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# CIOMS and ICH Initiatives in Pharmacovigilance and Risk Management

## Overview and Implications

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## Abstract

In this article we review the current initiatives by the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonisation (ICH) on pharmacovigilance planning that are due for general release during 2004. These initiatives could form the basis for applying concepts of risk management to medicines throughout their life cycle, from preclinical and clinical development to marketed use.

The CIOMS VI Working Group (with 28 senior scientists worldwide from drug regulatory authorities and pharmaceutical companies) is currently developing scientific guidance that relates to clinical trials for medicines during development. It recommends a developmental pharmacovigilance concept – a 'living' concept that would start early in drug development supporting the science and ethics of research leading up to licensing (marketing authorisation) and continuing to post-authorisation (postmarketing) pharmacovigilance.

This approach is seen as complementary to current ICH initiatives called 'Pharmacovigilance Planning'. ICH will introduce two concepts in pharmacovigilance management of medicinal products: the 'Pharmacovigilance Specification' and the 'Pharmacovigilance Plan'. The 'Pharmacovigilance Specification' will summarise important knowns and unknowns about the medicine. It will include safety risks identified at the licensing stage, potential risks and any key missing information. These elements will be essential to the formulation of pharmacovigilance plans.

Dialogue and common understanding between regulators and the pharmaceutical industry will be a key factor for developing pharmacovigilance plans during the life cycle of medicines. Appropriate interaction with health professionals and patients should also be planned for the future as regulatory systems become more transparent.

Where no significant issues are apparent at the licensing (marketing authorisation) stage, routine pharmacovigilance practices will be followed during the marketing phase. Where issues do exist or the data are limited, further study, including epidemiological approaches can be planned. All types of medicines (new drugs, biological agents, orphan drugs) may be involved in these concepts, as would major extensions to existing medicines.

Currently ongoing CIOMS and ICH initiatives are in line with emerging risk-management strategies in the US, the European Union and Japan aimed at early and proactive pharmacovigilance.

Pharmacovigilance regulation started in the aftermath of the thalidomide tragedy in the 1960s[1] in parallel with the development of spontaneous reporting systems. Since that time much has been achieved in terms of identification of risks associated with medicines and also in the actions taken to minimise such risks. In fact, more than 130 pharmaceutical products have been withdrawn over the last 4 decades on a worldwide basis due to safety concerns.[2,3] One-third of such withdrawals occurred within 2 years and half within 5 years of marketing. Despite the establishment of pharmacovigilance systems on a global basis, adverse drug reactions still remain a major worldwide cause of morbidity and mortality.[4] In this context it was estimated in 1994 that such reactions accounted for more than 100 000 deaths, the fourth largest cause of deaths in the US.[4] The need, therefore, for robust pharmacovigilance processes on a global basis is as important now as it ever was before.

Pharmacovigilance has been defined as: "the process of evaluating and improving the safety of marketed medicines".[5] Inherent in such a definition is a philosophy of separating the life cycle of a medicine to a developmental premarketing phase and a postmarketing phase. More recently, the WHO has widened the definition of pharmacovigilance to: "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".[6]

Knowledge of the safety profile of a medicine is a continuously evolving process and new information on its safety mirrors this evolution. Thus, there is no clear reason why, historically, the pharmacovigilance process should have been set in motion only after the medicine reached the marketplace. After all, many elements that shape the safety profile already start to gather during development. These include data from preclinical animal testing and *in vitro*, pharmacology experiments and human clinical trials. No one will dispute the fact that clinical trials conducted in support of documentation for a marketing authorisation (licensing) of a medicine only provide a provisional view of safety at that point in time.

'Real life' use in larger 'unselected' populations can then reveal risks, some of which are serious.

In view of the above comments, classical definitions of pharmacovigilance could be broadened. For this article we use the following definition: "Pharmacovigilance is the process of monitoring, evaluating and improving the safety of medicines in use and the prevention of adverse drug reactions". In this context, use of medicines will include clinical trial subjects as well as patients within the population at large receiving healthcare. Even though the definition does not explicitly mention communication, this is included indirectly. For instance, risk communication as well as provision of product information to healthcare professionals and patients are tools commonly used to promote safe use of medicines and to prevent adverse drug reactions.

