UK fast-tracks access to ground-breaking medicines
The new Voluntary Scheme for Branded Medicines Pricing and Access came into effect in the UK on 1 January 2019, replacing the Pharmaceutical Pricing Regulation Scheme. The government hopes that the new scheme will result in savings of £930 million, as it includes a cap of 2% growth on the annual total medicines bill, with the pharmaceutical industry liable to repay any National Health Service spending in excess of this limit. The scheme should also ensure that innovative new medicines reach patients up to 6 months earlier than at present. More details on page 6.

FDA encourages broader availability of companion diagnostics in oncology
The FDA has issued draft guidance designed to make it easier to obtain class labelling for diagnostic tests used with oncology therapeutic products. FDA Commissioner Scott Gottlieb has highlighted the challenge faced by manufacturers and regulators in the way that diagnostics are sometimes labelled. The draft guidance should make it easier for providers to use the same test across a class of oncology drugs rather than for just a single oncology drug in a given class. The eventual availability of oncology companion diagnostics with broader evidence-based indications should support better clinical use. See page 5.

GCP lessons: MHRA offers insight into GCP compliance in dose escalation studies
The Medicines and Healthcare products Regulatory Agency (MHRA) Inspectorate has highlighted in a blog post how the strict and transparent dose escalation process used in first-in-human (FIH) healthy volunteer trials is not always replicated in FIH patient trials. All dose escalation trials should be conducted with the same focus on high-quality data and the safeguarding of subjects/patients; the specific requirements for dose escalation are documented in legislation and early phase guidance. The article further explains what sponsors must do to ensure GCP compliance in all dose escalation studies. See page 7.

FDA claims 2018 as a year of new advances in drug therapy
The role of the FDA’s Center for Drug Evaluation and Research (CDER) in bringing innovative new drug therapies that are safe and effective to needy patients in 2018 is illustrated in a new annual report, ‘Advancing Health Through Innovation: New Drug Therapy Approvals’. The report emphasises some of the many innovative ways in which CDER was able to evaluate safety and efficacy for these new therapies, as well as the key regulatory tools used to enhance efficiency and expedite the review and approval of applications. More on page 2.

Review of the UK’s Good Pharmacovigilance Practice inspection process
A Good Pharmacovigilance Practice (GPvP) inspection aims to establish whether a marketing authorisation holder has a compliant pharmacovigilance system. In the next few issues of Advisor we will be examining how the UK GPvP Inspectorate plans and undertakes various types of GPvP inspections. We will also review the latest critical and major inspection findings, as documented in the agency’s most recent annual metrics report. Details on page 3.
FDA claims 2018 as a year of innovation, efficiency and new advances in drug therapy

The FDA’s Center for Drug Evaluation and Research (CDER) has issued its annual ‘Advancing Health Through Innovation: New Drug Therapy Approvals’ report.

The 36-page report notes that in 2018 CDER approved 59 novel drugs, either as new molecular entities under new drug applications or as new therapeutic biological products under Biologics License Applications. This compares with the approval of 46 novel drugs in 2017 and only 22 in 2016. CDER identified 19 of the 59 (32%) novel drug approvals as first-in-class, which is one indicator of a drug’s potential for a strong positive impact on public health. Other highlights from the report are outlined below.

Rare diseases
Among the 34 novel approvals to help patients with rare diseases, CDER approved the following:

- the first drug to treat patients with a rare inherited form of rickets that leads to impaired bone growth and development
- the first oral drug to treat Fabry disease, a rare and serious disorder that can cause pain and burning in the hands and feet, and damage to major organs
- a new drug to treat patients with phenylketonuria, a rare dietary condition where patients are born with an inability to break down protein, which can lead to brain and nerve damage.

Infectious diseases
CDER approved a number of novel anti-infective agents:

- the first-ever drug to treat smallpox (which could be used in the event of a bioterror attack)
- the first in a new class of drugs to treat patients with HIV-1 that has failed to respond to other therapy
- two new versions of a drug for malaria (one to prevent the relapse of a form of malaria and one to protect travellers to endemic areas from contracting the disease)
- a new single-dose treatment for influenza
- a new antibiotic formulation to treat patients with non-tuberculous mycobacterial lung disease under the Limited Population Pathway for Antibacterial and Antifungal Drugs (a pathway designed to streamline the development and approval of antibacterials for serious or life-threatening infections in a limited population of patients with unmet need).

