Global Harmonization Is Not All That Global: Divergent Approaches in Drug Safety

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I. INTRODUCTION

Pharmacovigilance3 is a global public health activity that is currently undergoing a considerable amount of regulatory, social and political change. The standards expected by society have been raised following high-profile product withdrawals. Industry, regulatory authorities and consumers are now focusing on a more proactive, risk management based approach to drug safety monitoring. There has been a shift from the formulaic collection, classification and reporting of adverse event reports to a more holistic focus on any information suggesting a change in a product’s risk benefit profile.

There has also been a realization that effective pharmacovigilance must be global. Companies and regulatory authorities must receive and react to information suggesting a change in risk-benefit profile wherever it arises. The past 20 years has therefore seen a steady drive towards global harmonization of safety reporting definitions and standards.

There is, however, evidence that this shift towards international harmonization is faltering as regulatory priorities and views diverge. There are increasing differences in the way different jurisdictions interpret, implement, and follow international safety reporting standards, in particular the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)4 guidelines on adverse drug reactions and safety reporting. In Europe, for example, the regulators have fully adopted ICH guidelines. They have accepted the ICH concept that manufacturers should report only those events that the reporting physician or the manufacturer believe have a possible causal relationship with a drug. However, the United States has been slow to adopt these standards and concepts, preferring companies to report all adverse experiences, irrespective of the likelihood of a causal relationship. Even where the U.S. has proposed the adoption of ICH standards it does so with qualifications. This has

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3 The term “pharmacovigilance” refers to the scientific activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem.  
4 ICH was created to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. It is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: the European Union (EU), Japan, and the United States. The six ICH sponsors are the European Commission (EC), the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association (hereinafter JPMA), FDA, and the Pharmaceutical Research and Manufacturers of America (hereinafter PhRMA). See http://www.ich.org/cache/compo/276-254-1.html. For many years now, the ICH Global Cooperation Group has been trying to bridge the gap between those represented in ICH, i.e. the United States, Canada, the EU, Switzerland and Japan, and those countries which do not have the privilege of taking part in the discussions and therefore do not feel obliged to take on board ICH decisions, e.g. Brazil, South Africa and the Association of Southeast Asian Nations (ASEAN) member countries.
resulted in significant differences in the information companies are reporting to regulators worldwide.

This can have significant practical implications for regulators, who may gain very different impressions of the scope and magnitude of an emerging safety issue. It can also affect the manner in which they treat manufacturers, either as a result of a manufacturer’s own reporting policies or those of manufacturers of products in the same class. A good example of such a circumstance arose in the context of safety concerns surrounding gadolinium contrast agents, discussed below. Different reporting practices amongst the manufacturers of these products resulted in European regulators regarding the issue as a single product concern, while the Food and Drug Administration (FDA) viewed it as a class effect.

Another threat to global harmonization of safety reporting is arising because of divergent approaches to the naming of medicinal products. Most reporting systems and standards rely on the World Health Organization (WHO) international non-proprietary name (INN) of a product as opposed to its brand name. This is because brand names can vary from jurisdiction to jurisdiction, as do prescribing and dispensing practices. Physicians in many jurisdictions prescribe and report using a product’s INN and pharmacists are often required to dispense by INN. This use of INNs is therefore necessary and also appropriate, provided regulators apply the WHO’s recommendations.

The EC has recently set an unhelpful precedent by approving two follow-on biological products, Epoetin alfa Hexal and Abseamed, with the same INN as the innovator product, Eprex/Erypro, in clear contravention of WHO guidance on drug naming. Biological products are sensitive to changes in manufacturing process and formulation and also have the potential for rare, but serious side-effects and so effective postmarketing surveillance is essential. The EC has proposed that doctors prescribe and report by brand name, and that pharmacists also dispense in that way, to overcome the problems associated with product identification. However, it is the authors’ view that such an approach will result in further threat to the harmonization of pharmacovigilance. Effective pharmacovigilance requires global harmonization of nomenclature, standards and definitions and it is unlikely that an approach relying on brand name reporting would be adopted internationally in the short term, because ICH safety reporting standards rely on the appropriate use of INNs. How can global safety monitoring and reporting work if those involved do not even speak the same language?

