

## Standardising Benefit:Risk Assessment Heads DIA EuroMeeting News

*Neena Brizmohun* describes how endeavours by regulators to create standardised frameworks for evaluating the benefits and risks of drugs are progressing and reports on other news from the Drug Information Association's 22nd Annual EuroMeeting in Monaco from 8-10 March.

Efforts by regulatory agencies around the world to standardise for the first time how they assess the benefits and risks of the drugs they review are advancing. New rules on clinical trial registry and transparency requirements are coming in the European Union and the US. And the creation of a global network for clinical research that would allow industry to share trial data more effectively is gathering momentum.

These and other notable regulatory developments were revealed at the Drug Information Association EuroMeeting and are described in detail in the series of articles below.

### Agency efforts to standardise benefit:risk assessment progress

The European Medicines Agency has released results from the first of a five-part project that aims to standardise for the first time the way in which it assesses the benefits and risks of medicines.

The findings were presented at the DIA EuroMeeting, where it was also announced that the regulatory authorities in Switzerland, Canada, Australia and Singapore are set to move into the second phase of their collaborative effort to develop a benefit:risk framework that their regulators can use when evaluating drugs.

The results from the first part of the EMA project showed that regulators from six European Union member states had divergent views on benefit:risk assessment, reported Xavier Luria, head of safety and efficacy of medicines at the EMA. There was no systematic approach and benefit:risk was found to be balanced intuitively, Dr Luria said, adding that the finding on methodologies used (or the lack of) does not mean that the assessments were wrong.

It has been recognised for some time that current approaches used to assess benefits and risks are inconsistent, Stuart Walker told DIA EuroMeeting delegates during another presentation on benefit:risk evaluation. Professor Walker, founder of the CMR International Institute for Regulatory Science, added that this is the case not only for regulators, where decisions can conflict, but also for companies, where data and submissions on benefits and risks are not always presented in a coherent and well structured manner. A standardised framework for benefit:risk assessment would support transparency in decision-making. There is a "need for a better understanding of why different agencies come to different conclusions when faced with essentially the same application data", Professor Walker explained.

### Five EMA work packages

Plans by the EMA to develop a systematic benefit:risk assessment framework were set in motion in 2006, when a working group of the agency's scientific committee, the CHMP, was set up to address the matter. In 2008, the CHMP released a reflection paper that recommended a revision of the benefit:risk balance section of CHMP assessment report templates in order to achieve a systematic approach throughout all 27 member states<sup>1</sup>. The paper called for the development of a structured list of benefit and risk criteria and guidance and said that further research should be carried out into the methodologies used to assess benefit:risk balance.

The CHMP working group has since agreed on a draft template. The draft template has been implemented into existing assessment reports and it was rolled out last year. "Assessors have been trained on how to use the new template," noted Dr Luria.

A task force has also been set up to review use of the template over the next few months. "It will be interesting to see how the new template is working for assessors and also if it needs amendment," Dr Luria said.

To research further into benefit:risk methodology, the EMA drafted a project comprised of five work packages that will develop and test tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products. The project is being carried out in collaboration with the London School of Economics, in the UK, and the University of Groningen, in the Netherlands. A CHMP and EMA steering group has also been set up to follow the project.

*Important regulatory developments were discussed*

### Benefit:Risk

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*The EMA's project to standardise benefit:risk assessment comprises five work packages*

Work package 1, the results of which were released at the DIA EuroMeeting, explored how assessors from different agencies currently assess benefit:risk for marketing applications submitted via the centralised procedure. It was also designed to identify opportunities for improvements and criteria for appraising current benefit:risk assessment tools and processes.

*A total of six agencies participated in work package 1*

A total of six agencies participated in work package 1 – from Spain, France, the Netherlands, Sweden, the UK, and more recently, Germany (the Paul-Ehrlich-Institut). Some 42 people were interviewed – assessors, statisticians, CHMP members, chairmen and directors. Interviews were based on a predefined protocol that included questions for agencies on their history and purpose, information flow, meaning of “benefits” and “risks”, benefit:risk assessment processes, consistency and existence of models.