Cancer
In 2018, CDER approved new advances for patients with breast cancer, prostate cancer and lung cancer. CDER also approved:

- combination use of two previously approved melanoma drugs to treat patients with highly aggressive thyroid cancer
- a new drug to treat patients with neuroendocrine tumours in the pancreas or gastrointestinal tract that no longer respond to hormone treatment
- the first FDA-approved drug for the treatment of pheochromocytoma or paraganglioma
- a new therapy to treat tumours with a specific genetic marker
- two new drugs to treat relapsed or refractory acute myeloid leukaemia and a new front-line treatment for acute myeloid leukaemia
- a new therapy to treat classical Hodgkin’s lymphoma
- a new therapy for acute lymphoblastic leukaemia
- a new treatment for adults with either of two forms of non-Hodgkin’s lymphoma.

Biosimilars
The regulatory framework that allows the FDA to approve biosimilars was designed to create competition, increase patient access and potentially reduce the cost of important therapies. In 2018, CDER approved seven new biosimilars.
Improved efficiency
Four regulatory pathways were used to ensure prompt and efficient expedited review for approval decisions:
• Fast Track
• Breakthrough
• Accelerated Approval
• Priority Review.
These pathways use a range of approaches, including more interactions between CDER staff and drug developers, greater programme design flexibility, and shortened timelines for the review of applications. In 2018, 73% of CDER’s novel drug approvals (43 of 59) were designated to one or more of these expedited review categories, which enable therapies to reach patients months or even years sooner than if the application went through the standard review process.

Drug safety


Review of the UK’s Good Pharmacovigilance Practice inspection process

In the first of a series of articles, we look at how the UK Medicines and Healthcare products Regulatory Agency (MHRA) provides oversight of compliance with Good Pharmacovigilance Practice (G PvP).

GPvP is a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU. GPvP applies to marketing authorisation holders (MAHs), the European Medicines Agency (EMA) and medicines regulatory authorities in all EU Member States. It covers medicines authorised centrally via the EMA and those authorised at national level.

In the UK, compliance with GPvP is overseen by the MHRA, and the agency has been conducting statutory GPvP inspections since 2003. Currently, any UK MAH or marketing authorisation applicant can be subject to an MHRA GPvP inspection, which may also include any of the inspected entity’s partners or service providers. If pharmacovigilance activities are performed outside the UK, the MHRA may also
• request inspectorates in other EU Member States to perform an inspection at site(s) in their country or to share results from recent inspections
• ask company personnel from other country sites to participate in an inspection at a UK site.

Using information from the MHRA website, below we provide an overview of the MHRA’s role in GPvP, with a particular focus on the types of inspection the agency undertakes. In future issues of Advisor we will look at how GPvP inspections are performed and their potential outcomes. We will also outline some of the critical and major inspection findings described in the MHRA’s most recent metrics report.

As discussed below, the MHRA performs five types of GPvP inspection: routine national inspections, EU inspections, triggered inspections, Committee for Medicinal Products for Human Use (CHMP)-requested inspections and service provider inspections. In most cases, an MHRA GPvP inspection will focus on the MAH’s pharmacovigilance system, ie. the system used by the organisation to
• fulfil its legal tasks and responsibilities in relation to pharmacovigilance
monitor the safety of authorised medicinal products
• detect any change in the risk-benefit balance of authorised medicinal products.

**Routine inspections**
GPvP inspections are scheduled under the MHRA’s national inspection plan using a risk-based approach, which reflects both the risk factors listed in EU statutory guidance (Good Pharmacovigilance Practice Module III) and an MAH’s previous inspection history.

The MHRA GPvP Inspectorate shares the list of planned and conducted UK national inspections with the EMA; the list is also available to all Member States. The MAH is usually notified of a routine inspection in advance. The timing of a subsequent inspection will be influenced by the inspection findings:
• if a routine inspection results in a critical finding, the MAH is likely to have a triggered re-inspection within 12–18 months, with a focus on the actions that were agreed following the last inspection
• if no critical findings are identified, there is no specific timeline by which an MAH must be inspected again. The frequency of inspection will be decided using the risk-based approach and an inspection may be performed at any time.