II. GLOBAL HARMONIZATION OF SAFETY REPORTING

Global adverse event reporting requirements have, for some time, been the subject of a concerted harmonization program. The purposes of harmonization are to increase worldwide consistency in the collection of safety information, increase the quality of safety reports, and expedite their regulatory review. Definitions for the terms adverse event (or experience), adverse reaction, and unexpected adverse reaction were first agreed by a consensus of more than 30 Collaborating Centers of

the WHO International Drug Monitoring Centre in 1994.\(^6\) However, the harmonization effort is now largely based on definitions, reporting formats and standards recommended by ICH and by the WHO Council for International Organizations of Medical Sciences (CIOMS).

A. ICH Guidelines

**ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A)**

The ICH E2A guideline was finalized in October 1994 and gives standard definitions and terminology for key aspects of clinical safety reporting.\(^7\) It also gives guidance on mechanisms for handling expedited reporting of adverse drug reactions in the investigational phase of drug development. The key definitions, for the purposes of this article, provided in ICH E2A are:

- **Adverse Event (or Adverse Experience)**

  *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*

  An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Adverse Drug Reaction (ADR)**

  In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:

  *all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.*

  The phrase “responses to a medicinal product” implies a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

  Regarding marketed medicinal products, ICH E2A provides the following, well-accepted definition of an ADR in the postmarketing setting:

  *A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.*\(^8\)

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\(^8\) ICH E2A cites “World Health Organisation Technical Report 498 (1972)” as the basis for this definition. This definition was subsequently adopted by ICH E2D: *Post-Approval Data Safety Management: Note for Guidance on Definitions and Standards for Expedited Reporting,* (Nov. 12, 2003) (hereinafter
• Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational medicinal product).

ICH E2B (M): Maintenance of the Clinical Safety Data Management including Data Elements for Transmission of Individual Case Safety Reports (as amended).9

The primary purpose of this guideline is to provide details of the minimum information needed to process an ADR report. The minimum information for the transmission of a report should include at least one identifiable patient, one identifiable reporter, one reaction/event, and one suspect drug (with certain exceptions). Because it is often difficult to obtain all the information, any one of several data elements is considered sufficient to define an identifiable patient (e.g., initials, age and sex) or an identifiable reporter (e.g., initials, address and qualification). It is also recognized that the patient and the reporter can be the same individual and still fulfill the minimum reporting criteria. Due to data privacy legislation in some countries, the patient’s initials and the reporter’s details cannot be exchanged between countries.

E2C (R1): Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (ICH E2C)

ICH E2C (R1) standard was finalized in November 1996 and gives guidance on the format and content of safety updates, which need to be provided to regulatory authorities at intervals after products have been marketed.10 The guideline is intended to ensure that the worldwide safety experience is provided to authorities at defined times after marketing with maximum efficiency and avoiding duplication of effort.

The addendum to the ICH E2C guidance was finalized in February 2003.11 The document was intended to provide additional guidance to address the disharmony between ICH regions caused by differing interpretation of the original ICH E2C guideline. The addendum takes into account recommendations and new concepts developed by CIOMS Working Group V to harmonize the practice of preparing

ICH E2D). ICH E2D was adopted by: (i) CHMP on (Nov. 20 2003), CPMP/ICH/3945/03; (ii) MHLW on (Mar. 28, 2005), PFSB/SD Notification 0328007; and (iii) FDA, Federal Register, (Sept. 15, 2003), Vol. 68, No. 178, pages 53,983-53,984. ICH E2D provides a standardized procedure for postapproval safety data management, including expedited reporting to the relevant authority. The definitions of the terms and concepts specific to the postapproval phase are also provided.


periodic safety update reports (PSURs). It addresses the following concepts not previously addressed by ICH E2C:

- summary bridging reports;
- addendum reports;
- proprietary information;
- executive summaries;
- risk management programs; and
- benefit-risk analysis.

B. CIOMS

CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949. It provides a range of guidance and opinions on issues ranging from bioethics, health policy, drug development and use and international nomenclature of diseases. As part of its role, CIOMS establishes working groups to provide guidance on the assessment and monitoring of adverse drug reactions.