In recent times experts in the field have identified a pressing need to modernise pharmacovigilance by:

- starting the process earlier (before the license is granted)
- being proactive, and
- changing the philosophy, i.e. towards demonstrating safety as opposed to looking for harm.

In this context, a new conceptual model[7] has been developed, that calls for the pharmacovigilance processes to be involved earlier in the life cycle of a medicine. At the same time, regulatory agencies in the European Union (EU),[8] and the US[9] are concentrating their efforts in formulating 'risk management' strategies to be applied in the future to the management of medicines throughout their life cycles. The reader should note that currently there is no internationally agreed definition for the concept of risk management. In some respects this concept

**Table I.** Council for International Organizations of Medical Sciences (CIOMS)[10] initiatives in pharmacovigilance

| CIOMS working groups | Topic | Completion date |
|---|---|---|
| I | Reporting of adverse drug reactions[11] | 1990 |
| II | Periodic safety update report (PSUR)[12] | 1992 |
| III/V | Core clinical safety information (CCSI)[13] | 1995 |
| | Developmental core safety information (DCSI) | 1999 |
| IV | Benefit-risk balance[14] | 1998 |
| V | Current challenges in pharmacovigilance[15] | 2001 |

overlaps with the principles of pharmacovigilance covering both the collection and analysis of safety information. It additionally includes strategies aimed at reducing risk to patients. The US FDA draft concepts[9] in this area have already been put out for public and stakeholder consultation while EU agencies have communicated likewise.[8] These strategies are expected to have common themes including dialogue between stakeholders and the formulation of risk-management plans for specific medicines at the time of licensing (authorisation).

In parallel with these regulatory activities, international groups with a known track record in pharmacovigilance have taken up new initiatives to support risk-management concepts in the area of medicines before and after licensing and marketing. These groups include the Council for International Organizations of Medical Sciences (CIOMS)[10] and the International Conference on Harmonisation (ICH). These organisations have recently set up working groups in order to develop the relevant scientific principles and guidance. The overriding aim of such activities remains one of public health protection.

## 1. CIOMS Initiatives in Pharmacovigilance and Risk Management

CIOMS is a non-governmental, non-profit organisation established in 1949 by the WHO and UNESCO. For more than 15 years now CIOMS has provided a useful forum and mechanisms for regulators and the pharmaceutical industry to discuss key topics of mutual interest. Some of the key CIOMS outputs are listed in table I.

Participating senior scientists in CIOMS working groups are chosen on the basis of their areas of expertise. In line with the philosophy of CIOMS, such experts represent their own ideas and scientific thinking even though they do consult their professional networks and organisations. The working groups have an equal number of representatives from private and public sectors.

The CIOMS output thus far has been widely reported, published and used. More importantly it has been the springboard for international harmonisation of pharmacovigilance reporting at the level of ICH. In this way the methods developed for collecting and reporting adverse reaction data, are widely used by both regulators and industry.

## 2. CIOMS Working Group VI

Formed in 2001, this working group is comprised of 28 senior scientists worldwide from drug regulatory authorities and pharmaceutical companies. It has been convened in response to increased public and professional awareness over clinical trial safety and ethics. Such awareness is mirrored by regulatory concerns over inconsistent practices that call for new scientific guidance and a best practice approach. Underpinning this is the pursuit of enhanced safety and ethical rights of subjects and patients involved in clinical trials. In addition, such a best practice approach should be developed in line with risk-management strategies for medicines throughout their life cycle. The working group is still in progress and the views expressed below may still change before final release towards the end of 2004 or early 2005.

The scope of CIOMS VI includes medicines under study in all phases of prelicensing develop-

ment. Prescription as well as non-prescription medicines will be included as will vaccines, biotechnology products and diagnostic agents. The principles could also apply to development programmes for pharmacogenetics and gene therapy, which are currently being considered in a CIOMS Working Group on Pharmacogenetics. The aim would be to develop appropriate and useful guidance for companies, regulators and academic sponsors of clinical studies. Such guidance would support the public health objective of maximising benefits and minimising risks associated with medicines during their developmental phase. The concept would then form the basis for risk-management planning when a medicine becomes marketed.

As a basis for initial discussion, the working group reviewed existing guidelines, regulatory documents and directives in pharmacovigilance, conduct of clinical trials and risk management from the three ICH regions as well as ethical guidelines currently in operation.