As well as showing that there were divergent views on benefits and risks among assessors, work package 1 found that there were no single, clear definitions of “benefits” and “risks”. There were different views on the relative importance of benefits and risks. On average, more time and effort were spent on positive benefits and less time and effort on uncertainty of harms. Work package 1 also showed that benefit and risk are balanced intuitively and are a matter of judgment. In addition, benefit:risk assessment was found to be the most difficult step in the approval process.

As for opportunities for improvement, work package 1 proposed that benefit and risk elements be separated into four distinct categories: favourable effects, uncertainty of favourable effects; unfavourable effects; and uncertainty of unfavourable effects. This is reflected in the CHMP assessment report template.

A report containing the full findings of work package 1 is due to be published on the EMA’s website soon.

### **Work packages 2-5**

*Work package 2 will assess the applicability of current tools and methods*

As for the next steps of the project, the EMA is currently developing work package 2, which will assess the applicability of current tools and methods and include a review of current status-literature. A draft of work package 2 was expected to be made available to the steering group at the beginning of April. It will be published following approval from the steering group.

Work package 3, which Dr Luria described as the “key” package, will involve field tests of existing tools and methods for assessing benefit:risk that have been identified in the previous work packages. It will also identify methods that can add value to benefit:risk evaluation. The third work package is expected to be conducted in 2010.

Work package 4 will involve developing new tools and methods for benefit:risk assessment. Finally, work package 5 will involve implementing a training module for assessors and it is expected to be launched in 2011.

### **2011 public workshop**

In 2011, the EMA hopes to hold a public workshop to discuss the findings from the first four work packages; an advanced draft report on the work packages is expected to have been completed before then. Stakeholders will be able to comment on the results, before the agency moves to adopting a final benefit:risk assessment framework.

### **Switzerland/Canada/Australia/Singapore consortium**

Regulators from Switzerland’s Swissmedic, Canada’s Health Products and Food Branch, Australia’s Therapeutic Goods Administration and Singapore’s Health Sciences Authority are also making progress on their collaboration to create a standardised benefit:risk assessment framework.

*The consortium is preparing to evaluate its draft framework in a pilot study this year*

The benefit:risk initiative, which started in 2008, has developed a draft framework. The draft currently comprises 16 pages and was made available at the end of January 2010. The consortium is now preparing to evaluate the draft framework in a pilot study this year; a feasibility study was completed in 2009.

The consortium aims to develop a qualitative framework for the benefit:risk assessment of medicines, said Petra Dörr, head of management services & networking at Swissmedic. The framework is expected to allow a systematic, standardised approach to the appraisal of medicines during regulatory review and post-marketing activities by Health Canada, Swissmedic, the TGA and the HSA, in order to facilitate the opportunity for joint or shared reviews between the four agencies, Dr Dörr explained.

The consortium is using as a basis for its work the EU assessment report templates, to which it has added the benefit:risk template it has developed; its benefit:risk template was developed together with the CMR International Institute. Its pilot study will involve each agency assessing two to three products.

The consortium is currently focusing on information sharing. Parallel reviews have already been carried out, where agencies have worked on the same dossier, exchanged assessment reports, analysed and compared their findings and then taken independent decisions. “Our next

step is work sharing," said Dr Dörr. Parts of the dossiers will be reviewed by one of the agencies. The assessment reports will then be shared, and decision making will be made independently.

Discussions on the pilot study's status are expected to take place in June at a CMR International Institute workshop in Washington, DC. A main study of the draft framework is expected to begin in 2011.

### Other frameworks and considerations

Besides the initiatives by the EU and the consortium comprising Switzerland, Canada, Australia and Singapore, a benefit:risk assessment framework is also being developed by US pharmaceutical industry association PhRMA. PhRMA's initiative, called Benefit Risk Action Team (BRAT), has involved a three-year plan and there have been suggestions that it might come to fruition at the end of this year. A spokesman for PhRMA told *RAJ Pharma*, however, that it was "too early in the process to comment" on how the initiative was progressing.

The US Food and Drug Administration has also been considering the development of a benefit:risk assessment framework. According to an agency spokesperson, however, neither the agency's biologics division, CBER, nor its drugs division, CDER, "has a proposed risk-benefit framework...and neither has information to relay" at this time. "This is for future discussion." A meeting on the subject is scheduled to take place in the US on 23 April<sup>2</sup>.

The CMR International Institute, which has been a key driver in various initiatives to develop a benefit:risk assessment framework for medicines, is currently working on refining a framework based on the multi-criteria decision analysis (MCDA) model and plans to study its practical application in regulatory environments<sup>3</sup>.