In 1997, CIOMS Working Group V started work on proposals for pragmatic approaches to dealing with issues such as: classification and handling of individual safety case reports from a variety of sources; new approaches to case management and regulatory practices; improvements and efficiencies in the format, content and reporting of periodic safety update reports; and determination and use of populations exposure date. This program of work was considered necessary, in spite of progress in the ICH harmonization, to gain consensus on standards for many difficult aspects of day-to-day pharmacovigilance management.

The group also looked at the state of expedited and periodic clinical safety reporting requirements around the world and made recommendations for enhancing the harmonization steps already made. The final report was published in 2001.

C. MedDRA

The Medical Dictionary for Regulatory Activities terminology (MedDRA) is a clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry in both pre-marketing and post-marketing regulatory reporting. It is used for data entry, retrieval, evaluation and presentation using a coding system. To code using MedDRA means that a term is selected to correspond to verbatim information reported from either a spontaneous source or a clinical trial investigator.

MedDRA has issued guidance on term selection, which has been endorsed by ICH, and gives examples of how to allocate “terms” in ADR/AE reports. It also gives some examples of information that is not generally considered to be an ADR/

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AE. In some cases, it suggests that these should be “classified” as medical/social
history rather than ADR/AE.

For instance, paragraph 3.9 of MedDRA’s guidance relates to terms for pre-
existing medical conditions. It states that pre-existing medical conditions that
have not changed should generally be classified as medical and/or social history
whereas pre-existing medical conditions that have changed can be classified as
ADR/AEs.

Further, paragraph 3.2.2 of the guidance states that the consequences of an
event, such as hospitalization and disability, are not generally considered to be
ADRs or AEs and so the term “hospitalization” should not be used to classify the
ADR/AE unless this is the only outcome reported, e.g. “a patient was hospitalized.”
However, if the report states “hospitalization due to congestive heart failure,” then
“congestive heart failure” should be selected as the ADR/AE and hospitalization
should be captured as the consequence of the event.

D. Implementation of International Standards in Europe

The safety reporting requirements in the European Community are embodied
No 726/2004.16 The former applies to all medicinal products, but imposes phar-
macovigilance obligations only in respect of products approved via the so-called
mutual recognition, decentralized and national procedures. The Regulation imposes
reporting obligations for products approved via the so-called centralized procedure.
The reporting requirements under these laws are similar, differing only in the identity
of the ultimate recipients of the reports. The requirements are also consistent with
ICH standards and definitions. The legislation requires the reporting of “adverse
reactions” as opposed to “adverse experiences or events” (see implementation in
the United States below). Thus, a causal relationship between the drug and the
adverse event must be at least a reasonable possibility.17

The EC has also adopted a significant body of associated guidance in Volume
9A or the Rules Governing Medicinal Products in the EU.18 The requirements set
out in Volume 9A were intended to incorporate ICH standards and definitions,
but go far beyond ICH requirements or the requirements of either the Directive
or the Regulation. Strictly speaking, Volume 9A is a guidance document. It was,
however, adopted by the EC pursuant to Articles 106 and 26 of the Directive19 and

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code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67. [Hereinafter the Direc-
tive]. This Directive has been amended most recently by European Parliament and the Council Direc-
laying down Community procedures for the authorization and supervision of medicinal products for
human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance)
18 EC, Rules Governing Medicinal Products in the EU, Notice to Applicants, Volume 9A, Phar-
macovigilance for Medicines for Human Use, (Mar. 2007). See http://ec.europa.eu/enterprise/pharma-
9A]. Although Volume 9A is guidance, marketing authorization holders are required to comply with it
Regulation, respectively, and is therefore entitled to a greater degree of deference than guidance without any such legal basis.

Volume 9A also provides further guidance on the causality element of spontaneous reports received from healthcare professionals. It states:

“Spontaneous reports of adverse reactions received from Healthcare Professionals should be reported by the Marketing Authorization Holder if:

- the Healthcare Professional has made a statement that a causal relationship between the event and the medicinal product is considered to be at least a reasonable possibility; or if
- the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown; or if
- the Marketing Authorization Holder considers that a causal relationship is at least a reasonable possibility.

If the Healthcare Professional has made an explicit statement that a causal relationship between the medicinal product and reaction has been excluded and the Marketing Authorization Holder agrees with this, the event should not be reported.”

