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Regulatory Newsletter
July - September 2016

Introduction

CROMSOURCE is committed to sharing our expertise with our clients and future clients. This reflects the first part of our 'Advise Agree Deliver' motto! In this spirit we have pleasure in making available this issue of our Regulatory Newsletter.

This newsletter is put together by our expert regulatory team and tracks the changes occurring in European regulations relating to clinical research performed in both medicinal products and medical devices.

The Newsletter is a quarterly publication distributed via email and posted on the CROMSOURCE website. We hope you find this information useful, and welcome feedback, questions and suggestions. Contact us on cromsource@cromsource.com at any time.

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News from the European Commission

New MEDDEV 2.7.1 Revision 4 has been released

Revision 4 of Clinical Evaluation guidance document MEDDEV 2.7.1 was released by the European Commission in June 2016 and replaced revision 3 from December 2009.

The new revision is more detailed and more focused on guidance for manufacturers. The Revision 4 promotes a common approach to clinical evaluation for medical devices regulated by directives 90/385/EEC and 93/42/EEC. Working with the updated MEDDEV will help manufacturers to prepare for the coming Medical Device Regulation (expected in the first quarter of 2020). Revision 4 does not concern *in vitro* diagnostic devices.

The new revision informs the CER is to be updated at least annually for high risk or new devices, and every two to five years for lower-risk, well-established devices. A justification for the frequency of updates will be required. For all risk classifications of devices, the CER will need to be updated whenever new information from the Post Market Surveillance (PMS) affects the evaluation or its conclusions. There are a list of new requirements for the expertise and experience of CER evaluators.

As a general principle, the evaluators should possess knowledge of: research methodology, information management, experience with relevant databases, regulatory requirements and medical writing. With respect to the particular device under evaluation, the evaluators should in addition have knowledge of the device technology and its application, diagnosis and management of the relevant conditions, treatment standards and alternatives. The evaluators should have at least a degree from higher education in the respective field and five years of documented professional experience or 10 years of documented professional experience if a degree is not a prerequisite for a given task. In circumstances where the evaluator expertise is less or different this should be documented and justified.

The requirements of the CER to be linked to specific safety, performance and risk-benefit endpoints are more clear than in the previous revision. Detailed guidance is provided in Section 7, Appendix 5 and The Clinical Evaluation Checklist in Appendix A10.

The new revision places much greater emphasis on demonstrating the scientific validity of data, including statistical considerations; see Section 9.3.1 “How to evaluate methodological quality and scientific validity”. The guidance helps to identify pertinent data and provides key elements of literature search and literature review protocol (Section 8 and Appendix 5). It also provides instructions on appraisal of clinical data with examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety (Section 9 and Appendix 6) and the analysis of data and demonstration of conformity (Section 10 and Appendix 7). The requirements for demonstration of equivalence are described in detail in Appendix 1.

The new requirement is that the Notified Body challenge the manufacturer’s access to data on the equivalent device(s) (Appendix A12.2.3). This is considered a transition point for the Regulation, which will require a manufacturer to have a contract in place allowing access to data for competitor devices with which equivalence is claimed.

Appendix 2 describes when additional clinical investigations should be carried out.

New Revision 4 shows the links between clinical evaluations, Post Market Surveillance (PMS) and Post Market Clinical Follow-up (PMCF). In Appendix 12 the requirement for Notified Bodies has been highlighted to ensure that PMCF is planned and appropriately justified in light of the data retrieved and conclusions documented in the CER.

The full guideline may be found here:

http://ec.europa.eu/DocsRoom/documents/17522/attachments/1/translations/

New EU Medical Device Guidance on Standalone Software

On 15 July 2016, the European Commission updated MEDDEV 2.1/6 Guidance on the qualification and classification of standalone software used in Healthcare within the Regulatory framework of Medical Devices. The updated version replaces an earlier version of MEDDEV 2.1/6 issued by the European Commission in January 2012.

MEDDEV 2.1/6 generally stands as a valuable resource to assist software developers in the assessment of whether software is a medical device. The purpose of this guidance is to clarify the distinction between different types of medical software, namely medical software that is:

- Part of Medical Device or IVD (*in vitro* diagnostic medical device)
- Accessories
- Standalone oftware
- Not a medical device

Standalone software must have a medical purpose to be qualified as medical device. It should be noted that only the intended purpose as described by the manufacturer of the product is relevant for the qualification and classification of any device and not by virtue of the way it may be called.