"We looked at the MCDA model and developed the framework on that basis," Professor Walker told *RAJ Pharma*. "But the difference in our approach is that we're using a qualitative approach to the benefit:risk assessment rather than a quantitative approach." Regulatory authorities currently use a qualitative approach to benefit:risk and the CMR International Institute wanted to "mirror" that, Professor Walker explained, adding that, long-term, the aspiration is for regulators to use a quantitative approach.

The CMR International Institute's MCDA model comprises the following five critical steps:

- step 1: identifying the options to be appraised, such as the subject medicine and the comparators used in the pivotal clinical trials;
- step 2: identification of the relevant benefit and risk criteria and organisation in a value tree, which includes identification of the efficacy and safety data set;
- step 3: assessing the performance of each option against the criteria, which involves constructing the value scale for each criterion for each option and scoring each option on each criterion;
- step 4: assignment of a weight to each criterion relative to other criteria, carried out by group on subjective basis; and
- step 5: the benefit:risk assessment expert judgement.

"We're at the stage where we've developed a framework, we've written the proforma and produced an electronic version and we're able now to carry out a pilot study," Professor Walker said, adding that the model is being used by the Switzerland/Canada/Australia/Singapore consortium.

The model is also being considered by the EMA as one of "several contributions from academia and industry", Dr Luria told *RAJ Pharma*.

Professor Walker noted that his development of the MCDA model was based on the CHMP reflection paper released in March 2008.

As for creating a single global framework for systematically assessing benefit:risk, Professor Walker reiterated that this was a long-term aim. "I would hope that in the next three to five years the different agencies will have developed and validated their frameworks and the approaches that they are using. There is the hope that we will share the information during that period and see if we can't come together... with a global framework."

The CMR International Institute held a workshop on benefit:risk last year that resulted in a number of recommendations.

For example, said Professor Walker, it would be of value to compare the strengths and weaknesses of the different frameworks using a case study approach. A scorecard to evaluate agency/sponsor feedback on these benefit:risk frameworks would be useful. The role of payers and health technology assessment in the development and validation of the frameworks should be explored. A framework should evolve from being predominantly qualitative with minimal data in early development to increasingly quantitative and detailed. It should also incorporate clear data collection methodology and allow the opportunity for additional stakeholders' input regarding different perspectives such as patients, physicians and payers.

*A main study of the draft framework is expected to begin in 2011*

*The CMR International Institute is working on refining a benefit:risk assessment framework based on the multi-criteria decision analysis model*

*The model is being considered by the EMA as one of "several contributions from academia and industry"*

## References

1. CHMP Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use, 19 March 2008, [www.ema.europa.eu/pdfs/human/brmethods/1540407enfin.pdf](http://www.ema.europa.eu/pdfs/human/brmethods/1540407enfin.pdf)
2. Risk-Benefit Considerations in Drug Regulatory Decision-Making, The New York Academy of Sciences, [www.nyas.org/Events/Detail.aspx?cid=ba88a2a4-9dd3-4150-b8c6-021cfc899310](http://www.nyas.org/Events/Detail.aspx?cid=ba88a2a4-9dd3-4150-b8c6-021cfc899310)
3. Mussen F, Salek S, Walker S, Benefit-Risk Appraisal of Medicines: A systematic approach to decision-making, August 2009, Wiley-Blackwell

## Clinical Registries

*Regulators are now starting to focus on results databases rather than just registries*

### Standardisation of clinical trial transparency requirements needed

There is a desperate need to standardise the increasingly differing transparency requirements around the world for clinical trials, according to a DIA EuroMeeting presentation on clinical registries and disclosure requirements.

"We have multiple [clinical trial] registries, with multiple formats and requirements – with more coming on line all the time," said Jacqueline Sayers, quality projects manager, pharma development quality, Roche Products Ltd, UK. Moreover, regulators are now starting to focus on results databases rather than just registries, "which will make the problem even worse", said Dr Sayers, who also provided an update of imminent and impending transparency requirements in some of the major markets.

Inconsistencies in clinical registry and transparency requirements result in duplicate and multiple efforts on the part of companies and individual investigators, Dr Sayers explained. This, in turn, leads to confusion for patients and doctors trying to find details on a specific trial. It also creates the potential for discrepancies between entries and increases the likelihood of inadvertent non-compliance.

