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Pharmacovigilance during the Pre-Approval Phases

An Evolving Pharmaceutical Industry Model In Response To ICH E2E, CIOMS VI, FDA and EMEA/CHMP Risk-Management Guidelines

Craig G. Hartford,[1] *Kasia S. Petchel*,[2] *Hani Mickail*,[3] *Susana Perez-Gutthann*,[4] *Mary McHale*,[1] *John M. Grana*[2] and *Paula Marquez*[5]

1 Pfizer Worldwide Development Safety and Risk Management, Sandwich, UK
2 Pfizer Inc., New York, New York, USA
3 Clinical Safety and Epidemiology, Novartis Pharma, AG, Basel, Switzerland
4 Pfizer Worldwide Development Safety and Risk Management, Barcelona, Spain
5 Spanish Drug Agency, Madrid, Spain

Abstract

Pharmacovigilance science has traditionally been a discipline focussed on the postmarketing or post-authorisation period, with due attention directed towards pre-clinical safety data, clinical trials and adverse events. As the biological sciences have evolved, pharmacovigilance has slowly shifted toward earlier, proactive consideration of risks and potential benefits of drugs in the pre- and peri-approval stages of drug development, leading to a maturing of drug safety risk management. Further advances in biology, pharmacology and improvements in computational applications to medicine have led to the development of more complex medicines previously unobtainable and have also permitted a more thorough assessment of risks and potential benefits even earlier in the development process. Elevated public concern with the safety of more sophisticated medicines, combined with new science, have led pharmaceutical innovators, regulators and healthcare professionals to collaborate to develop guidelines, which drive enhanced pharmacovigilance and safety risk management earlier in drug development.

In this paper, we review international guidelines on pharmacovigilance planning applicable to the pre-approval phases of medicines development and provide author opinion on these guidelines' potential drug safety implications. We discuss the possible evolution of a pharmaceutical industry model to respond to these guidelines; a view on multidisciplinary safety management teams is provided to encourage refinement of safety-signal identification and risk assessment early in drug development and to communicate important safety concerns to internal research efforts, patients, investigators and regulators. We further describe these functions in the context of the complexities of vulnerable populations, including the example of medicines research for paediatric populations. We also discuss the

special role of epidemiology in pre-approval drug development and the impact on epidemiological science of changes to the pharmacovigilance paradigm.

1. Recent Events Influencing Assessment of the Benefits and Risks of Drugs

As for all human activities, taking medicine entails a certain amount of risk. No drugs are risk free and all drugs have potential safety concerns. There simply is no such thing as 'zero risk'.[1] When we decide whether or not to undertake an activity, we weigh the benefits of that activity against its risks. Similarly, with the licensing of medicinal products for marketing, regulatory authorities assess drugs on the basis of the balance of their benefits and risks. Demonstrated benefits must outweigh known risks.[2-4] Knowledge about medicines accumulates over time and this balance is not 'static'; therefore, licensing status may also change after initial approval.

Innovators of human pharmaceuticals have always been vigilant in looking for new risks and benefits of their products, but that activity has intensified recently as the biological sciences in medicine have blossomed. An increase in available safety data and data accessibility[5-7] and the imperative of patient safety,[8] has forged more extensive collaboration among pharmaceutical manufacturers, regulators and the health professional community aimed at ensuring the benefit-risk balance for medicines is favourable. This has meant a ramping up of resources[9] dedicated to safety, with scientific and clinical experts being joined by experts in technology, electronic support and communication to translate even more complex benefit-risk assessments into a language understood by patients.

The authors consider that collaboration among industry, regulators and health professionals encourages a more proactive approach to early recognition of potential safety issues.[10] Collaboration facilitates more frequent and open discussions on safety and risk-management strategies between safety stakeholders, and directs attention to safety risk management earlier in drug development. One goal of early recognition of potential safety issues and the development of an early risk-management strategy, is to improve patient safety while allowing continued safe development of needed new medicines.[11,12] Enhanced risk identification and assessment may identify therapies lacking a positive benefit-risk profile early on, thereby reducing unnecessary exposure and costs. Collaboration facilitates the implementation of important new regulatory requirements that are consistent with technical and scientific reality, avoiding the potential for unnecessary delays in patient access to new drugs.[13]

2. Incremental Focus on Drug Safety Risk Management in Pre-Approval Development

The new framework encouraging earlier safety risk management was developed in part by stakeholder collaboration through the International Conference on Harmonisation (ICH) and the Council for International Organizations of Medical Sciences (CIOMS),[14] and by formal regulatory guidelines from the Committee for Medicinal Products for Human Use of the European Medicines Agency (CHMP/EMEA)[15] and the US FDA.[16-18] The efforts often appeared to overlap during a flurry of activity that took place primarily in recent years, in particular the 2004–5 period.

Key driver documents from these initiatives are listed in table I. The documents describe methods and provide clarification and harmonisation of practices for overall safety surveillance, early risk detection and risk-management processes, including those for pre-authorisation drug development.