The European requirements therefore require that either the manufacturer or the reporting physician consider that there is at least a possible causal relationship between an event and a drug. Under Volume 9A and ICH standards, therefore, manufacturers are not permitted to contradict a physician’s determination that such a relationship may exist, and must construe a reporter’s silence as an implied causality assessment. If a manufacturer disagrees, it can, however, indicate this in the comments section of the adverse event report to the authorities. Reports from physicians are, therefore, reportable per se unless the physician indicates that he or she does not suspect a causal relationship.

As regards harmonization of terminology, the EMEA has required the use of MedDRA for single case reports received electronically since January 2002, and for all ADR reporting since January 2003. Both clinical trial suspected unexpected serious adverse reactions (SUSARs) and post-authorization individual case safety reports (ICSRs) reported to the EudraVigilance database must be submitted electronically and coded using MedDRA. MedDRA has also made its way into the EC’s labeling guideline; the latest revision of the summary of product characteristics calls for MedDRA terms to be used in the “undesirable effects” section and it gives further guidance in Annex 2 on how to aggregate MedDRA-coded data to estimate the frequency of events.

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21 Volume 9A, supra note 17, at page 55.
22 EudraVigilance is a central computer database created by the EMEA in Dec. 2001. It contains adverse reaction reports to medicines licensed across the EU. Such reports are received from the EU regulatory agencies and from pharmaceutical companies. See http://eudravigilance.emea.europa.eu/human/EVBackground(FAQ).asp.
E. Implementation of International Standards in the United States

U.S. applicants for new drug applications (NDAs), abbreviated new drug applications (ANDAs), manufacturers of marketed prescription drugs for human use both with or without approved NDAs or ANDAs, and licensed manufacturers under approved biologic product license applications (BLAs) are required to report adverse experiences to FDA under 21 CFR §§ 310.305, 314.80, 314.98, 600.80 and 600.81. This means that all adverse events/experiences must be reported, regardless of any potential causal relationship with the treatment. This contrasts with the European and ICH requirement that a causal relationship must be at least a reasonable possibility. For those products subject to an investigational new drug application, similar reporting obligations arise under 21 CFR § 312.32.

Although the reporting obligations under these FDA Regulations do not reflect fully the ICH standards, FDA has adopted selected ICH requirements in the form of rules and guidance. In 2003, it published a significant proposed rule that would, if adopted, amend its pre- and postmarketing safety reporting regulations for human drug and biological products to:

- Implement definitions and reporting formats and standards recommended by the ICH and by CIOMS;
- Codify the agency’s expectations for timely acquisition, evaluation, and submission of relevant safety information for marketed drugs and licensed biological products;
- Require that certain information, such as domestic reports of medication errors, be submitted to the agency in an expedited manner; and
- Clarify certain requirements and make other minor revisions.

The FDA Proposed Rule would also require that manufacturers take a much more proactive approach to product risk management and expand considerably requirements relating to company specific safety reporting systems, processes and infrastructure.

In addition, it would adopt MedDRA terminology, bringing the United States in line with other jurisdictions such as Europe and Japan, which have already adopted MedDRA into their safety reporting systems. This provides reassurance that FDA does not intend using an alternative terminology for this purpose, something that would entail a significant waste of resource and effort by both industry and FDA in conversion to yet another terminology.

A number of aspects of the FDA Proposed Rule have been the subject of some debate, including its definition of Suspected Adverse Drug Reaction, the ability to follow-up reports to the proposed standards, and the requirements to submit interim periodic safety reports. These issues are discussed below.

F. Inconsistencies between U.S. Proposals for Harmonization and the International Approach.

The FDA Proposed Rule introduces a number of FDA-specific requirements that would be contrary to the stated intent of international harmonization and common understanding of basic definitions.

1. Definition of a Suspected Adverse Drug Reaction (SADR)

The proposals include replacing the long-used term “adverse drug experience” with “Suspected Adverse Drug Reaction (SADR).” FDA proposes that this term be used consistently throughout the pre- and post-approval regulations. SADR is defined in the FDA Proposed Rule as:

A noxious and unintended response to any dose of a drug product for which a relationship between the product and the response to the product cannot be ruled out. 27 (Emphasis added).