The stakeholders were identified as patients, volunteer subjects, regulatory authorities, healthcare professionals, academia, ethics committees, data monitoring boards or committees and pharmaceutical companies or their agents (such as contract research organisations).

A survey was performed looking at current practices of pharmaceutical companies in relation to clinical safety and pharmacovigilance processes during drug development. It confirmed the need for improvement and for a consistent harmonised approach.

Current terminologies and definitions used for safety assessment in clinical studies could differ from those used in postmarketing pharmacovigilance activities. CIOMS VI, therefore, sees the need to better define such terminologies. Within the area of coding standards for adverse drug reactions a separate working group of CIOMS[10] is dedicated to the development of standardised Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) that would be applied to safety datasets of spontaneous adverse drug reactions. This is in order to facilitate retrieval of cases and signal detection within the hierarchical, multiaxial architecture of MedDRA.[16] The same concept of analysis could be considered also for clinical trial safety data.

Current methodologies and statistical methods used to analyse clinical safety datasets have been reviewed by the CIOMS VI working group. One of the key outputs will be detailed proposals regarding the collection, reporting, analysis and evaluation of clinical trial safety information. In this respect the possible role of data monitoring boards will be reviewed. In support of general risk-management concepts, the CIOMS VI working group proposes the concept of a pharmacovigilance planning process starting early in development.

### 2.1 Developmental Pharmacovigilance Process

The developmental pharmacovigilance process could result in a list of 'points to consider' before starting the development of a medicine in humans based on pharmacology, toxicology and other preclinical testing of new pharmaceutical substances. Such a concept would support a systematic approach to identify, evaluate and minimise risk to subjects and patients during clinical trials. Any safety knowledge gained through the different developmental phases should result in timely amendments to the initial plan for the product. This would allow one to gain the best possible knowledge necessary to protect the patients involved in clinical trials and to prepare a comprehensive pharmacovigilance plan to be applied once the medicine is authorised and marketed. Practically, the CIOMS VI concept will recommend the systematic review of:

- background information
- risk criteria, and
- points to consider on risk evaluation and management.

Within the developmental pharmacovigilance process detailed knowledge should be obtained of background information on the particular medicine and the disease to be treated. The compound's chemical structure and mechanism of action will be reviewed and reference made to preliminary data on

preclinical and clinical aspects in order to identify potential risks.

As regards the specific profile of the patient population, this will be assessed according to the natural history of the disease, current therapeutic standards, likely concomitant diseases and concomitant medication. This would necessitate the collection of all epidemiological data available and sometimes the support of new studies.

Consideration will also be given as regards use in special populations such as children, the elderly and those with organ dysfunction (hepatic, renal) or genetic predisposition.

Based on the background information the developmental pharmacovigilance process will identify potential risks and include evaluation of risk criteria. These will be categorised as to whether they are acceptable, justifiable or unacceptable.

Early identification of possible risks will enhance the collection, coding and analysis of safety data and the evaluation of the consequences of the safety knowledge progressively gained through the development of the medicine.

CIOMS VI concepts as described above should facilitate risk assessment and pharmacovigilance planning. Such planning should include an overview of general safety measures in place for routine surveillance and signal detection. Where actual or potential safety issues are identified, specific plans should be considered giving a clear description of the particular issue as well as action plans for further evaluation, outcome measurements and accountabilities for follow-up. If a risk is confirmed, risk management activities are envisaged.

## 3. ICH Topic E2E, Pharmacovigilance Planning

ICH[17] brings regulators, industry and other experts together to harmonise technical requirements for the registration of medicines in the US, EU and Japan. It also aims to contribute to public health from an international perspective and to optimise the resources, or at least to prevent duplication of effort.

Topic E2E[1] has been initiated in response to requests from the three ICH regions to support similar risk-management strategies relating to the licensing (authorisation) and use of medicines. The output will be a guideline that will be released towards the end of 2004 or early in 2005. This guideline is intended to aid industry and regulators in planning pharmacovigilance activities, particularly in the early postmarketing phase.