### Public access to EudraCT results imminent

In the European Union, the dates are getting closer for new requirements to make available to the general public both protocol information and results of trials held in EudraCT, the EU database on clinical trials. The provisions are being made in accordance with two rules: Article 57(2) of Regulation (EC) No 726/2004, which relates to all clinical trials in EudraCT; and Article 41 of Regulation (EC) No 1901/2006, which relates to paediatric clinical trials.

The requirement to make trial protocol information available will be implemented via EudraCT Version 8. According to Dr Sayers, Version 8 is due to go live in July 2010. She warned, however, that this date may be pushed back, as previous launch dates have been missed.

The requirement to make trial results available to the public will be implemented via EudraCT Version 9, which, according to Dr Sayers, will be launched no earlier than the end of 2010.

For paediatric trials, results-related information will have to be submitted within six months of a trial's completion and made public immediately after submission, Dr Sayers said. Data entry is to be completed by the marketing authorisation holder, sponsor or paediatric investigation plan (PIP) addressee via the European Medicines Agency. For all other EudraCT database trials (except for Phase I trials), including trials of products without a marketing authorisation, results must be submitted within one year of the end of the trial, via the EMA. As with the paediatric trial results, the information will be made public after it is submitted.

Dr Sayers said that while the format for posting results had not yet been confirmed, it would probably be based on the International Conference on Harmonisation E3 guideline on structure and content of clinical study reports, a format with which industry is already familiar.

### Expanded results disclosure nears in the US

In the US, there is a provision in the Food and Drug Administration Amendments Act of 2007 to expand, by rulemaking, clinical trial results disclosure on the FDA's ClinicalTrials.gov database no later than 27 September 2010.

Currently, ClinicalTrials.gov requires the submission of results from trials of drugs, biological products and medical devices that have been approved by the FDA; unlike in the EU, results are made available in the US only after a product is approved. In general, results must be submitted not later than 12 months after the trial completion date, which is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. Protocols must be registered on ClinicalTrials.gov within 21 days of the first patient being enrolled. The US database requires tabulated data and does not accept ICH E3 format.

Dr Sayers noted that the US regulators have not yet confirmed what the expanded disclosures will involve. There might be requirements to post lay and technical summaries of results and full protocols if they are needed to interpret results. There might also be a requirement to post results from trials of unapproved drugs.

*The EudraCT Version 9 database that will make trial results available to the public is not expected to be launched before the end of 2010*

*US regulators have not yet confirmed what their expanded disclosures will involve*

Complicating clinical trials transparency requirements in the US, the state of Maine has adopted its own clinical trials transparency requirements and other states, such as Minnesota, New York and Pennsylvania, have legislation pending on the matter, Dr Sayers noted.

### Rest of the world

As for the rest of the world, Dr Sayers said that mandatory transparency requirements are in place – or soon will be – for the following countries: Argentina, Brazil, Croatia, the Czech Republic, France, India, Iran, Israel, Italy, Malaysia, the Netherlands, Norway, Peru, South Africa, Spain, Taiwan and Turkey. Most of these countries have – or will have – their own registry, Dr Sayers said. She added: “France is the only country on the list at the moment that requires mandatory posting of results [in French] but many of the others are likely to follow.”

Voluntary registration is in place or pending in Africa (Pan African Registry), Australia, Canada, Chile, China, Cuba, Germany, Hong Kong, Japan, Latin America, New Zealand, Sri Lanka and the UK. Registration may become compulsory in many of these countries, Dr Sayers predicted.

### Call for standardisation

The global clinical trial registry and results database arena is becoming increasingly complex. Standardisation “is desperately needed”, Dr Sayers said, adding that inconsistencies in clinical transparency requirements are likely to become worse as regulators shift their focus from registries to results databases. “With registries you’ve got basic information that needs to be posted so requirements are only slightly different,” Dr Sayers explained. “But different bodies are asking for different things with regards to the postings they want for results.”

### Global network for clinical research gains momentum

The development of a non-profit, independent, non-governmental organisation dedicated to creating a global network for clinical research that would allow industry to share trial data more effectively is gaining momentum.

