both an increase in the total number of inspections and a shift towards more inspections being performed outside the USA. Interestingly, over the 5-year period, inspections of clinical investigators consistently represent a higher proportion of the total number of inspections annually within the USA (47%-57%) than they do overseas (30-39%). Although based on much smaller numbers, a similar pattern is seen for sponsor inspections.

Table 1. Number of inspections overseen by the Office of Scientific Investigations/Office of Study Integrity and Surveillance (fiscal years 2014–2018).

Inspection type	2014	2015	2016	2017	2018
Clinical investigator	469	451	432	521	547
Sponsor	60	60	67	74	86
Institutional review board/RDRC	93	90	97	102	95
PADE	90	96	87	87	72
REMS	16	15	17	10	14
Bioequivalence	291	327	430	489	485
Good Laboratory Practice	27	29	28	31	29
Total	1046	1068	1158	1314	1328

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Table 2. Location of inspections overseen by the Office of Scientific Investigations/Office of Study Integrity and Surveillance (fiscal years 2014–2018).

Inspection location/type	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	2017 *n* (%)	2018 *n* (%)
All inspections within the USA	623 (66)	596 (62)	664 (64)	698 (58)	669 (55)
Clinical investigator	347 (56)	310 (52)	313 (47)	355 (51)	380 (57)
Sponsor	52 (8)	52 (9)	61 (9)	59 (8)	73 (11)
All inspections outside the USA	314 (34)	367 (38)	380 (36)	507 (42)	550 (45)
Clinical investigator	122 (39)	141 (38)	119 (31)	166 (33)	167 (30)
Sponsor	8 (3)	8 (2)	6 (2)	15 (3)	13 (2)
Total[a]	**937**	**963**	**1044**	**1205**	**1219**

[a] *Excluding inspections of institutional review boards/Radioactive Drug Research Committees and inspections performed in relation to Risk Evaluation and Mitigation Strategies.*

Sponsor-investigator inspections

The total number of GCP-related sponsor inspections performed annually from 2014 to 2018 is provided Table 3, and includes inspections of contract research organisations and of investigators who are acting as the sponsor of a trial. The total number of annual inspections has increased over the past 3 years, with the increase spread across the three different types of sponsor inspection. Although the total number of sponsors and sponsor-investigators conducting trials in any given year is unknown, intuitively one might assume that sponsor-investigators are a very small proportion of the total, and that in 2018 they experienced a disproportionately high percentage of the total number of sponsor inspections performed by OSI/OSIS.

Warning letters

Significant findings documented during an FDA inspection may result in a warning letter and/or a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE). The inevitable time lag between

Table 3. Overview of sponsor inspections overseen by the Office of Scientific Investigations/Office of Study Integrity and Surveillance (fiscal years 2014–2018)[a].

Sponsor type	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	2017 *n* (%)	2018 *n* (%)
Sponsor	50 (83)	34 (57)	40 (60)	51 (69)	47 (55)
Contract research organisation	6 (10)	21 (35)	19 (28)	18 (24)	23 (27)
Sponsor-investigator	4 (7)	5 (8)	8 (12)	5 (7)	16 (19)
Total	**60**	**60**	**67**	**74**	**86**

[a] *Due to rounding, percentages may not add up to 100%.*

Table 4. Number of warning letters and NIDPOEs issued (fiscal years 2014–2018).

Warning letters/NIDPOEs	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	2017 *n* (%)	2018 *n* (%)
All warning letters	16	6	12	6	2
Clinical investigator	11 (69)	4 (67)	7 (58)	4 (67)	1 (50)
All NIDPOEs	5	3	0	0	1
Clinical investigator	4 (80)	3 (100)	0	0	1 (100)
Total	**21**	**9**	**12**	**6**	**3**

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an inspection and a subsequent warning letter/NIDPOE means that it is not appropriate to directly compare the number of investigator inspections with the number of warning letters/NIDPOEs issued to investigators in any fiscal year.

Table 4 summarises the annual number of warning letters and NIDPOEs issued from 2014 to 2018, both overall and specifically to investigators. In recent years, the number of warning letters issued annually in response to a GCP inspection has fallen; and although warning letters to clinical investigators have accounted for at least half of all such warning letters issued in the past 5 years, it is difficult to draw any further conclusions. The frequency of NIDPOEs remains low.

Source: <https://tinyurl.com/y23glaun>

UK continues to prepare for the EU Clinical Trial Regulation

The UK is piloting an integrated process for the submission and review of applications for clinical trials of medicinal products (CTIMPs).

The UK's Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA) have been exploring how to improve the service being offered for the approval and ongoing management of CTIMPs. In March 2018 they launched a 'combined ways of working' pilot programme, to streamline the process for the submission and review of applications for CTIMPs. Feedback on the first year of the pilot has now been published.

The rationale for seeking collaborative working pathways was to help UK sponsors as they prepare to perform clinical trials under the EU Clinical Trial Regulation. The pilot is currently open to applications by prior agreement only; the expectation is that it will be available for all CTIMP applications as it develops.