FDA gives the following example:

In some cases an adverse event may most probably have occurred as a result of the patient’s underlying disease and not as a result of the drug, but since it cannot usually be said with certainty that the product did not cause the adverse event, it should be considered an SADR. 28

There is, therefore, a key difference between the manner in which FDA has proposed to implement the ICH definition of an AR and the manner in which European regulators have done so. While the European rules require that a there is at least a possible relationship FDA requires reporting unless the manufacturer can rule out a causal relationship. It is inconsistent with the subsequent recommendation in ICH E2A, which clearly states that “reasonable causal relationship is meant to convey that there are facts or arguments to suggest a causal relationship.” 29

FDA has indicated that the term “reasonable possibility” is “potentially confusing.” 30 It is, however, a well established and understood principle that has found support in a number of other areas, including guidelines on safety reporting obligations under the European Clinical Trial Directive, 31 which states:

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

27 FDA Proposed Rule, supra note 26, at section III A.1., page 12,417.
28 See id.
30 FDA Proposed Rule, supra note 27.
Further, the ICH E2D guideline\(^{32}\) cross-refers to the ICH E2A definition of adverse reaction, indicating an international consensus that supports the definition of ADR in its entirety.

In addition, in cases of adulteration of food under 21 U.S.C. § 342(a)(4), it is necessary to show a “reasonable possibility” that, by virtue of the insanitary conditions under which the food is prepared, packed, or held, an article of food may have been rendered filthy or injurious to health.\(^{33}\)

In reality, FDA’s proposed amendment to the ICH definition of an ADR is most likely linked to a degree of skepticism about what would be a significant change in the manner in which companies report to FDA. FDA has historically required the reporting of all adverse experiences, with the only issue being the degree of association between a drug and an adverse event necessary to trigger a reporting obligation. As presented, the FDA Proposed Rule would result in little change to the manner in which the majority of postapproval spontaneous events are handled. This is because almost every adverse event occurring after drug administration would then be regarded as a suspected adverse reaction, given that a temporal relationship inevitably means that the role of the investigational product in the causation of an adverse event cannot be totally “ruled out.” The FDA Proposed Rule would thus arguably negate any value in the distinction drawn between an adverse event and an adverse reaction, because use of FDA’s definition would result in almost every serious unexpected adverse event, including incidental events, being reported to FDA.

The European Federation of Pharmaceutical Industries and Associations (EFPIA)\(^{34}\) has suggested that the FDA Proposed Rule would result in a significant increase, estimated as approximately tenfold,\(^{35}\) in the number of Investigational New Drug (IND) Safety Reports\(^{36}\) submitted to FDA and to investigators and Institutional Review Boards (IRBs), particularly for long term postmarketing studies that can extend over several years.

Critics of the proposal, such as EFPIA, argue that this increase would make the detection of true safety signals more difficult due to the increased “noise.” They suggest that investigators and IRBs already complain about the current abundance of uninformative IND Safety Reports, and that the proposed change would increase their administrative burden without adding any true value.

Another possible impact of the revised definition of “reasonable possibility” under the FDA Proposed Rule relates to the need to unblind all serious unexpected adverse events, potentially compromising the integrity of clinical trials that have a large number of serious adverse events. In clinical trials, for example, protocols routinely require investigators to observe and report all untoward or unexpected events, regardless of likely causation.\(^{37}\) Determining whether individual events are

\(^{32}\) ICH E2D, supra note 7 at paragraph 2.2 :  
\(^{33}\) See Berger v. United States, 200 F.2d 818, 821 (8th Cir. (1952)).  
\(^{34}\) EFPIA represents the pharmaceutical industry operating in Europe. Its mission is to promote pharmaceutical research and development in Europe. Founded in 1978, its members consist of 18 national pharmaceutical industry associations and 43 pharmaceutical companies involved in research, development and manufacturing of medicines for human use. 
\(^{36}\) 21 C.F.R. §312.32. 
\(^{37}\) According to Directive 2001/20/EC, Art. 16.4, of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1/5/2001 p. 34 - 44) [hereinafter the EU Clinical Trial Directive], the sponsor of a clinical trial shall keep detailed records of all adverse events and he shall submit these records on request to the Members States in whose territory the clinical trial is being conducted.
likely to be caused by the drug, and not the underlying disease or other intervening factors, occurs after the data are collected. That determination may include comparisons between patients administered the drug in question and patients taking a placebo or other treatment. Based on this analysis, the investigator decides whether a causal relationship is “likely,” “improbable” or “very unlikely.” Ruling out a causal relationship absolutely is often impossible.