The Alliance for Clinical Research Excellence & Safety (ACRES) aims to complete the documents necessary for its incorporation by the summer of 2010, delegates at the DIA EuroMeeting learnt. Its main focus is to create a network of professional, accredited clinical research sites around the world. It also plans to create a central warehouse of real-time trial data accessible to sponsors, regulators and investigators via the web.

ACRES plans to establish by the summer its organisational structure and its bylaws, terms of reference and fundamental operating policies and procedures, Greg Koski, the US physician who conceptualised the ACRES initiative, told *RAJ Pharma*. Dr Koski, associate professor of anesthesia at Harvard Medical School, Boston, Massachusetts, said that a small steering committee of around five members from industry and academia was, at present, working on these objectives and that ACRES’s strategic plan was also being developed.

Currently, companies are required to place their clinical trial information and data in multiple, disconnected national registries and databases. A central warehouse of real-time trial data that sponsors, regulators and investigators can access to conduct analyses in a secure manner would allow trial data to be shared more efficiently and effectively, said Dr Koski. ACRES’s approach would make it possible for companies to, among other things, reduce costs, shorten their product development cycle time, enhance patient enrolment and simplify their business processes, according to Dr Koski. “Proper mining of the warehouse would allow industry to not only look at health and safety issues but also at issues surrounding quality and performance and operational efficiencies that will benefit them enormously in trying to go forward.”

The ACRES system, said Dr Koski, would be designed to promote and facilitate policy and process harmonisation and standardisation; operational integration, innovation and efficiency and regulatory simplification “according to the highest standards of ethics, professional integrity, responsible conduct of clinical research and good business practices”. The organisation would promote the use of existing tools, policies and processes rather than re-invent them.

Dr Koski added that the ACRES initiative could facilitate regulatory oversight and review, support data monitoring committees and improve safety. In fact, he believes that a “properly constructed database together with all the required elements that would be developed in conjunction with regulatory agencies could become a tool that could make it unnecessary to maintain multiple national databases”. He pointed out that the model for ACRES is analogous to that for the International Air Transport Association. Founded in 1945, IATA has been the prime vehicle for inter-airline co-operation in promoting safe, reliable, secure and economical air services, for the benefit of the world’s consumers, he said.

*France is the only country on the list that requires mandatory posting of results*

### Research Network

*ACRES main focus is to create a network of professional, accredited clinical research sites around the world*

*A central warehouse of real-time trial data would allow data to be shared more efficiently and effectively*

*ACRES would be funded through an independent trust fund supported by grants, donations and user fees*

Dr Koski expects ACRES to be incorporated in an "international" venue such as Switzerland, Finland or Austria. It would be funded through an independent trust fund supported by grants, donations and user fees. According to Dr Koski, the ACRES global network could be created with a small capital investment by the principal stakeholders. He also believes that it could be implemented within 36 months and could be fully supported by user fees amounting to a fraction of current costs for conducting clinical trials.

"Once we have the basic organisational structure all together, we hope to work with key international parties to convene a stakeholders conference that would bring the major players from industry together along with regulators to flesh out the concepts more and see where the major challenges could be so we can work on those." Another principal person involved with developing ACRES is Beat Widler, global head of quality assurance for F Hoffmann-LaRoche.

### Co-operation

### US/EU alliance on paediatric drug development proves positive

Efforts by US and European Union regulators to collaborate in the area of paediatric product development in a way that will enhance the science and decrease risks to children are producing positive results.

Between August 2007 and January 2010, the FDA provided the European Medicines Agency with information on 635 EMA paediatric investigation plans for 573 products, Jean Temeck, international pediatric lead at the FDA's Office of Pediatric Therapeutics, told delegates at the DIA EuroMeeting. Of the 573 products, 188 underwent discussion. In addition, 104 of the 188 product discussions included participation by FDA review divisions. A total of 17 general topics were discussed that were not product specific.

Interchanges between the FDA and EMA on paediatric drug development are "very successful", Dr Temeck said, adding that the agencies "have developed a trust in each other... and have a very open and scientific exchange". The agencies had reached compatibility during many of their discussions, she said. "When compatibility is not reached, we understand the rationale for the difference. For example, differences may be due to standard of care and marketing status of products."

Dr Temeck pointed out that the communication did not mean that paediatric development programmes would have exactly the same paediatric protocols or ask the same questions or arrive at the same regulatory decisions.