Standalone software that does not meet the definition of a medical device or of an IVD medical device but is intended by the manufacturer to be an accessory to a medical device, or an IVD medical device, falls respectively under the scope of Directive 93/42/EEC or Directive 98/79/EC.

It is to be noted that to be qualified as an IVD medical device, standalone software must first fulfill the definition of a medical device.

Where a given product does not fall under the definition of medical device, or is excluded by the scope of the Directives, other Community and/or national legislation may be applicable.

There are a lot of clarified definitions: for example “software” is a “set of instructions that processes input data and creates output data“ and quite important definitions of “input data” and “output data”.

“Input data” is defined as “any data provided to software in order to obtain output data after computation of this data.” This can include: data given through the use of a human data-input device such as a keyboard, mouse, stylus, or touch screen, data given through speech recognition, and digital documents formatted for general purpose such as Word file or pdf file or jpeg image, formatted for medical purpose such as DICOM file or ECG records or Electronic Health Record, unformatted document. Note that digital documents have to be differentiated from software able to read such documents, data received from/transmitted by devices.

"Output data" is defined as "any data produced by a software." This includes: Screen display data (such as layout with number, characters, picture, graphics etc.), print data (such as layout with number, characters, picture, graphics etc.), audio data, digital document (formatted for a general purpose such as Word file or pdf file or jpeg image, or formatted for medical purpose such as DICOM file or ECG records or Electronic Health Record, unformatted document), and haptic buzzing as an alternative to audio sound mobile applications.

The updated version also contains a new definition of "Software as a Medical Device" (SaMD) as meaning "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."

The full guideline may be found here:

http://ec.europa.eu/DocsRoom/documents/17921/attachments/1/translations

Commission welcomes new agreement for safer use of medical devices

The European Parliament and the Council have reached an agreement for better surveillance and traceability of medical and *in vitro* diagnostic devices.

This new agreement between the European Parliament and the Council from 15 June 2016 takes on board some key concerns of the Commission indicated at several stages of the negotiation and contains a series of important improvements to the current system:

- Stricter pre-market control of high-risk devices with the involvement of a pool of experts at EU level
- The reinforcement of the criteria for designation and processes for oversight of notified bodies in charge of certifying medical devices
- The inclusion of certain aesthetic products which present the same characteristics and risk profile as analogous medical devices under the scope of these Regulations
- The introduction of a new risk classification system for diagnostic medical devices based on international guidance
- Improved transparency through the establishment of a comprehensive EU database on medical devices and of a device traceability system allowing to trace the device from its manufacturer through the supply chain to the final user
- The introduction of an EU-wide requirement for an 'implant card' to be provided to patients containing information about implanted medical devices
- The reinforcement of the rules on clinical data, including an EU-wide coordinated procedure for the authorisation of multi-centre clinical studies on devices
- The reinforced requirement for manufacturers to collect data about the real-life use of their devices
- Improved coordination between Member States in the fields of vigilance and market surveillance.

The regulations establish a modernized and more robust EU legislative framework that is crucial to ensure a better protection of public health and patient safety.

They will also contribute to innovation in this sector, to the competitiveness of the EU industry and to the better functioning of the internal market in this strategic sector.

Next steps

The Council has planned to approve the agreement at the Ministers' level in September. Following their legal-linguistic review, the two draft regulations will be then adopted by the Parliament and the Council, probably at the end of 2016 or early 2017.

The new rules will apply three years after publication for medical devices and five years after publication for *in vitro* diagnostic medical devices.

http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=8863&lang=en%29

Harmonised standards for demonstrating conformity of medical devices

In order to demonstrate the conformity of a medical device with the essential requirements laid out in Directives 85/16/EC, 90/385/EEC, 93/42/EEC and 98/79/EC, 95/, the medical device manufacturer must use harmonised standards as adopted by the European Union. A harmonized standard is defined as a standard developed by a recognized European standards organization, such as the European Committee for Standardization (CEN), the European Committee for Electrotechnical Standardization (CENELEC) or the European Telecommunications Standards Institute (ETSI). - See more at: http://www.raps.org/Regulatory-Focus/News/2016/05/13/24946/European-Commission-Publishes-New-Harmonized-Standards-for-Devices-Implants-IVDs/#sthash.oNJPpJfx.dpuf

The updated list of the harmonised standards to be used was published in the Official Journal of the European Union on 13 May 2016.