Under the current FDA rules, if the sponsor of the study concluded that the event was a recognized consequence of the patient’s underlying disease and thus unlikely (but not impossibly) due to the drug, no report would be required. However, the proposal would make such an event reportable. More importantly, it may also make the event reportable on an expedited basis. Presumably, for this reason, FDA suggests that protocols could be written to exclude certain disease-related events that are study endpoints or in high morbidity/mortality studies from expedited reporting. Indeed, FDA observes that in many situations, expedited reports of events may not be very informative. For example, in studies in cancer, fatalities are common because of the underlying disease. FDA states that it does not want to require “over-reporting” and suggests that, in individual cases, it would be willing to consider alternative ways to handle specific foreseeable events or outcomes that are likely to be due to the disease.

2. “Incidental” Events

In the course of investigating spontaneous reports from healthcare professionals, companies may receive information on events, adverse or otherwise, that occurred after the drug was administered, but that were not the intended subject of the spontaneous report. Alternatively, a physician may mention an adverse experience while communicating with a company on an unrelated issue, again with no intention to generate a spontaneous report. These types of events, which do not prompt contact with the pharmaceutical company or regulator and for which there is no indication of drug causality, are referred to as “incidental events” by the CIOMS V Working Group. The CIOMS V group endorses reporting incidental events as either medical history or concurrent conditions and not as suspected ADRs on which regulatory reporting decisions are made, unless a causal relationship is implied or stated by the reporter, the medical records, or company review staff.

The MedDRA Term Selection Guide instructs users to code every reported ADR/AE or medical concept described by the reporter, regardless of perceived relationship to drug product. The rationale for this is that by not coding all AEs, there is a risk of missing adverse events that were thought to be unrelated to a drug, but were later determined to be drug-related. If this reasoning were followed, then by not coding all concomitant drugs as suspect drugs, there is a risk of missing

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38 FDA Proposed Rule, supra note 26, at section III A.1, page 12,418.
39 See id.
40 FDA suggests one such alternative would be to include in study protocols or other documentation a list of known consequences of the disease that would not be submitted to FDA in an expedited manner as individual case safety reports (e.g., events that are the endpoints of the study). These endpoints would, however, be monitored by the sponsor, manufacturer or applicant and, if they indicated in the aggregate by comparison to a control group or historical experience, that the product in the clinical study may be causing these events, the information would be submitted to FDA in an expedited manner as an information sufficient to consider product administration changes report. FDA Proposed Rule, supra note 37.
41 CIOMS V supra note 12.
42 MedDRA, Term Selection: Points to Consider, supra note 13 at paragraph 2.5.
drugs that were thought to be unrelated to the adverse event, but that were later determined to be causal for the AE. Some commentators argue that this approach creates “noise” in spontaneous reporting databases, (i.e., non-serious and/or incidental adverse events), which detracts from the ability of reviewers to detect true potential serious ADR signals and protect the public health.43

However, regulatory agencies do not currently recognize incidental events, and there is no field or category for recording “concurrent events” on spontaneous report forms or electronic file formats. The European definition of an ADR, with its inherent causality assessment, means that companies will be able to exercise some discretion not to report. FDA, on the other hand, is likely to expect companies to report whenever incidental information received by a healthcare professional satisfies the four minimum criteria necessary for an adverse event report, (i.e., an identifiable patient, an identifiable reporter, a reaction/event, and one suspect drug).

G. Practical Consequences of Divergent Approaches to Pharmacovigilance

These current differences in the safety reporting requirements can have significant practical implications for regulators, who may be faced with differing bodies of safety data and hence different impressions of the scope and magnitude of an emerging safety issue. It can also have implications for manufacturers whose differing reporting practices can affect regulators’ perceptions of their products’ safety profiles. A classic example where the U.S. and European regulators took different approaches in respect of the same issue was in 2006 when data suggested that gadolinium (Gd) contrast agents may be associated with the onset of nephrogenic systemic fibrosis (NSF).