**EU inspections**
The EMA co-ordinates a programme of inspections for pharmacovigilance systems that include centrally authorised products. Although the programme follows a routine 4-yearly cycle, the outcome from national risk assessments may result in more frequent scheduling of inspections. The MHRA performs inspections as part of the EU programme when the Pharmacovigilance System Master File is located in the UK. These inspections typically follow the same approach as routine national inspections.

**Triggered inspections**
The MHRA may perform a triggered inspection of an MAH in response to the receipt of specific risk information, such as information about a possible GPvP breach received from a whistle-blower, another MHRA department or another regulatory authority. Triggered EU inspections may also be requested by the CHMP. The MAH will typically receive little or no advance notification of a triggered inspection.

**CHMP-requested inspections**
Where a GPvP inspection is requested by the CHMP, the supervisory authority for the inspected organisation will typically lead the inspection. Such inspections are often requested to address a specific issue that may concern more than one national competent authority, and the supervisory authority may therefore be supported by other authorities in the inspection.

**Service provider inspections**
With the growing trend for MAHs to outsource some or all of their pharmacovigilance activities, it is important to understand that contract service providers are subject to MHRA inspections. However, following a pilot programme of standalone service provider inspections, the MHRA concluded that a routine programme of inspections of pharmacovigilance service providers is not currently viable. Nonetheless, activities performed by service providers are still inspected in the context of MAH inspections, and standalone inspections may be performed where deemed necessary to evaluate the provider’s overall system and procedures based on available risk information.

Contracts with pharmacovigilance service providers should include provisions that cover the availability of data, documentation and appropriate support to the MAH and inspectors during a GPvP inspection.

*Source: <https://tinyurl.com/ya8uolg46>*
FDA encourages broader availability of companion diagnostics in oncology

The FDA has issued new draft guidance entitled ‘Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products’.

The document describes development and labelling considerations for in vitro companion diagnostics to support the indicated uses of multiple drug or biological oncology products, when appropriate. The availability of oncology companion diagnostics with broader evidence-based indications should facilitate better clinical use.

In the past 12 months, the FDA has approved the first cancer treatment based on a common specific genetic feature (a biomarker) rather than on the primary location of the tumour within the body. In effect this means that all (solid) tumours featuring a specific biomarker could potentially be treated with the same drug, regardless of the tumour's location.

Precision (targeted or personalised) medicine aims to match therapeutic products to those patients (and only those patients) who will positively respond to that therapeutic product, to maximise the benefits and minimise the risks from receiving the product. Companion diagnostics are essential to identifying those patients, both during routine clinical care and in drug development. They enable clinicians to choose the most appropriate therapeutic product based on a patient’s biomarker status and help to improve patient care.

During clinical development, a sponsor typically uses just one companion diagnostic, primarily to ensure the robustness of the trial data generated. However, this may mean that a companion diagnostic is typically labelled for use with a specific therapeutic product only. As a result, during routine clinical care a clinician may need to order a different companion diagnostic (ie. one that includes other therapeutic products in the labelling), to obtain an additional biopsy from a patient, or both, in order to have additional therapy treatment options.

Expanded policy

The new draft guidance expands on existing policy on broader labelling, which notes that in some cases – if evidence is sufficient to conclude that the companion diagnostic is appropriate for use with a specific group or class of therapeutic products – the companion diagnostic's intended use/indications for use should name the specific group or class of therapeutic products, rather than specific products. To describe the FDA's thinking on the topic, the draft guidance discusses companion diagnostics for a specific biomarker, disease and specimen type, namely epidermal growth factor receptor (EGFR) mutations in tumour tissue from patients with non-small-cell lung cancer.

The draft guidance describes the considerations for when broader labelling may be scientifically appropriate and when it may not. The FDA recommends that

• developers of therapeutic oncology products and associated companion diagnostics collaboratively consider development programmes that may result in the broader labelling of companion diagnostics that are most clinically useful
• developers discuss development programmes that could result in broader labelling with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH) or the Center for Drug Evaluation and Research, in coordination with the Oncology Center of Excellence as appropriate, as early as possible to determine if the approach described in this guidance is applicable.

Developers whose approved companion diagnostics may be appropriate for broader labelling are encouraged to contact CDRH/CBER.