The ICH E2E,[19] CIOMS VI,[20] US FDA and EMEA guidelines on safety risk management are all clearly similar in their intent and indeed complementary; thus, in this review, we focus comment on the more globally applicable ICH E2E and CIOMS VI guidelines, which embrace the principles of sound pre-approval safety risk management also

Table I. List of applicable regulatory and other guidelines

Title	Web address[a]	Publication date
EU phamacovigilance working group guidelines		
EMEA/CHMP Working Group with Patients Organisations, Outcome of Discussions: Recommendations and Proposals for Action	http://www.emea.eu.int/pdfs/human/patientgroup/14947904en.pdf	17 March 2005
EU safety		
EMEA/CHMP/96268/2005 Guideline on Risk Management Systems for Medicinal Products for Human Use	http://www.emea.eu.int/pdfs/human/euleg/9626805en.pdf	14 November 2005
EMEA Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data	http://www.emea.eu.int/pdfs/human/phvwp/31366605en.pdf	14 November 2005
European Risk Management Strategy: Progress to date and next steps. EU Heads of Medicines Agencies	http://www.emea.eu.int/pdfs/human/phv/13625305en.pdf	11 May 2005
Action Plan to Further Progress the European Risk Management Strategy. EU Heads of Medicines Agencies	http://www.emea.eu.int/pdfs/human/phv/11590605en.pdf	4 May 2005
US risk-management guidelines		
US FDA Guidance for Industry: Pre-marketing Risk Assessment	http://www.fda.gov/cder/guidance/6357fnl.htm	March 2005
FDA Guidance for Industry: Development and Use of Risk Minimisation Action Plans	http://www.fda.gov/cder/guidance/6358fnl.htm	March 2005
FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment	http://www.fda.gov/cder/guidance/6359OCC.htm	March 2005
FDA Reviewer Guidance: Conducting a Clinical Safety Review on a New Product Application and Preparing a Report on the Review	http://www.fda.gov/cder/guidance/3580fnl.pdf	February 2005
FDA Guidance for Industry: Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling	http://www.fda.gov/cder/guidance/5917dft.pdf	October 2004
FDA Guidance for Industry: Establishing Pregnancy Exposure Registries	http://www.fda.gov/CbER/gdlns/pregexp.htm	August 2002
International – pharmacoepidemiology		
Guidelines for Good Pharmacoepidemiology Practices (GPP). International Society for Pharmacoepidemiology	http://www.pharmacoepi.org/resources/guidelines_08027.cfm	Revised, August 2004
ICH		
ICH E2E: Pharmacovigilance Planning	http://www.ich.org/LOB/media/MEDIA1195.pdf	18 November 2004
ICH E1A: The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions	http://www.ich.org/cache/compo/475-272-1.html#E1	27 October 1994
CIOMS		
Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI	http://www.cioms.ch/frame_management_of_safety_information.htm	April 2005

a Accessed 3 May 2006.

CHMP = Committee for Medicinal Products for Human Use; **EMEA** = European Medicines Agency.

contained in the FDA and EMEA guidelines on risk management (table I).

2.1 ICH E2E (Pharmacovigilance Planning) Guideline and Pre-Approval Drug Development

The Japanese Ministry of Health and Welfare (MHLW) was instrumental in conceptualisation of the early E2E work. Members of MHLW, later also to become ICH E2E topic rapporteurs, proposed a brainstorming of post-authorisation topics for the ICH meeting in Tokyo in 2001, towards further development of postmarketing guidelines that promote and secure safety of new drugs. Here the MHLW provided the concept of 'early-phase post marketing vigilance' (EPPV), introduced in Japanese regulation, as an example of an early postmarketing risk-management plan. This topic was debated and went through considerable evolution at the Tokyo meeting and subsequently at the Brussels meeting in February 2002. In June 2002, in London the concept was finalised in preparation for consideration by the ICH Steering Committee as a formal working group. The early concept paper laid the foundation for ICH work that 3 years later in November 2004 culminated in the finalised ICH E2E guideline, reviewed below.

The ICH E2E guideline instructs how to further characterise important identified risks of a drug, important potential risks, and important missing information, and suggests how a safety specification and a pharmacovigilance plan should be developed, with special focus on the early post-authorisation period, whilst also emphasising the need for better and earlier planning of pharmacovigilance activities before a product is approved or a license is granted. ICH E2E introduces the concepts that the planning of pharmacovigilance activities should occur throughout the product lifecycle and be based on scientific evidence of risk with documentation thereof.

ICH recommends that company pharmacovigilance experts get involved early in product development; planning and dialogue with regulators should also start long before license application. ICH E2E pharmacovigilance planning consists of:

- The 'safety specification', which can be built initially during the pre-marketing phase and presented when approval is sought. It should reflect the status of issues that were being followed during development and include review of non-clinical as well as clinical data.
- The 'pharmacovigilance plan', which is based on the safety specification and describes actions for safety concerns identified. The plan would normally be developed by the sponsor and can be discussed with regulators during drug development prior to approval. Regulators consider the plan when assessing the licensing application. It is important to note that while, going forward, all new drugs will be required to have pharmacovigilance plans, routine pharmacovigilance may be sufficient to satisfy safety needs, especially in those instances where safety risks have been well characterised and no major risks are expected.