Pharmacovigilance planning was initially proposed by Waller and Evans[7] based on a new model of 'Excellence in Pharmacovigilance' developed by the UK regulatory agency, the Medicines and Healthcare products Regulatory Agency (MHRA). Based on this new thinking in pharmacovigilance, ICH topic E2E proposes the concepts of a pharmacovigilance specification, and pharmacovigilance plan. The scope of the guideline will apply to new medicines coming up for licensing and marketing, biotechnology derived products and significant modifications to existing medicines (e.g. new indications/populations) In addition to the specification and plan, the guideline from ICH will give high level guidance on good practice in the design and conduct of post-authorisation safety studies. An annex to the E2E guidance will contain practical explanations on tools currently available to support good pharmacovigilance practices.

### 3.1 Pharmacovigilance Specification

This is a summary of the identified risks, the potential risks and any important missing information. In developing the specification all relevant data would be evaluated, including preclinical (non-clinical) toxicology, pharmacology, target organ findings and potential for interactions.

Clinical data include all phases of drug development and the overall safety database. The limitations of such databases are well recognised particularly the limited duration of exposure, highly selected patient population and limited sample size.

In determining specifications, the patient population to be exposed to the new medicine should be

1 ICH topic E2E is currently in development at Step 2 of the ICH process.

identified and comparisons made with the clinical trial population. In addition, populations not studied (e.g. children, elderly, pregnant women and patients with hepatic or renal disease) should be specified and the potential effects of genetic polymorphism mentioned. Where the medicine had already been marketed in a particular region, the postmarketing safety data already gathered should be summarised in terms of safety signals and regulatory actions undertaken for safety reasons.

The pharmacovigilance specification should summarise the safety profile of the medicine based on known adverse reactions and their potential impact on the benefit-risk balance. It should also include potential risks where signals are not yet confirmed but cannot yet be excluded.

Particular attention should be paid to known or potential interactions particularly if the resulting adverse reactions could impact on the balance of benefits and risks. The epidemiology of the disease under treatment and that of any adverse reactions occurring with the medicine should also be taken into account when drawing up the pharmacovigilance specification. Finally, class effects for the medicine in question should be considered. The concluding part of the specification should clearly point out:

- important identified risks
- important potential risks, and
- important missing information.

### 3.2 Pharmacovigilance Plan

It is recommended that this plan is based on the pharmacovigilance specification, addressing the risks involved or the lack of information in particular areas. For medicines where there are no significant identified or potential risks and no gaps in the knowledge, then routine pharmacovigilance processes can be put in place. These include passive surveillance with spontaneous reporting and periodic safety update report (PSUR) data on safety and postmarketing exposure. Coupled with such activities, are routine signal detection and updating of product information for prescribers and patients.

However, in situations where the specification identifies key issues to be addressed the plan will include appropriate proposals. These could take the form of safety (including epidemiological) studies. For each issue where an action is proposed the plan will include the rationale for such action, the objectives to be achieved and milestones for evaluation and reporting.

It is recognised that the possible impact on the benefit-risk balance may differ between the various safety issues to be addressed in the plan. For this reason ICH will recommend that the pharmacovigilance plan should also include a summary section that gives an overview of all actions to be taken forward in addition to individual sections covering each specific safety issue.

This overview will aid in general project planning of the various pharmacovigilance activities. The concept of milestones to be introduced by ICH is an interesting one. Current experience with the PSUR concept involves a ‘one size fits all’ approach to all medicines irrespective of the level and speed of market exposure. The ICH working group suggests that the milestones should be set based on the level of patient exposure to the medicine and taking into account the feasibility of conducting safety or epidemiological studies of sufficient sample size. It will be challenging to accommodate this. Some degree of flexibility or creativity will be needed in trying to align the new concepts with the existing regulatory milestones such as the PSUR reporting cycles.

In the Annex of E2E, the ICH working group summarises the methodologies available to industry and regulators in conducting good pharmacovigilance; a ‘toolbox’ for the stakeholders, particularly in the area of safety data collection. It also includes a high level section on good epidemiological study practices, which will be directly relevant when observational studies are part of a pharmacovigilance plan.

## 4. Risk-Management Strategies in Pharmacovigilance

Within the ICH regions there are discussions currently ongoing to take forward some general concepts of risk management. Such concepts have already been published by both EU and US regulatory agencies.[8,9] The FDA's draft definition of risk management: "the overall and continuing process of minimising risks throughout a product's life cycle to optimise its benefit/risk balance", concentrates on minimising risk. In addition, the FDA concept papers stress that risk information emerges continuously during the product life cycle during marketed use 'on-' and 'off-label'. Risk management itself is considered to be a continuous process of:

- evaluating benefits and risks
- minimising risks through appropriate interventions
- evaluating such interventions as new knowledge is gathered, and
- revising such interventions accordingly.