Examples of diseases that have been subject to discussion by the agencies are paediatric Type 1 and Type 2 diabetes. Regarding Type 1 diabetes, specific insulin products discussed included short- and long-acting insulin analogues and combinations. General approaches to the study of insulin products were also considered. Examples of therapeutic drug classes for Type 2 diabetes are dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.

The discussions for both diabetes types resulted in compatibility between the agencies on many discussion points, although their approaches were not necessarily identical. "We shared the same safety concerns and recommended adequate clinical monitoring of these safety issues," said Dr Temeck. Both agencies recommended that studies in Type 2 diabetes begin in children aged ten years and older. They recommended that studies of both types of diabetes use HbA1c as the primary endpoint. They agreed that extrapolation from Type 1 diabetes to Type 2 diabetes was not appropriate because of the differences in pathophysiology of the disease.

As for an example where discussion resulted in a different approach, the FDA is recommending the study of patients with Type 1 diabetes for ages four years or older, while the EMA is recommending study of patients down to one year of age.

The FDA and the EMA hold monthly teleconferences to discuss product-specific paediatric development and general scientific, regulatory and safety issues related to product classes. Documents are exchanged through a secure link, Eudralink. Agency interaction on paediatric product development is based on the International Conference on Harmonisation E11 guideline<sup>1</sup>.

In addition to exchanging information on PIPs, which sets out a programme for the development of a medicine in the paediatric population, the agencies exchange information on summary reports by the EMA's Paediatric Committee (PDCO), which decides on the content of the PIP, and on written requests issued by the FDA to sponsors asking for paediatric studies to be conducted. They also communicate on requirements under the US Pediatric Research Equity Act, completed, ongoing and planned trials, safety concerns and approaches to study of therapeutic areas.

According to Dr Temeck, because of paediatric legislation in the US and Europe, products are continuing to be appropriately studied in paediatric patients and labelled for safe and effective use. "Paediatric legislation", she said, "is driving global paediatric product development."

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*Discussions for both diabetes types resulted in compatibility between the agencies on many discussion points, although their approaches were not necessarily identical*

Dr Temeck concluded that to achieve the goals of ICH E11, namely, that children receive therapeutics that have been evaluated in an appropriate and timely and ethical manner, the agencies must work together.

#### References

1. ICH E11, Clinical Investigation of Medicinal Products in the Pediatric Population, 20 July 2000, [www.ich.org/LOB/media/MEDIA487.pdf](http://www.ich.org/LOB/media/MEDIA487.pdf)

### EU pharmacovigilance project eyes code of conduct adoption

The steering group of European Medicines Agency-led pharmacoepidemiology and pharmacovigilance project, ENCePP, is expected to finalise and adopt a code of conduct in the second quarter of 2010.

A methodological research standards checklist that researchers will be able to use to help improve the quality of post-authorisation studies conducted under ENCePP is also expected to be finalised in the second quarter of the year and adopted by the steering group, said Henry Fitt, head of co-ordination & networking, pharmacovigilance and risk management at the EMA. In addition, a first version of ENCePP's electronic registry of post-authorisation studies is planned for release in June 2010.

ENCEPP – the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance – is part of the EMA's European Risk Management Strategy (ERMS), which is intended to ensure a more proactive approach is taken to monitoring the safety of drugs throughout their life-cycle. ENCePP was set up in 2006 to make the most of available expertise in the post-authorisation monitoring of medicines and to generate reliable data for proactive pharmacovigilance. When completed, it will comprise research and medical care centres, healthcare databases, electronic registries and existing networks on rare diseases and adverse events.

The code of conduct and methodological research standards checklist were released for public consultation in November 2009<sup>1</sup>.

The code elicited comment from a broad spectrum of stakeholders, Mr Fitt told DIA EuroMeeting delegates. It is designed to ensure transparency and promote scientific independence in the conduct of studies carried out under ENCePP. It is essentially a charter of rights and obligations covering protocol agreement, data ownership and publication of results. The key trial investigator will be required to sign a declaration and checklist to show compliance with the code.

The methodological research standards checklist, which is also to be signed by the lead investigator, is designed to stimulate researchers to consider important epidemiological principles when writing a study protocol and promote awareness and transparency regarding study methodologies and design. It comprises the following ten sections: research question; study population; study design; data sources; exposure measurement; endpoint definition and measurement; biases; analysis plan; quality assurance and feasibility; and ethical issues.