It can be found on:

http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=uriserv:OJ.C_.2016.173.01.0100.01.ENG

Consultation documents on clinical trials

Risk proportionate approaches in clinical trials
http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_4_consult.pdf

Summary of Clinical Trial Results for Laypersons
http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_3_consult.pdf

Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)
http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_2_consult.pdf

Ethical considerations for clinical trials on medicinal products conducted with minors
http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_1_consult.pdf

The results of the consultation will be presented in the next Regulatory Newsletters.

News from the European Medicines Agency

Multi-Media Tutorials launched by European Clinical Trial Database (EudraCT)

These tutorials aid sponsors in a step-by-step guide to provide results in EudraCT. It is recommended to read the overview document which explains how to save and view the tutorials. Multi-media tutorials are demo presentations which help Sponsors new to EudraCT to enter results of trial information, subject disposition, baseline characteristics, end-points and adverse events.

The link to overview document and multi-media demos is:

https://eudract.ema.europa.eu/multimedia_tutorials.html

Proposals to revise guidance on first-in-human clinical trials

On 21 July 2016, the European Medicines Agency (EMA), in cooperation with the European Commissionand the Member States of the European Union, proposed changes to current guidance on first-in-human clinical trials to further improve strategies to identify and mitigate risks to trial participants. These changes are outlined in a new concept paper which has been released for public consultation. Comments on the proposals were to be sent to FIH-rev@ema.europa.eu until 30 September 2016.

The release of the concept paper is part of a review of the EMA guideline published in 2007 that provides advice on first-in-human clinical trials, in particular on the data needed to enable their appropriate design and allow the initiation of treatment in trial participants. This review identified those parts of the current guideline which need to be amended to take into account the evolution of practices in the conduct of these studies since the guideline was first published. The review also takes into account the lessons learned from the tragic incident which took place during a Phase I first-in-human clinical trial in Rennes, France, in January 2016, where one person died and five were hospitalized.

The proposals are available here:

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2016/07/WC500210845.pdf

The current 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' is available here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf

The results of the public consultation will be presented in the next Regulatory Newsletters.

New adopted guidelines on good pharmacovigilance practices (GVP):

- Guideline on good pharmacovigilance practices (GVP): Product- or population-specific considerations II: Biological medicinal products

On 16 Aug 2016 the EMA published a new guidance on good pharmacovigilance practices for biological medicinal products regardless of the regulatory pathway of approval or market exclusivity status, i.e. it applies to biological medicinal products (medicinal substances derived from blood and plasma,

biotechnology-derived medicines (e.g. using recombinant DNA technology), all types of prophylactic vaccines and advanced therapy medicinal products (ATMPs), to biosimilars (products that contains a version of the active substance of an already authorised reference product in the EEA, and which has shown similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise) and to products which contain the same or closely related active substance but not authorised as biosimilars (e.g. different versions of interferon beta-1a, factor VIII or normal human immunoglobulin).

This GVP Module does not apply to vaccines and ATMPs.

This Module P.II. is therefore intended to be read and followed alongside the process-related GVP Modules when developing and implementing pharmacovigilance for biologicals to ensure that these challenges are addressed. P.II.A. describes some of the specific issues and challenges, P.II.B. provides guidance on addressing these in the context of the main pharmacovigilance processes described in the GVP and P.II.C. provides guidance related to operation of the EU network.

The full guideline may be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf

- Revised guideline on good pharmacovigilance practices (GVP) Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev 2)

This addendum provides additional information on legal requirements and recommendations for the submission of study protocols, progress reports and final study reports of non-interventional post-authorisation safety studies (PASS) to national competent authorities and the Agency. It also provides additional information in regard to the registration of non-interventional PASS in the EU PAS Register. It does not provide recommendations for the transmission of information to ethics committees, national review boards or other bodies in place according to national legislation.

Date for coming into effect of Revision 2 was on 9 Aug 2016.