Risk-management concepts at the EU level are also under development as a joint exercise of the European Agency for the Evaluation of Medicinal Products (EMEA) and the national regulatory agencies of the member states.[8]

The aim of these strategies is to maximise the benefits and minimise risks associated with the use of medicines, thereby better protecting the public health of EU citizens. The EMEA approach is to target four areas to be addressed as follows:

- risk detection
- risk assessment
- risk minimisation, and
- risk communication.

In the area of risk detection, the EMEA will utilise data reported electronically into its central EudraVigilance database.[18] In the near future this system will also collect suspected, unexpected serious adverse reactions arising from clinical trials. This presents a unique opportunity to support the handling of adverse reactions throughout the product life cycle on an EU-wide basis. The methodologies for analysis of clinical trial safety data alongside spontaneous reports are not currently available at an EU level and need to be developed.

The EU risk-management strategy will also involve the identification of specialised expertise to advise on life cycle management of medicines. Such areas of expertise will include, among others, specialists in pharmacovigilance, clinical safety, epidemiology, biostatistics as well as emerging therapies such as cellular, tissue and pharmacogenetic products. In addition to the expert network, the EU will be looking towards the new pharmaceutical legislation that introduces the concept of risk management plans to licensing of medicines. The scope of such plans could cover new medicines including biologics and orphan drugs. In the future this concept may also involve major extensions to existing medicines.

## 5. Discussion

Pharmacovigilance processes have become well established over several decades. Their approach, however, is often reactive and concentrates primarily on detecting harm as opposed to demonstrating safety.[7]

Against this background, new models in pharmacovigilance have been put forward proposing an evidence-based approach in order to conduct pharmacovigilance more objectively. The aim is to promote safer use of medicines for the public.

In response, many authorities in the field of pharmacovigilance now call for a change of philosophy from reactive to an earlier more proactive approach, starting before a medicine reaches the market.

In this environment, international 'think tank' groups from CIOMS and ICH are currently developing guidelines to support life cycle management of medicines. The output from these groups is likely to lead to pharmacovigilance planning both pre- and post-authorisation and marketing. The main emphasis of both concepts is to continuously study the benefit-risk profile of a medicine as it goes through its life cycle and to do this in an informed well-planned way. This means a broader definition of

pharmacovigilance towards risk management of medicines.

The next step in this evaluation could well be to extend risk-management concepts to other key stakeholders, the healthcare professionals and patients. In this context, appropriate education and communication initiatives involving such stakeholders should be planned in future.

Apart from the above initiatives, there will be other areas that could be developed in the future. For instance, there are interventions in pharmacovigilance that should be assessed for actual impact on public health. Such interventions include regulatory measures such as changes to marketing authorisations introducing safety recommendations. Recent publications[19,20] indicate that such interventions may not be sufficient in effecting safer use of medicines.

## 6. Conclusion

This is a review of two major initiatives in pharmacovigilance planning. Scientific guidance from CIOMS and ICH due later this year, or early in 2005, will cover medicines during development, at the authorisation (licensing) stage and subsequently while on the market.

They will recommend the formulation of a developmental pharmacovigilance process followed by a pharmacovigilance specification and plan to coincide with approval of a medicine for marketing. These are all to be 'living' concepts that evolve alongside the scientific evidence being generated on each medicine. Dialogue and common understanding between regulators and the pharmaceutical industry, will be a key factor for developing pharmacovigilance plans during the life cycle of medicines.

Other stakeholders such as healthcare professionals, academic researchers and patients should also be taken into account in the future when risk-management strategies for medicines are further developed. To this end it will be essential to develop and implement appropriate education and transparency initiatives.

At the level of the EU, safety data from clinical trials and postmarketing sources will already be linked from mid-2004 within the EudraVigilance database. This could allow the further evaluation of how to integrate such data and to further investigate their value in pharmacovigilance.

Pharmacovigilance should be done early and proactively to support life cycle risk management of medicines. In this respect, the pharmacovigilance planning concepts proposed by CIOMS and ICH are to be welcomed.

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