In Japan, every drug to be marketed should undergo early phase marketing vigilance for 6 months following drug launch, which consists of active solicitation, such as visits to prescribers, of any experience associated with early drug use. Particular attention is paid towards collecting and documenting serious adverse events (SAEs), and sponsors are required to submit the EPPV plan, and a report following 6 months experience.[21-23] The safety specification and the pharmacovigilance plan, in some instances, may require post-approval safety studies for products with risks or concerns, for example for at-risk groups that have not been studied during the development phases. These studies will typically also rely on the tools of epidemiology (more on this in section 5).

As per CIOMS VI, discussed in the following section, the basis for the pharmacovigilance plan should be prepared during the product development phase and amended as more becomes known about the drug's risks and benefits. CIOMS VI further recommends that findings of the early plan lead to a description of any required changes to the clinical

development plan, investigators' brochures, development core safety information and informed consent as well as regulatory and legal implications.

2.2 CIOMS VI (Management of Safety Information from Clinical Trials) Guidance on Early Development Pharmacovigilance/ Risk-Management Plan and Alignment with ICH E2E

CIOMS VI aims to enhance awareness of the ethical and technical issues associated with safety in clinical trials and to point out the need for increased care and scrutiny in the conduct of research. The report recommends preparation of a formal development pharmacovigilance/risk management plan, discussed later that forms the basis for the (ICH) pharmacovigilance plan chapters 3 and 5 and are of particular relevance to pre-approval drug development.

When planning the development of most new medicines, there are certain drug toxicities that should always be explicitly considered. CIOMS VI recommends these include altered cardiac electrophysiology, hepatotoxicity, drug-drug and food-drug interactions, immunogenicity, bone marrow toxicity, potential for reactive metabolic formation and hypersensitivity reactions. These are common reasons for drug SAEs.

In addition, CIOMS VI speaks to adverse events of special interest that, although not always 'serious', could require careful data capture and review. These include precursor symptoms or signs of a more serious condition or potential toxicities identified in preclinical studies or with similar compounds (for example, specific ECG changes such as corrected QT interval prolongation; increases in laboratory values above a predefined limit; muscle pain and elevated creatine phosphokinase, which together are indicative of potential rhabdomyolysis). The guideline suggests that it is advantageous to predefine these in clinical study protocols to allow prompt collection of the data along with all SAEs, processing in the safety database and monitoring on an ongoing basis. Careful attention is also encouraged for those special cases where deviations from protocol-specified dosing occurred. This would include overdosing and medication errors, including inappropriate route of administration and unexpected exposure during pregnancy.

CIOMS VI advocates that appropriate management of individual case safety reports from studies should be fully documented with diligent follow-up of each case, as needed, the reporter's verbatim adverse event (AE) terms should be retained within all relevant databases and the coding of these terms should be carried out using an accepted dictionary (e.g. the Medical Dictionary for Regulatory Activities [MedDRA]). The primary analyses of AE data should be based on the investigator's assigned terms or diagnoses; additional analyses using the sponsor's assignments can be conducted, but explanations for any differences between the two analyses should be given. Where the SAE data are collected in a separate database, the sponsor should have a procedure to ensure that both safety and clinical trial databases are reconciled regarding SAE data.

2.3 Implications of the ICH and CIOMS Guidelines

Both guidelines are likely to initiate modifications to the internal safety structure and intensify safety risk-management procedures in pharmaceutical companies (see the framework model in this paper; section 3). Traditionally, efficacy has been a major focus of drug development: the mandatory evaluation of safety was compliant with the then current standards. The focus of attention on safety will now evolve in response to the newer guidelines. For example, any potential doubt about the extent of diligence that companies must demonstrate in studying and preparing the safety of new candidates will be minimised. Drug development project teams will increasingly ensure that safety assessment is offered priority (in the unlikely event that this is not already the case) and stakeholders will need to be confident that safety issues are given a prime position in global drug-development strategies. The new framework attempts to promote transparency, ensure that all stakeholders address safety ethical issues and make safety risk management more continuous through-

out the life cycle of the product by initiating safety evaluation in the early development phase.[24-26]

Although the term 'pharmacovigilance' has traditionally been associated more with post-authorisation activities largely because of ICH and CIOMS initiatives, it is now being increasingly applied throughout the lifecycle of the drug, encompassing the pre-marketing process for collecting, managing and assessing safety information during pre-clinical and clinical development of drug candidates. Likewise, the concepts of risk assessment and risk minimisation, together contributing to risk management, are terms that are as applicable to the pre- as the post-authorisation phases, where drug safety risk management is defined as the provision of comprehensive and proactive scientifically based methodologies to identify, assess, communicate and minimise risk throughout a drug's life cycle so as to establish and maintain a favourable benefit-risk profile in patients.[27]

It is important to note that safety risks can be both real and hypothetical, and provision for describing important theoretical risks as contraindications in drug license labelling is necessary in some circumstances.

In a sense, ICH E2E, CIOMS VI, and the new EMEA and US FDA guidelines orientated around them, provide the framework to perform 'pre-approval planning of postmarketing pharmacovigilance': a prospective planning of pharmacovigilance and risk-management activities. The major focus is the creation of a document to be discussed with regulators prior to the approval that describes both the company's plan for gathering additional information to fill remaining gaps in safety knowledge and interventions to minimise the known risks.