The full guideline may be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129147.pdf

- Revised guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 2)

This Module VIII concerns both interventional and non-interventional a post-authorisation safety study (PASS), with a main focus on non-interventional ones. It does not concern pre-clinical safety studies.

The purposes of this Module are to:

- provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted voluntarily or pursuant to an obligation imposed by an EU competent authority
- describe procedures whereby an EU competent authority may impose on a marketing authorisation holder an obligation to conduct a PASS
- describe procedures that apply to non-interventional PASS pursuant to an obligation imposed by an EU competent authority for the protocol oversight and reporting of results and for subsequent changes to the marketing authorization

In GVP Module VIII some legal requirements which are mandatory to non-interventional PASS conducted pursuant to an obligation imposed by an EU competent authority are recommended for non-interventional PASS conducted voluntarily in order to support the same level of transparency, scientific standards and quality standards. This applies, for example, to the format and content of the study protocol and of the final study report and its abstract.

For non-interventional PASS, this guidance applies to studies that involve primary collection of safety data directly from patients and healthcare professionals as well as those that make secondary use of data previously collected from patients and healthcare professionals for another purpose.

Date for coming into effect of Revision 2 was on 9 Aug 2016.

The full guideline may be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf

PSUR repository

From 13 June 2016, all periodic safety update reports (PSURs) for human medicines authorised in the European Union (EU) must be submitted electronically to the PSUR repository.

The use of the PSUR Repository is mandatory as of 13 June 2016. The PSUR repository is a single, central platform for PSURs and related documents to be used by all regulatory authorities and pharmaceutical companies in the EU.

Marketing authorisation holders must also now use the repository as a single point for all submissions and should no longer submit their PSURs to national competent authorities. PSUR submissions to the repository are made through the eSubmission Gateway/Web Client:

http://esubmission.ema.europa.eu/psur/psur_repository.html

New EudraVigilance system

From 13 June 2016, changes are being implemented to the EudraVigilance registration system including: a 'regulatory contact point' for marketing authorisation holders, mandatory password change functionality for first time users, editable fields and affiliate categories, new troubleshooting functionality, and separate adverse drug reaction (ADR) and XEVMPD user rights.

A document detailing the registration user management is here:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/06/WC500208954.pdf

The updated EU pharmacovigilance legislation brought significant changes to electronic reporting requirements for suspected adverse reactions. EMA has launched a project to deliver a new EudraVigilance system with enhanced functionalities in November 2017.

A modular training programme will be provided in 2016 and 2017.

The new EudraVigilance website: https://eudravigilance.ema.europa.eu/Decommissioned/Decommissioned.html is being de-commissioned. The public information on this website has been incorporated into the European Medicines Agency corporate website.

Guidelines/Recommendations

Guideline on the clinical investigation of medicinal products in the treatment of lipid disorders

On 1 January 2017, Revision 3 of the guideline on clinical investigation of medicinal products in the treatment of lipid disorders will come to effect. The guideline details the main regulatory requirements that are expected to be followed in the development of a lipid modifying medicinal product.

It was aligned with other relevant EMA guidance (i.e. reflection paper on assessment of cardiovascular safety profile of medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187801.pdf) ; guideline on the clinical investigation on medicinal products in the treatment of hypertension (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209943.pdf); guideline on the clinical evaluation of medicinal products used in weight management (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209942.pdf).

The guideline EMA/CHMP/748108/2013, Rev. 3 can be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209944.pdf

Guideline on the clinical development of medicinal products for the treatment of HIV infection

A revised guideline (revision 3) on the clinical development of medicinal products for the treatment of HIV infection will come into effect on 1 January 2017. It has been updated to include a recommendation to perform drug-drug interaction studies prior to marketing authorisation.

This document provides guidance on the clinical development of direct-acting antiretroviral agents for the treatment of HIV infection. It defines the patient population in such studies as “treatment naïve” , i.e. the patients who have not previously received antiretroviral therapy and who are infected with HIV without mutations conferring drug resistance in their major viral populations, as determined by standard genotypic assays (i.e. virus that is predicted to be fully susceptible to antiretroviral drugs of all classes).