#### Electronic registry of ENCePP studies nears

The signed declaration and checklists and the study protocol are to be provided to the ENCePP Secretariat before the study commences. Before a study is commenced, it should be included in ENCePP's electronic registry of post-authorisation studies, which Mr Fitt said is still under development by the EMA. "We're hoping to release a first version [of the electronic registry] in June 2010."

ENCEPP's inventory of research resources is already available on ENCePP's website ([www.encepp.eu/](http://www.encepp.eu/)).

#### References

1. EMEA draws up code of conduct for post-authorisation studies, *RAJ Pharma* online, 18 November 2009

### New international standard on safety reporting edges closer

The final version of a major international standard for post-market drug safety reporting is expected to be published in 2011.

The new standard on individual case safety reports (ICSRs) of adverse events is expected to be issued in April next year and adopted by the International Conference on Harmonisation by the middle of 2011, said Andrew Marr, director, global e-regulatory development, at GlaxoSmithKline R&D, in the UK.

"Within the next two to three years your pharmacovigilance systems will need to change to a new reporting standard," Dr Marr told market application holders, vendors and suppliers of services attending the DIA EuroMeeting conference.

#### Safety

*A first version of ENCePP's electronic registry of post-authorisation studies is planned for release in June 2010*

*The methodological research standards checklist is designed to stimulate researchers to consider important epidemiological principles when writing a study protocol*

#### Safety Standard

*The new international standard on individual case safety reports of adverse events is expected to be issued in April next year*

*Stakeholders were urged to provide the ICH with feedback when the Step 3 consultation takes place*

A ballot on a draft version of the standard is planned to take place in May/June 2010; an initial ballot took place in April 2009, but it did not pass. In addition, an ICH implementation guide that will define how the standard should be used is also expected to undergo consultation by the three ICH regions (the US, the European Union and Japan) in late 2010. Dr Marr urged stakeholders to provide the ICH with feedback when the Step 3 consultation takes place.

The new standard relates to a revised ICH guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (E2B(R3))<sup>1</sup>, which was released for public consultation in May 2005. In 2006, the ICH decided that it would no longer develop its own technical specifications. Instead, technical specifications would be created in collaboration with standards development organisations to enable wider inter-operability across the regulatory and healthcare communities and avoid competing, incompatible standards. E2B(R3) was submitted for development as an international standard.

The International Organization for Standards (ISO), Health Level 7 (HL7) and the European Committee for Standardization (CEN) formed a joint initiative through which a single, common standard for the ICSR could be advanced. ICH representatives have been heavily involved in this initiative in addition to other experts from beyond the ICH community. The overall standard is based on the HL7 ICSR model, which is capable of supporting a wide range of product types such as human medicinal products, veterinary products and medical devices. The standard will be known as ISO 27953 parts 1 and 2. Its framework for adverse event reporting is described in the draft standard ISO/DIS 27953-1<sup>2</sup>. Details of the reporting requirements for human pharmaceuticals are defined in ISO/ DIS 27953-2<sup>3</sup>.

*The implementation guide will define the use of the data elements as outlined in E2B(R3)*

There are significant differences between the E2B(R2) and E2B(R3) models, noted Dr Marr. The ICH's implementation guide, when finalised, will define the use of the data elements as outlined in the E2B(R3) guideline. In addition, a harmonised approach to ensure backwards and forwards compatibility between the current ICH ICSR message specifications and the new standard – a major aspect during the transition phase until all stakeholders have upgraded their pharmacovigilance systems – will be addressed in the implementation guide.

Dr Marr reminded industry that there would be an opportunity to improve the implementation guide during Step 3 of the ICH's consultation.

*A standard for the identification of medicinal products is also under development*

### Identification of medicinal products standard on the horizon

Also under development, in parallel to the ICSR standard, is a standard for the identification of medicinal products (IDMP) that will allow unambiguous identification of products across regions to improve the robustness of pharmacovigilance. The development of the IDMP standard is one stage behind developments for the ICSR standard, according to Dr Marr. The target is to move to a draft international standard ballot in mid-2010. The ICSR standard can work without the IDMP standard, but it will be improved by its use, Dr Marr noted.

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