3. A Proposed Framework for Effective Risk Management in the Pre-Approval Period

The pharmaceutical industry has collaborated with regulators and other experts to clarify and formalise risk-management guidelines, the implementation of which takes many forms in companies of differing sizes, depending on available expertise and resources. In this section, we discuss evolution of a pharmaceutical industry model to respond to such guidelines: the authors view on the use of multidisciplinary safety management teams (SMTs) is provided, in part based on CIOMS VI and in part personal experience, to encourage refinement of safety signal identification[28] and risk assessment at early stages,[29] and to communicate important safety issues to internal research efforts, clinical study subjects, external investigators and regulators.

3.1 Multidisciplinary Safety Management Teams (SMT)

The new lifecycle risk-management paradigm encourages drug developers to establish multidisciplinary SMT, or effect equivalent function(s), during drug development. SMTs are responsible for timely review, evaluation and communication of safety data.[30] The SMT, or equivalent function(s), is typically chaired by a person skilled in safety and risk management, and comprises safety stakeholder representatives from any of the research, development or commercial project teams, plus other subject matter experts, according to the technical knowledge needs at each stage of the compound's life cycle.

We recommend that SMTs operate according to a formal charter, such as a standard operating procedure or good-practice guideline that describes the regular review of safety data and the management of risks as they arise during development.

It is important to note that establishing an 'advanced safety culture' within companies is advantageous, such that regulatory compliance arises there from rather than in response to internal procedures or external enforcement alone. The SMT (or similar structures/equivalent function[s]) would:

- Facilitate the accession and use of data from clinical and safety databases as well as preclinical, toxicology[31] and other safety sources (internal and external);
- Anticipate, detect, analyse and respond to safety signals or safety issues;

- Develop risk-management strategies to deal with safety issues in both pre-approval and post-approval environments;
- Communicate safety concerns to drug development teams, investigators, regulators and the public;
- Assure documentation and formal sharing of findings.

3.2 SMT Role in Individual, Cumulative and Aggregate Safety Review; Safety Signal Identification and Risk Assessment

The decision to develop and approve a drug is based on it having a satisfactory balance of benefits and risks within the conditions specified in the development plan and target product labelling[19,32,33] determined from information available at the time. Knowledge related to the safety profile of the product changes with time, for example through increasing drug exposure, including new populations. SMT evaluation of new information should be an ongoing process.[34-37]

Challenges to SMTs safety-signal identification during pre-approval drug development include: small sample sizes; short duration of exposure; restricted populations; limited detection power for weak safety signals; few specific safety hypothesis-testing studies. Pre-approval studies cannot usually be statistically powered to readily identify low-frequency safety events of concern.[38-40] It is commonly agreed that, to be 80% powered to identify risks occurring at 1 : 1000 patients, a minimum of 300–600 patients are treated for 6 months at dosage levels intended for clinical use; 100 patients exposed for a minimum of 1 year is also advised.[41] Most drug-development programmes will exceed this, but these are the commonly accepted basic requirements for all types of drugs, including those intended for long-term treatment of non-life-threatening conditions. For orphan drugs and those fulfilling the requirements for accelerated approval, the database may be smaller.

A key role of the SMT is identification of safety signals[42] and evaluation of their importance. All appropriate sources of data should be used to identify and evaluate risks, including early information from class-labels, literature reports and pre-clinical experience (toxicology, safety pharmacology), and subsequently clinical, epidemiology and spontaneously reported safety data.

Vigilant collection of information on adverse events during clinical trials provides the main source of information for ongoing monitoring and evaluation of the clinical safety of new compounds in the pre-authorisation stage. Real-time single case medical review and assessment should be performed in parallel with analysis of cumulative (intra-individual clinical studies) or aggregate (across-studies) data sets. A standard event-specific AE or SAE follow-up questionnaire is helpful to optimise the completeness and accuracy of collected data. It is also vital to place this assessment into context with information on population background rates and population based estimates of risks (epidemiology data).

SMTs should identify key safety milestones and plan to proactively review aggregate safety data generated at those points. To allow effective safety-signal detection through cumulative safety review, SMTs should proactively document with project teams what safety-data reviews will be performed in addition to annual reviews such as investigator brochures. The SMT may request the generation of listings, special case series and other safety data analyses as appropriate, and develop positions on the management of safety risks. Importantly, resources for generation of cumulative safety tables (blinded) for review during clinical studies should be identified in advance; measures and thresholds are best specified in advance to minimise possible bias. A comprehensive cumulative safety review (unblinded) for an individual clinical study also should take place during preparation of clinical study reports.

SMTs should also facilitate the work of independent persons or groups – for example, scientific advisory boards (regular), scientific/medical expert panels (*ad hoc*), internal and external data monitoring committees and external data safety monitoring boards (DSMBs)[43] – to perform safety reviews (as stipulated in EU Directive 2001/20/EC),[44] blinded

to potentially differing but appropriate degrees. Cumulative safety reviews of potentially non-blinded data (for example, safety data from some oncology studies[45]) should be performed in a manner that ensures the study protocol is not compromised. Data-monitoring committees and DSMB should propose changes to protocol design where appropriate, including (alteration of inclusion/exclusion) and stopping rules criteria for the study they are overseeing.