In the previous Revision 2 it was recommended that placebo-controlled studies with a statistical superiority design and with virological endpoints at 24-48 weeks should be performed in patients who were failing on their treatment regimen in order to obtain an indication for use in "treatment experienced" patients. However, due to the introduction of numerous new antiretroviral agents in recent years, and to use of pharmacokinetic enhancement ("boosting") the development of extensive resistance de novo is now rare in patients who are treated with optimised regimens in the EU. As a result, placebo-controlled superiority designs may no longer be feasible in all cases, and non-inferiority trials in such populations are fraught with methodological problems.

Therefore for all new agents, it is proposed that data on safety and efficacy are generated in randomised double-blind controlled trials in "treatment naïve" patients.

In line with this approach it is recommended that the antiviral activity, specificity and capacity for selection of resistant variants initially be characterised *in vitro*, and that all viral isolates from patients failing therapy be characterised genotypically as well as phenotypically if not previously investigated.

The full guideline EMEA/CPMP/EWP/633/02 Rev. 3 may be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209918.pdf

Draft guideline on the development of new medicinal products for Ulcerative Colitis - Revision 1

On 01 August 2016, the EMA published a new draft guidance on the development of new medicinal products for the treatment of Ulcerative Colitis. The main aim of this first revision is to update the guidance on the design of studies in adult patients, especially on potential claims, primary and secondary endpoints and comparators. It is also intended to give further guidance with regards the possibility for extrapolation from adults, or the need to generate separate data in children and to give recommendations regarding the exploration of PK/PD in paediatric drug development.

The full guideline may be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211431.pdf

The guidance is available for comment by 31 January 2017. Email address for submission: gastroenterologydg@ema.europa.eu

Draft guideline on the development of new medicinal products for Crohn's Disease - Revision 2

On 01 August 2016, the EMA published a new draft guidance on the development of new medicinal products for the treatment of Crohn's Disease. The main aim of this 2nd revision was to update the guidance on the design of studies in adult patients, especially on potential claims, primary and secondary endpoints, and comparators. It is also intended to give further guidance with regards the possibility for extrapolation from adults, or the need to generate separate data in children and to give recommendations regarding the exploration of PK/PD in paediatric drug development.

The full guideline CPMP/EWP/2284/99 Rev. 2 may be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211430.pdf

The guidance is available for comment by 31 January 2017. Email address for submission: gastroenterologydg@ema.europa.eu

Initiatives

Signal detection and management information day

On 02 December 2016, the EMA office in London will hold Signal Detection and Management Information Day. This Information day will review signal detection and management activities essential to the overall risk management process of a medicinal product. The event will explain the impact of the implementation of the 2010 pharmacovigilance legislation, with a strong focus on signal detection and management within the European Union, emphasizing the requirements to be implemented in 2017.

Agenda and registration form:

http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2016/09/WC500212634.pdf

Outcome of UK referendum on EU membership-EMA Statement

On 6 July 2016, the EMA published the official statement on the outcome of the UK referendum.

The European Medicines Agency (EMA) acknowledges the outcome of the referendum of 23 June 2016 on the United Kingdom's (UK) membership of the European Union (EU). Its implications for the Agency's location and operations depend on the future relationship between the UK and the EU, which is still unknown.

The future location of the Agency will depend on the future relationship between the UK and the EU. Representatives of the Member States will determine the Agency's location by common agreement.

EMA's procedures and work streams are not affected by the outcome of the referendum. The Agency will continue its operations as usual, in accordance with the timelines set by its rules and regulations.

The Agency is in close contact with the EU institutions. As soon as concrete information is available, EMA will share it with its stakeholders.

The statement is available at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002566.jsp&mid=WC0b01ac058004d5c1

News from Individual Countries

The Netherlands: Non-WMO Law Studies

From July 1, 2016, the management of the review process and the Standards Framework for clinical drug studies not covered by law WMO (Medical Research involving Human Subjects Act, Wet Medisch Wetenschappelijk Onderzoek met Mensen, 26 February 1998, effective 1 December 1999) initiated or funded by pharmaceutical companies is covered by the DCTF (Dutch Clinical Trial Foundation).

If the research does not fall under the scope of the WMO then it does not have to be reviewed by an accredited MREC (Medical Ethical Reviewing Committee) or the CCMO (Central Committee for Research Involving Human Subjects) in the Netherlands.