Combined process

The pilot focuses on the use of a single CTIMP application dossier, which is submitted for both clinical trial authorisation and the Research Ethics Committee (REC) opinion. In England and Wales, the same submission will also incorporate HRA and Health and Care Research Wales (HCRW) approval, respectively. Although the submission is reviewed independently by the regulatory agency and REC, efficiencies are gained through subsequent combined communications if there is a need to request any further information, as well as a single communication to confirm the final decision.

Currently only certain RECs are participating in the pilot, but the number continues to increase. Moreover, applicants must also comply with the requirement to submit their application within the chosen REC meeting's stated submission period. An application submitted to the pilot outside the submission period for a chosen REC will be allocated to the next available REC meeting.

To date the pilot has reviewed 40 applications. Some of the highlights noted from the first year include the following:

- a mean approval time of 42 days from submission to authorisation, including HRA/HCRW approval where relevant
- co-ordinated requests for further information between the REC and MHRA achieved for all applications
- responses to requests for further information from applicants received within the 14-day requirement
- applicant guidance documents developed and published to support organisations joining the pilot.

Source: <https://tinyurl.com/yy9suwqb>

Harmonising global regulatory approaches to innovation

The establishment of a global approach for coordination on innovation by the International Coalition of Medicines Regulatory Authorities (ICMRA) should deliver therapeutic benefits for patients.

ICMRA has released a short report outlining how regulators across the globe are collaborating to identify and address future regulatory challenges arising from new categories of therapeutics and new tools for drug development.

The Coalition is a global alliance of the leaders of more than 30 medicines regulatory authorities. It acts on a voluntary basis, providing strategic leadership and coordination in regulatory approach and thinking. It also works to address current and emerging human medicines regulatory and safety challenges.

In recent years there have been significant advances in therapeutic approaches to the treatment and management of life-threatening and highly debilitating diseases. These innovative products, technologies and production models have the potential to be hugely transformative for patients and the health system. Examples include

- the use of 3D printing to print human tissues and organs
- genome editing to advance drug discovery and development, and to treat diseases
- artificial intelligence to assist in disease detection and diagnosis, and treatment monitoring.

However, these innovations are often complex in nature. Current regulatory systems and licensing pathways that have previously produced positive outcomes are ill-suited for managing them. More adaptive and flexible regulatory approaches are therefore needed to keep pace with innovation, and to enable the delivery of novel and safe treatments for patients, particularly in areas of high unmet need.

Medicines regulators at national, regional and global levels can, at an early stage, identify future innovations, key scientific uncertainties and the

engaging with legislators and policy makers – as well as addressing internal organisational capabilities and culture – are key to ensuring success and delivery for patients and healthcare systems.

Flexible frameworks

The new report notes that ICMRA formally approved a 'Strategic Priority on Innovation' in October 2017. The establishment of a global approach for coordination on innovation has been a key outcome. This includes

- the utilisation of best practices for early horizon scanning
- the evaluation of the applicability of existing regulatory approaches, including novel licensing systems
- the identification of potential barriers and future expertise needs.

The report highlights the critical need, from the perspective of regulators across the globe, for flexible regulatory frameworks with better adaptive capability. It notes that it is "incumbent on all regulators to continue to build capacity in order to embrace the development of new standards and processes that will enable these innovations to safely proceed to be developed and continuously improved as the technology evolves and knowledge and understanding of products and processes is advanced."

ICMRA now calls for regulators, legislators and policy makers to work together on the following:

- developing greater awareness of trends and challenges in innovation, to identify the necessary approaches and evidence standards that will facilitate innovation and timely access to medical products while protecting patient safety

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challenges and provide timely solutions to support innovative research and product development
- ensuring that regulation/policy and product lifecycle oversight are flexible and adaptable, with the capacity to remain fit for purpose when applied to current and future innovations
- strengthening international collaboration in the areas of advanced technologies and other innovations to maximise the early potential for harmonised coherent global approaches that can support regional and local regulation.

Source: <https://tinyurl.com/y2ckctq4>, <https://tinyurl.com/yyqpcyua>

FDA provides framework for clinical trials in pregnancy and lactation

Two new draft guidance documents outline the FDA's recommendations on conducting pregnancy safety studies and lactation studies.

Women who are pregnant or breastfeeding are typically excluded from participation in clinical trials. However, on 9 May 2019 the FDA released two draft guidance documents relating specifically to the conduct of clinical trials in these two special populations.

The lack of robust clinical data does not mean that women are not using medicines during pregnancy. A study published in the *American Journal of Obstetrics and Gynecology* in 2011 found that 70% of a sample of over 25,000 pregnant women had taken at least one prescription medication during their pregnancy. Without reliable data on the safety of drugs and biological products during pregnancy or breastfeeding, clinicians and women may be making decisions about drug use without truly knowing the maternal or fetal safety risks, or the risks of drug exposure to breastfeeding babies. Thus, it is important that sponsors generate relevant data for drugs that are likely to be used by women of reproductive age, or where there is evidence of use or anticipated use by women who are pregnant or breastfeeding.