Following identification of a safety risk, the SMT may propose appropriate enhanced pharmacovigilance activities. To better understand and characterise risks, the SMT may recommend new clinical or epidemiology studies, development of pre-approval data capture aids or convening of appropriate scientific safety expert panels. Certain risks may require implementation of intra-development risk minimisation actions, such as changes to the protocol or development programme, informed consent and investigator brochure updates and other investigator and patient education.

3.3 Safety Communication Pre-Approval

After identifying potential and real safety signals and assessing their risks, SMTs should communicate all safety concerns or changes in the benefit-risk profile to key parties.[46]

3.3.1 Early Communication with the Research and Development Team

For the research and development teams, formal SMT minutes, including findings from regular safety reviews and a log of actions and follow-ups arising can be useful for dissemination of safety issues. The SMT may bundle these and other risk assessments into safety position papers for presentations to project and product teams, suggested changes to protocols, and recommendations on development plans to internal governance bodies. Advice to investigators on safety risks should be included in investigator brochures and amendments to informed consent documents, where appropriate, as soon as possible.

3.3.2 Early Risk-Management Plans

A CIOMS VI-recommended development risk management plan would describe the anticipated product profile and an overview of the target disease and its treatment, including background information on the treated population, expected morbidity and mortality rates, and the known safety profile of the candidate compound and similar products in the same class. The plan would reflect the SMTs identification and assessment of known, anticipated or potential risks. Where applicable, the SMT should also identify necessary safety actions and monitoring plans towards risk mitigation, where risks are carefully balanced against benefits.[47-50]

3.3.3 Reporting to Regulators and Investigators

Pharmaceutical companies, and any other sponsor of clinical studies, should follow expedited and periodic reporting rules. Regulations establish the obligation to report safety information to regulatory authorities, investigational review boards (IRBs), investigational ethics committees (IECs) and to investigators. However, there are some areas that might be better developed to enhance understanding communication of safety hazards during clinical development:

- Notifying investigators by sponsors: there are potential differences between investigational new drug (IND) and ICH requirements about the investigator-notification process;
- Notifying DSMBs by sponsors;
- Clarifying certain roles of IRB/IEC versus DSMB;
- Clarifying the role of contract research organisations as intermediary on behalf of sponsors;
- Specifying the sponsor amendment process for investigator brochures.

CIOMS VI strongly recommends replacing the current practice of sending large numbers of individual case reports to investigators and ethics committees with more practical approaches for example, periodic and *ad hoc* communications that include an update of important safety information as well as the evolving safety risk profile. The ICH has also undertaken initial evaluation of this topic and is looking

for best practices to recommend global approaches, including:

- Significant new information based on a single case report that has implications for the conduct of a clinical trial or warrants an immediate revision to the informed consent would still be communicated expeditiously;
- Quarterly line listings or periodic communication based on the assessment of aggregated data (consistent with the EU Clinical Trial Directive).[44]

3.3.4 Development Safety Update Report

CIOMS VI proposes a new form to report periodically safety information emerging from the pre-authorisation phase. This is named, following a parallelism with the post-authorisation stage ('periodic safety update report' [PSUR]),[51] the 'development safety update report' (DSUR).

The periodicity of this report could be annual. The suggested content would be harmonised and standardised to the new EU Annual Safety Update Report defined in the EU Clinical Trial Directive, and with US FDA IND annual reports. The new CIOMS VII Working Group is already working on such a format and content. The 'core data safety information' (CDSI) would be attached to the annual DSUR highlighting any safety changes since the last update, as well as amendments proposed for study protocols, informed consent and other reference documents. For products with well established safety profiles, and where most clinical trials are in the approved indication, the DSUR might be replaced by PSURs.

3.3.5 Communication to Patients

Ever-increasing attention is being paid worldwide to the safety of medical products, and communicating the risks associated with their use.[52-54] In an environment where patients increasingly expect that they be given ready access to all relevant safety information as well as ready access to medicines, there is greater need for education of the public on how to interpret benefit and risk information and how to make decisions, which are appropriate for them as individual patients. An important message for all patients, including those partaking in clinical studies, whilst also avoiding unnecessarily frightening them away from taking a background or comparator medicine, is that medicines never come without risk; another is that they should assess the benefits and risks of a drug – with their investigator – on an individual basis,[55] since no two people react to the same drug in the same way.

Communication should be balanced, provide transparency and include all necessary information to support the assessment of the safety profile of the product. Communication of the safety profile and benefit-risk tradeoffs to patients should be in a format and language that they can understand.[56] Patients often have a limited understanding of risk and how what they read is applicable to them. The communication and risk minimisation process should also ensure that the patient-investigator and patient-physician special relationship is preserved and indeed enhanced as, ultimately, this is the point at which individual benefit-risk decisions are made.[57-59]

Informed consent and package insert leaflets (PIL), for marketed comparators or background therapies, are communication tools used to inform patients and healthy volunteers participating in clinical trials about risks. Patient understanding may also rely on investigator communication skills and the level of trust the investigator will impart. In this sense, current discussion on aspects of the future of clinical trials[60] may drive culture for communication about benefit-risk balance for drugs under development. Although there are no EU guidelines developed specifically to address the presentation of risk information to patients in clinical trials setup (see also informed consent), a document[61] from the Committee on Safety Medicines in the UK for post-authorisation has bearing. It recommends putting the most important information first, including information on benefit, using the right words, and using numbers appropriately to convey risk. In addition to providing guidance on the optimal presentation of risk in PILs, this committee has considered developing a supplementary leaflet about the general risks and benefits of medicines.