Source: <https://tinyurl.com/yczjlscd>
UK fast-tracks access to ground-breaking medicines

Cutting-edge and best value drugs will be fast-tracked under the new Voluntary Scheme for Branded Medicines Pricing and Access, providing a more flexible and streamlined commercial process and making the UK more attractive to investors.

The 2019 Voluntary Scheme for Branded Medicines Pricing and Access could give patients access to new ground-breaking medicines up to 6 months earlier. The scheme is currently being finalised with the pharmaceutical industry and replaces the Pharmaceutical Pricing Regulation Scheme, which expired on 31 December 2018. It offers potential savings for the UK’s National Health Service (NHS) of almost £1 billion on medicines in 2019.

Extent of agreement
The UK government and the Association of the British Pharmaceutical Industry (ABPI) reached a deal on the new voluntary scheme, which came into effect on 1 January 2019. In principle, this major milestone should see the most transformative and best value medicines made available on the NHS more quickly, through better horizon scanning, earlier commercial dialogue and faster appraisals from the National Institute for Health and Care Excellence (NICE).

Government Health Secretary Matt Hancock said, “This new deal will be good for patients, good for the NHS and good for the UK life sciences industry. Cutting-edge and best value medicines will be fast-tracked and we will cut our medicines bill by £930 million next year following tough but constructive negotiations with the pharmaceutical industry – money we can redeploy into better NHS services, alongside the NHS Long Term Plan.”

The agreement will ultimately benefit patients by ensuring that the NHS gets the best value and most effective medicines into use more quickly, through:

- faster NICE appraisals – patients should have access to new medicines up to 6 months earlier
- more NICE technology appraisals, so that all new medicines are assessed by NICE, with the NHS funding all those recommended for use
- the smoother and faster introduction of transformative medicines via better horizon scanning and early engagement with companies, to ensure that clinicians and the NHS infrastructure are ready to use these medicines
- more commercial options to incentivise better value for the NHS.

Mike Thompson, ABPI Chief Executive, commented, “This agreement is a commitment by the Government and the NHS to work with us to support innovation for the benefit of patients. This means that people across the UK should see better and faster access to the most effective new medicines and vaccines.

Under the scheme the NHS will have absolute certainty that the sales of branded medicines will not grow by more than 2% in any of the next 5 years – or industry refunds the money.”

The scheme is designed to keep growth in the branded medicines bill predictable and affordable, by:

- placing a 2% cap on the growth in sales of branded medicines to the NHS, with pharmaceutical companies repaying the NHS for spending above that limit
- supporting smaller companies through payment exemptions and targeted case management
- simplifying price controls by reducing unpredictability and complexity
- enabling faster and more flexible commercial discussions in order to get the best value and most effective new medicines into use as quickly as possible.

Source: <https://tinyurl.com/ya6udgfbz>
MHRA offers insight into GCP compliance in dose escalation studies

Irrespective of whether a clinical trial involves healthy volunteers or patients, according to a recent Medicines and Healthcare products Regulatory Agency (MHRA) Inspectorate blog post, the dose escalation practices should be the same.

Writing in her first blog post, Jennifer Martin (a Lead Senior GCP Inspector at the MHRA) has drawn on her experience of inspecting Phase I and first-in-human (FIH) healthy volunteer studies – as well as undertaking assessments under the Phase I accreditation scheme – to evaluate observed differences in the conduct and GCP compliance of dose escalation studies. Specifically, she highlights why the level of risk mitigation applied to patient FIH studies should be the same as that used in healthy volunteer studies. In reality, while dose escalation in FIH healthy volunteer studies is a thorough, detailed and well-documented process, this does not always seem to be the case in multicentre patient studies.

GCP expectations

The blog outlines why healthy volunteer studies and patient studies may be treated differently by sponsors, and explains the GCP expectations for any dose escalation study. Martin highlights the relevant EU and UK regulations and the MHRA Phase I accreditation scheme that require dose escalation procedures to be described transparently in the study protocol. More specifically, for a dose escalation study to be GCP-compliant there should be a formalised procedure detailing how the dose escalation process will be undertaken and transparency in the protocol.