Clinical lactation studies

A 13-page guidance document provides recommendations for sponsors conducting clinical lactation studies, which are required by the FDA in certain circumstances under the Food, Drug, and Cosmetic Act. Sponsors may also, in some circumstances, elect to conduct lactation studies where there is no requirement or at the FDA's request.

The guidance outlines the FDA's current recommendations on pre- and post-marketing lactation studies. It provides information to facilitate the conduct of such studies, which can subsequently inform drug labelling on breastfeeding/lactation. It notes that sponsors should consider ethical considerations for three populations of lactating women who may potentially participate in clinical lactation studies:
- women who are prescribed a drug that is the subject of a lactation study, as part of standard clinical care
- women in a research setting who are administered an investigational drug
- healthy volunteers who are administered an investigational drug for the purpose of clinical research.

It also outlines appropriate types of clinical lactation study and how a sponsor might minimise the burden of data collection on a mother while obtaining adequate data.

The document replaces the 2005 draft guidance 'Clinical Lactation Studies – Study Design, Data

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Analysis, and Recommendations for Labeling', and reflects discussions at the 2007 Pediatric Advisory Committee meeting and the 2016 Lactation Workshop on how data from clinical lactation studies can inform the safety of a drug when used during lactation.

Pregnancy

The second draft guidance document ('Postapproval Pregnancy Safety Studies') provides sponsors and investigators with recommendations on how to design studies to assess the outcomes of pregnancies in women exposed to drugs and biological products regulated by the FDA (ie. pregnancy safety studies). The goal of post-approval pregnancy safety studies is to provide clinically relevant data about the safety of drugs and biological products (through the inclusion of information in product labelling), to inform healthcare providers who are treating or counselling patients who are pregnant or anticipating pregnancy.

The guidance describes three general approaches – pharmacovigilance, pregnancy registries and complementary data sources – that can be used in the post-marketing setting to evaluate the safety of drugs and biological products during pregnancy. Each of these offers something unique to the overall safety assessment. When selecting any one or combination of these assessments, it is recommended that sponsors consider previous experience with similar drugs/biological products; knowledge of the underlying disease and its risks (both maternal and fetal); the potential use of the drug/biological product in females of reproductive potential and pregnant women; existing knowledge of a safety concern; and the potential for capturing the same pregnancy in two different assessments.

The FDA held a 2-day public meeting in 2014 where stakeholders – including experts in birth defects – discussed the use of pregnancy registries and other epidemiological studies to collect post-marketing safety data on the use of drugs and biological products during pregnancy. The FDA also conducted reviews of pregnancy registries, including an assessment of pregnancy registry methods and enrolment.

In the years since the FDA issued its previous guidance on this topic, pregnancy safety studies required by the agency have expanded beyond those using data from pregnancy exposure registries (pregnancy registries) to include other types of epidemiological studies and pregnancy surveillance programmes. The new 30-page draft guidance should be used in conjunction with other epidemiological literature on the design, conduct and interpretation of observational studies. The design and development of pregnancy safety studies requires specialised knowledge in a variety of areas, including expertise in epidemiology, clinical teratology, obstetrics, paediatrics, clinical genetics and statistics.

Comments on the draft guidance documents are invited by 8 July 2019.

Source: <https://tinyurl.com/yywfaktu>, <https://tinyurl.com/y48lbjbv>

News *in brief*

EMA offers early dialogue to overcome antimicrobial resistance

The European Medicines Agency (EMA) has announced that the early dialogue available through its Innovation Task Force (ITF) is now open to all medicines developers working on the treatment or prevention of bacterial and fungal infections. The ITF – a forum for discussion between regulators and developers of innovative emerging therapies, methods and technologies in the early stages of research and development – is usually reserved for innovative medicines. However, with the growing threat to public health from antimicrobial resistance and the need for new treatments, the EMA is inviting all developers working on medicines for the treatment or prevention of life-threatening infections to begin early dialogue with the agency to help strengthen the drug development pipeline for new antimicrobials. The ITF will facilitate early interaction and broad-ranging discussions between innovators and the regulatory authorities, which will help developers' orientation and subsequent use of formal regulatory tools such as EMA scientific advice.

Source: <https://tinyurl.com/y3cnve5h>

FDA delays final rule on combination product safety reporting

On 24 April 2019, the FDA announced an update to the immediately in effect guidance 'Compliance Policy for Combination Product Postmarketing Safety Reporting', originally issued on 21 March 2018. The agency published a final rule for post-marketing safety reporting for combination products (21 CFR 3.2(e)) in December 2016. The final rule applies to combination products that are subject to pre-marketing review by the FDA, and includes certain obligations for combination product applicants. The subsequent guidance (March 2018) describes the FDA's compliance policy for combination product applicants with respect to post-marketing safety reporting. However, the agency has now stated that it will delay the enforcement of certain provisions within the final rule relating to post-marketing safety reporting for combination products, to ensure that applicants have sufficient time to

- update reporting and record-keeping systems and procedures, including information technology systems
- comply with these requirements
- consider the recommendations and technical specifications that the FDA intends to provide through guidance to support compliance

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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