But risk communication is not only about providing risk information: combining methods may well

improve overall risk communication, because there are societal and psychological factors that must be considered in attempting to maximise effectiveness. As Vogt[62] remarked, there are "recent parallel developments in the fields of medicine and the social sciences that are providing us with new insights and resources that have the potential for improving the effectiveness of drug safety communication and decision-making". These developments include medicine's new look at patient safety with its emphasis on complex adaptive systems, education's new appreciation for learning as an internal change process, and evolving recognition that relevant knowledge may not be the exclusive property of 'experts'. Although Vogt's paper is about risk communication in post-authorisation phases, the eight principles he remarks are notable:

1. There cannot be a safer drug until there is a safer system;
2. All stakeholders are equal partners and have an equal voice in all deliberations;
3. Paternalism must be eliminated;
4. The expertise for determining acceptable benefit and risk is dispersed throughout society;
5. Patients and all stakeholders serve as both teachers and learners;
6. All stakeholders are involved in the identification of their learning needs, processes and evaluation of outcomes;
7. In a complex adaptive system all individual actions are interconnected;
8. Patients must be involved in the continuous feedback and redesign of the evolving drug safety information system.

4. Necessary Approaches to Vulnerable Populations: the Example of Paediatrics

During safety review and risk assessment special attention should be paid to potentially more vulnerable populations, for example children, pregnant and lactating women[63-65] and the elderly. Here we discuss approaches to risk-management strategies for children to illustrate the additional safety requirements demanded by special populations in pre-approval drug development, and general issues raised that may require good risk management.

It is now widely accepted that it is vital for children to be recruited into clinical trials to allow appropriate and safe prescribing and to protect the safety and well being of children who will receive therapies following approval. There are a number of regulations that provide guidance specific to the inclusion of children in clinical trials (table II). Coupled with the recently published EMEA draft guideline on conduct of pharmacovigilance for medicines used by the paediatric population (27 July 2005),[66] these guidelines provide a framework for pharmacovigilance and risk-management approaches in children, including risk communication and risk mitigation. While the adult safety paradigm is broadly applicable, as with many clinical development aspects the adult model needs adapting to the different age groups that make up 'paediatrics'.[67] The many additional complexities include: small safety databases (and also smaller studies); limited parental concerns; limited acceptability of placebo groups,[68] difficulty in postmarketing data collection; potential for long-term or delayed safety issues (e.g. as a result of growth and development); risks and issues related to the specific phases of childhood; and lack of detailed normative ranges in some populations, growth and development/age and weight.

Risk-management strategy for paediatrics should follow standard principles described in this paper for adults. When approaching paediatric risk management, one should utilise the knowledge from the adult programme and utilise the standard tools and techniques, but also understand their limitations and adapt them to be useful for paediatrics. For example, childhood is made up of many stages; thus, for each stage of paediatric development, the issues may change[69] and the risk-management strategy must be addressed as appropriate for a particular age group.

To perform risk assessment, safety data must be of a high standard. For paediatric studies, this requires an understanding of the limitations on data collection and procedures and careful study design to ensure that the data collected are as useful as

Table II. List of applicable paediatric guidelines

Title	Web address[a]	Publication date
EU Paediatric Working Group guidelines		
EMEA/CHMP/PEG/194605/2005 Draft Concept Paper on the Impact of Liver Immaturity when Investigating Medicinal Products Intended for Neonatal Use (released for consultation 28 July 2005)	http://www.emea.eu.int/pdfs/human/peg/19460505en.pdf	28 July 2005
EMEA/CHMP/PEG/194810/2005 Reflection Paper: Formulations of Choice for the Paediatric Population (released for consultation June 2005)	http://www.emea.eu.int/pdfs/human/peg/19481005en.pdf.	23 June 2005
CPMP/PEG/35132/03 Discussion Paper on the Impact of Renal Immaturity when Investigating Medicinal Products Intended for Paediatric Use	http://www.emea.eu.int/pdfs/human/peg/3513203en.pdf	16 December 2004
CPMP/PhVWP/4838/02 Concept Paper on Conduct of Pharmacovigilance for Medicines used by Children	http://www.emea.eu.int/pdfs/human/phvwp/483802en.pdf.	17 October 2002
EU efficacy		
EMEA/CHMP/313666/2005 Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post Authorisation Data (released for consultation June 2004)	http://www.emea.eu.int/pdfs/human/phvwp/31366605en.pdf	14 November 2005
CPMP/EWP/422/04 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis (released for consultation June 2005)	http://www.emea.eu.int/pdfs/human/ewp/042204en.pdf	23 June 2005
EMEA/CHMP/EWP/147013/04 Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (released for consultation February 2005)	http://www.emea.eu.int/pdfs/human/ewp/14701304en.pdf	17 February 2005
EU safety		
EMEA/CHMP/203927/2005 Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (released for consultation March 2006)	http://www.emea.eu.int/pdfs/human/swp/20392705en.pdf	23 March 2006
EMEA/CHMP/114218/2006 Concept Paper on the Impact of Lung and Heart Immaturity when Investigating Medicinal Products Intended for Neonatal Use	http://www.emea.eu.int/pdfs/human/peg/11421806en.pdf	23 March 2006
EMEA/CHMP/SWP/169215/2005 Guideline on the need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications (released for consultation 11 October 2005)	http://www.emea.eu.int/pdfs/human/swp/16921505en.pdf	29 September 2005
EMEA/CHMP/235910/2005 Draft Guideline on Conduct of Pharmacovigilance for Medicines used by the Paediatric Population (released for consultation 27 July 2005)	http://www.emea.eu.int/pdfs/human/phvwp/23591005en.pdf	27 July 2005
EMEA/CPMP/SWP/3404/01 Concept Paper on the development of a CPMP Note for Guidance on the need for Pre-clinical Testing of Human Pharmaceuticals in Juvenile Animals	http://www.emea.eu.int/pdfs/human/swp/340401en.pdf	15 November 2001
CPMP/SWP/373/01 Concept Paper on the development of a CPMP Note for Guidance on Risk Assessment of Medicinal Products on Human Reproductive and Development Toxicities: from Data to Labelling	http://www.emea.eu.int/pdfs/human/swp/037301en.pdf	27 June 2001