Examples of non-WMO studies: observational (non-interventional) research, retrospective database search, non-direct patient-related research (e.g. research from a biobank).

Phases 1, 2, 3 and 4 studies are under WMO studies (should be submitted to the Competent Authority/Ethics Committee).

By evaluating non-WMO studies the DCTF contributes to:

- Quality, relevance and scientific value of the investigation
- Better protection of the rights and privacy of participants in the study
- Public transparency about the research carried out
- Preventing unwanted commercial motives
- Avoiding wasting money and time

The developed Review and Standards Framework for non-WMO liable research has been implemented primarily for drug research initiated and financed by the pharmaceutical industry.

The application can be submitted through the website: www.nwmostudies.nl. The applicant can download the review framework, which is a Word document in Dutch. After completing the document, it should be saved and then submitted together with all relevant documents (as listed in the review framework) to nwmo@dctf.nl (new address from July 1, 2016). The approval is received in up to six weeks. The cost of submission for non-WMO study is 2000€.

The testing framework has been established with support from the Ministry of Health.

The DCTF (Dutch Clinical Trial Foundation) website is: http://nwmostudies.nl/nl/Home

For more information if a study is covered by the law WMO, please go to: http://www.ccmo.nl/en/help-me-on-my-way

UK: HRA Approval: the new process for the NHS in England

HRA (Health Research Authority) approval is the new process for the NHS in England that brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK research ethics service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England. This allows participating organisations to focus their resources on assessing, arranging and confirming their capacity and capability of delivering the study.

From 31 March 2016, HRA Approval is the process for applying for approvals for all project-based research in the NHS led only from England. This means that:

- Research described by any of IRAS filter question 2 categories (except those for "Research Tissue Bank" and "Research Database") can apply for HRA Approval if the lead NHS R&D Office is in England
- HRA Approval will be used wherever the project involves NHS organisations in England
- Where a project also involves NHS/HSC organisation(s) elsewhere in the UK (i.e. other than England) the study will be supported through existing UK-wide compatibility systems by which each country accepts the centralised assurances, as far as they apply, from national coordinating functions (http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/) without unnecessary duplication
- Projects that have previously sought or gained NHS permission for participating NHS organisations in England, or applied for REC review, will come under HRA Approval

For any new studies that are led from outside England but have English NHS sites, the national R&D coordinating function of the lead nation will share information with the HRA Assessment team who can issue HRA Approval for English sites and thereby retain existing compatibility arrangements.

The HRA has streamlined the previous complex approval process so that researchers and NHS sites can rely on the HRA's approval to address both legal and ethical aspects of the study in an integrated way. This will allow local research teams to work with their NHS site to set up and deliver the study.

The process has been developed in collaboration with a range of stakeholders and implemented through a phased roll-out, which was completed on 31 March 2016.

Studies which have already applied for REC review but have not applied for R&D review, or need to add new NHS sites in England, or have new amendments, will be brought under HRA Approval so that NHS sites can work with sponsors in the new way.

Important and useful information at links:

"HRA approval" guidance: http://www.hra.nhs.uk/about-the-hra/our-plans-and-projects/assessment-approval/

"Before you Apply" guidance: http://www.hra.nhs.uk/research-community/before-you-apply/

Switzerland: electronic pharmacovigilance reports

Due to a steady increase in the number of reports of adverse drug reactions (ADR) in recent years, the Swissmedic (the Competent Authority in Switzerland) will, in the future, generally prioritise ADR reports submitted electronically, particularly those from authorisation holders. The required tools are available in the form of the E2B Gateway and the ElViS electronic reporting system.

The E2B Gateway is reserved for use by companies with high reporting volumes. By the end of 2016, 25 authorisation holders will be able to actively use the E2B Gateway.

The ElViS electronic reporting system, which is ideal particularly for small- and medium-sized companies, has now been in operation since the end of 2014. From 1 September 2016, companies with low report volumes will have to submit their ADR reports via the ElViS electronic reporting system because from

that date Swissmedic will only forward ADR from the regional pharmacovigilance centres to companies in electronic format via the E2B Gateway or ElViS.

More information: https://www.swissmedic.ch/aktuell/00673/03110/index.html?lang=en

ElViS training courses (in French and German only):
https://www.swissmedic.ch/aktuell/00283/00399/02449/index.html?lang=en