Potential issues

Being able to make scientifically justifiable decisions on dose escalation requires access to, and consideration of, all relevant data. The blog lists the following issues that might result in approved protocol stopping criteria being missed, with dose escalation proceeding when it should have stopped:

- no procedures in the protocol or another document such as an SOP, charter or study-specific plan for how dose escalation will be conducted
- a lack of documented evidence of quality control of the safety data listings provided to the dose escalation committee, resulting in the use of poor-quality data for the dose escalation decision
- serious adverse events (SAEs)/adverse events (AEs) in the source data missed or not transcribed
- SAEs/AEs with no causality/severity assigned
- safety data missing from the data listings
- pharmacokinetic data or other data outlined in the protocol for review not presented to the dose escalation committee.

The blog then goes on to explore whether dose escalation issues are a new phenomenon.

Quality by design

Martin suggests that a risk assessment and mitigation strategy is key to complying with GCP in dose escalation. Points for consideration include the following:

- are all the subjects in the cohort needed to make a dose escalation decision? If not, this should be described with a clear justification in the protocol.
- how does the protocol handle withdrawn subjects? Could replacing them inadvertently affect the size of the cohort?
- are all data from all timepoints in the cohort needed to make a dose escalation decision? If not, are the key assessments and the minimum timepoints needed described with a clear justification in the protocol?
- what are the stopping criteria and what is actually meant by ‘stopping’? This should be clearly defined in the protocol.
- what are the quality parameters for data used to make a dose escalation decision? How will they be verified?

MHRA’s approach

Sponsors should understand that MHRA GCP inspectors inspect against the legislation and the relevant early phase guidance. They expect to see a formalised procedure for dose escalation, and for a specific clinical trial to be able to reconstruct the dose escalation as described in the formalised procedure and approved protocol. Inspectors require evidence of the following:

- that the relevant data have been collated, verified for accuracy and provided to the dose escalation committee
- the dose escalation meeting minutes
- the dose escalation decision agreed by the dose escalation committee, including the principal investigators
- circulation of the dose escalation decision to all relevant people.

In terms of process, inspectors will want to see that the sponsor has

- built quality by design into the protocol
- risk assessed the trial design
- ensured decisions are transparent to the regulators and ethics committees reviewing the protocol
- a Trial Master File from which the dose escalation process can be easily reconstructed.

The MHRA’s primary objectives are to protect public health and ensure the quality of data. It can offer guidance to sponsors and others, and dose escalation queries can be sent to ctddhelpline@mhra.gsi.gov.uk.

Source: <https://tinyurl.com/yarpqtnl>
Updated EMA guideline on new antibacterial agents

The European Medicines Agency (EMA) has issued a draft revised guideline on the evaluation of medicines to treat bacterial infections. The guideline replaces the ‘Guideline on the Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections, Rev 2’ (CPMP/EWP/558/95 Rev.2) and the ‘Addendum to the Guideline on the Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections’ (EMA/CHMP/351889/2013).

Source: <https://tinyurl.com/yd7fn3ft>

FDA extends consultation on informed consent with minimal risk

On 15 November 2018, the FDA published a proposed rule in the Federal Register that allows for a waiver or alteration of informed consent when a clinical investigation poses no more than minimal risk to the subject, and includes appropriate safeguards to protect subjects’ rights, safety and welfare. The proposed rule will implement the statutory changes made to the Federal Food, Drug, and Cosmetic Act by Section 3024 of the 21st Century Cures Act. It will permit an institutional review board to waive or alter certain elements of informed consent or to waive the requirement to obtain informed consent, under limited conditions – for certain minimal risk clinical investigations. On 14 December 2018, the FDA extended the comments period on the proposed rule to 13 February 2019 in response to a request from a stakeholder for an extension.

Source: <https://tinyurl.com/yb27vcao>

EMA relocation to Amsterdam

The European Medicines Agency (EMA) has confirmed that it will relocate to Amsterdam on 1 March 2019; the Dutch authorities officially handed over the Spark building (the agency’s temporary premises) on 9 January. Following the relocation:

- from 4 to 8 March the agency will operate on the basis of extended teleworking, with a small number of staff present in the new building to deal with any emergencies
- from 11 to 15 March EMA staff will gradually move into the Spark building
- from 15 March 2019 all EMA meetings will take place in the Spark building.

Source: <https://tinyurl.com/yd25qf7t>