Continued next page

Table II. Contd

Title	Web address[a]	Publication date
General		
CPMP/3833/03 Discussion Paper on Contraindications in Pregnancy concerning Sections 4.3, 4.6 and 5.3 of the Summary of Product Characteristics	http://www.emea.eu.int/pdfs/human/regaffair/383303en.pdf	23 June 2004
EMEA/CPMP/EWP/569/02 Note for Guidance on Evaluation of Anticancer Medicinal Products in Man. Addendum on Paediatric Oncology (CPMP released for consultation July 2003)	http://www.emea.eu.int/pdfs/human/ewp/056902en.pdf	July 2003
US risk-management guidance		
Guidance for Industry: Nonclinical Safety Evaluation of Pediatric Drug Products	http://www.fda.gov/cder/guidance/5671fnl.htm	February 2006
ICH		
E11 Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99 - adopted July 2000)	http://www.emea.eu.int/pdfs/human/ich/271199EN.pdf	January 2001

a Accessed 3 May 2006.

CHMP = Committee for Medicinal Products for Human Use; **CPMP** = Committee for Proprietary Medicinal Products; **EMEA** = European Medicines Agency; **EWP** = Efficacy Working Party; **PEG** = Paediatric Expert Group; **PhVWP** = pharmacovigilance working party.

possible. Consideration needs to be given to practical limitations, such as limited blood volume, technical difficulties performing assessments (e.g. blood pressure measurements), variations in the ability of the child (both inter- and intra-child variation) and lack of tolerance of repeated testing. An understanding of the normal process and timing of organ maturation,[70,71] puberty and ongoing growth and development of the child helps determine what and when data need to be collected and improves interpretation of the data.

AE reporting can be more difficult in children, where the parent rather than the child often reports the events. Children can find it difficult to describe symptoms accurately. All these factors may lead to ascertainment bias, especially if those participating in the study are unaware of the potential reporting issues. Currently, inconsistency in paediatric safety data ascertainment is a major limitation, particularly in paediatric psychopharmacology, which is likely to impair the ability to promptly and accurately identify drug-induced adverse events.[72] Creating a more standardised approach to safety data collection from inherently smaller paediatric studies would enable data to be compared and combined, facilitating clearer understanding of potential safety issues. Consideration of active rather than passive surveillance may be merited in some instances.[73]

Neonates are an extremely vulnerable population with their own specific issues.[74] To be able to perform risk minimisation and risk quantification successfully, awareness of areas requiring consideration is needed. These include the developing retina, lung function, the risk of cerebral haemorrhage, neonatal jaundice, alterations in blood parameters and immune function, changes in diet and feeding, and ensuring appropriate age correction.

5. The Special Role of Epidemiology in Pre-Approval Drug Development

We discuss the role of epidemiology in pre-approval drug development as the basis for good post-approval support. Epidemiologic activities constitute a continuum throughout a therapy's discovery, development and post-approval life cycle. As such, epidemiologic tools bring value to risk-management plans, and thus may speed up the process to better understand and quantify unknown risks.

Epidemiology studies the distribution and determinants, both risk and preventive factors, of disease and health status of populations. For a long time, epidemiological studies on the use and effects of

therapeutic agents and their target disease indications, have been key in evaluating the safety of therapeutic agents as used in final patient populations.[75,76] Many of these studies were observational, i.e. non-interventional in nature, such as cohort and case-control studies. Increasingly, an interventional component is used as well, such as in large simplified safety trials. So far, post-approval safety-focused studies have been the best know contribution of epidemiology as applied to therapeutics. Their goal is usually to address important limitations of traditional randomised clinical trials, which include: time frames too short to identify mid- to long-term effects, too small to identify moderately infrequent events, populations too narrow to allow generalisation to final patient population of users, and other limitations to the interpretation of safety in clinical trials such as the impact of intent to treat analysis, differential drop outs, and the use of p-values as decision criteria.[77]

5.1 Applications of Epidemiology in the Pre-Approval Period

In the pre-approval setting, epidemiologists have two key objectives during drug discovery and development: First, to work closely with safety, clinical, regulatory and other teams and decision boards in order to identify safety issues, quantify the impact on the population of pre-clinical and early development findings, evaluate case clusters in the development programme, and plan and implement epidemiologic studies and regulatory document sections as required by recently issued risk-management guidelines. A second objective is to provide the epidemiological component of disease knowledge that will help plan and implement other non-safety activities such as identifying unmet medical needs, targeting development programmes, designing clinical trials, and supporting outcomes evaluations of orphan drug applications.[78]

Pre-approval, the goal of an epidemiological research portfolio will be to learn about the occurrence and natural history of the diseases for which therapies will be developed, and about the patient characteristics, and treatment patterns,[79] and safety issues associated with these treatments in different populations.[80-82] On occasion, and when no direct data are available, modelling and simulation can provide estimates of potential safety impact.[83,84] Different observational designs can be used, such as follow-up (cohort), case control, and surveys. Increasingly, hybrid designs, such as the large simplified trial[85] or randomised epidemiology are used as well. From the data collection perspective, traditional *de novo* data collection methods can be used, but the availability of automated health data have allowed pharmacoepidemiologists to conduct studies in large numbers of patients in a timely and efficient manner.[86]

5.2 Triggers for Pre-Approval Epidemiology Study

A key activity pre-approval is to continuously evaluate the development programme for areas that will need further epidemiological research once the treatment is available post-approval. One area is the investigation of any gaps in the knowledge of natural history of disease or patient population that have not been addressed pre-approval. Typically, these are questions raised during late development, or those that require long-term study periods. A second area aims at learning as early as possible:

- What type of patients use the newly introduced treatment;
- What are the utilisation patterns;
- How the new treatment modifies the patterns of use of prior medication.

Early epidemiology research focusing on safety is usually fully integrated in the approval application's risk-management plan in the form of draft protocols, concept proposals, or discussion of options. The goal of these studies is to evaluate, in a real patient use setting, potential safety issues based on findings during the development phase, or theoretical risks based on the compound mechanism of action. Likewise integrated in risk-management plans are epidemiological studies to evaluate the effectiveness of risk minimisation interventions. Studies often require extensive planning periods: consultation with experts on the topic or methods in

academia and regulatory agencies, or the design and evaluation of feasibility and piloting activities. An early start in the discussion and planning of the post-approval portfolio has become a requirement for a successful filing.

5.3 The Impact of New Risk-Management and Pharmacovigilance Guidelines on Epidemiology

Therapeutic risk-management initiatives across the world have started to change the way the benefit-risk balance of therapeutic agents is evaluated and improved. The implementation of CIOMS ICH, EMEA and FDA guidelines will result in important changes in the way epidemiological activities are carried out in the EU, US and other countries and regions. Epidemiology plays an important role in pharmacovigilance and risk-management plans, so as the application of therapeutic safety risk-management approach evolves, pharmacoepidemiology studies will grow both in number and in relative importance in the study portfolios.

6. Conclusion

Several initiatives, including ICH E2E, CIOMS VI, FDA and EMEA/CHMP risk-management guidelines, and recent publications like the 'Action Plan to Further Progress in European Risk Management Strategy' (Heads of Medicines Agencies),[87] have reinforced the importance of safety risk management during the early stages of drug development. These requirements are emphasised by the ever-increasing demands from patients and the public for adequate protection of public health, through the availability of safe and effective medicines.[88]

Pharmaceutical companies in conjunction with regulatory agencies and other stakeholders (for example, health professionals, educators, communicators, but also patients and patients' associations) must jointly ensure enhancing methods to further improve patient safety. They should continue to create an adequate framework which strikes the right balance between timely access to medicines by patients and the extent of safety knowledge required for a medicine at initial licensing, paralleled by appropriate post-licensing routine and enhanced pharmacovigilance or risk minimisation programmes.

Ideally, if appropriately applied, new tools and the guidance documents as well as the complementary initiatives that regulators and others may choose to undertake, will lead to creation of a collaborative environment that is conducive to timely access to new safe and effective medicines. In this context, the guidance provided by ICH E2E, CIOMS VI, EMEA/CHMP and FDA helps the pharmaceutical industry develop a well structured, standardised approach to safety risk management, including communication of risk during and after clinical studies.

The complex process of setting up dedicated SMTs, or equivalent functions, during drug development to generate risk-management strategies and pre- and post-authorisation pharmacovigilance plans, will likely lead to more effective safety risk identification, assessment, communication and minimisation. The activities will be the key to successfully protecting subjects and patients who voluntarily participate in clinical research as well as those populations exposed to the drugs in the post-approval phase.

With the new risk-management paradigm's proposals in place, reviewed, discussed and agreed among all stakeholders, accepted by regulators, and adopted through legislation, the authors of this paper, as well as CIOMS VI Working Group, believe that we will have better, more structured pharmacovigilance and risk-management practices implemented during the pre-approval drug-development phase.

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Correspondence and offprints: Dr *Craig G. Hartford*, Safety and Risk Management, Pfizer Global Research and Development, 509/2.766 i.p.c. 582, Ramsgate Road, Sandwich, Kent, CTI 39NJ, UK.