NSF is a rare, but serious, acquired systemic disease. It generally affects patients with renal insufficiency, particularly those with severely impaired renal function who are on or approaching dialysis. NSF was first described in 1997, but since then there has been little progress in elucidating the etiology of the disease. Although the precise cause of NSF is still under investigation, safety data suggested that exposure to Gd-based magnetic resonance contrast media may be a factor in some patients. The first reports of NSF in patients exposed to gadolinium contrast agents occurred in early 2006 and all involved GE Healthcare’s gadodiamide injection product, OMNISCAN.44 While OMNISCAN was the first agent to be reported with cases of NSF, additional cases of NSF were subsequently reported with other Gd-based contrast media, indicating the possibility that this may be a Gd class issue not limited to one product.

The numbers of reported Gd-associated cases were largely based on spontaneous postmarketing reports, thus making it difficult to calculate a reliable estimate of an incidence rate or to make determinations regarding the relative safety of Gd-based contrast media. However, it soon became clear that the European regulators had a very different picture of the emerging safety profiles of various gadolinium products.

In Europe, the issue was first discussed at the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) in June, 2006 and further data were discussed at the November, 2006, PhVWP meet-

At that stage, the data available to the PhVWP suggested that 48 (validated) and 40 (under validation) cases of NSF were associated with gadodiamide (OMNISCAN), with only two possible cases were associated with gadopentetate dimeglumine (Magnevist), and no cases with other Gd-containing contrast agents.

Data available to FDA painted a different picture. Reports of NSF were filed with the agency following administration of all five FDA approved Gd-based contrast agents OMNISCAN, Magnevist, OptiMARK, MultiHance and ProHance. However, some of the NSF adverse event reports did not include complete information on patients’ exposure history. Also, reports indicated that some patients received more than one Gd-based contrast agent prior to an NSF diagnosis. The lack of complete information on exposure along with similarities among all these gadolinium-based contrast agents made it difficult for FDA to definitively determine whether the extent of risks for developing NSF were the same for all the Gd-based contrast agents. However, information available from the manufacturers of Gd-based contrast agents suggests that FDA was in receipt of a much higher number of NSF reports across a broader range of gadolinium-based products. For instance, GE Healthcare reported that, as of February 2007, FDA had received the following numbers of NSF case reports: OMNISCAN (85), Magnevist (21), OptiMARK (6), MultiHance (1, this patient was also exposed to OMNISCAN). Further, Bayer Healthcare Pharmaceuticals, which markets Magnevist, reported that it had received 53 reports of NSF “in which a relationship to Magnevist could not be ruled out.”

As a result, FDA regarded NSF to be an effect of the entire class of Gd-based contrast media and issued consistent Public Health Advisories (PHAs) applicable to all such products. By contrast, while European regulators accepted that caution should be exercised with the use of all Gd contrast agents, they regarded NSF to be predominantly associated with OMNISCAN. The PhVWP recommended an urgent safety restriction, i.e., contraindication of OMNISCAN in patients with severe renal insufficiency and in liver transplant patients, and a relative warning for all other Gd products. The European regulators ultimately also concluded that NSF was a class effect of a number of Gd contrast agents, but not until June 2007, 12 months after FDA did so.

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The different stances of the U.S. and European regulators most likely resulted from differences in the product-specific safety data at their disposal, which may have been attributable to the different safety reporting requirements in the United States and EU and the manner in which manufacturers have interpreted and applied them. As discussed above, FDA requires the reporting of all serious unexpected adverse events, whereas the European regulators require the reporting of serious “adverse reactions.” It is difficult to determine why the safety data before the U.S. and European regulators were so different. Taking Magnevist as an example, it appears that, at roughly the same time (February 2007), FDA was in receipt of nearly ten times the number of reports of NSF associated with this product compared with their European counterparts. It may be that GE Healthcare provided FDA and European regulators with the same body of safety data, whereas other manufacturers may have applied different reporting standards and procedures for Europe and the United States.

If you can draw any conclusion, it is that the U.S. reporting requirements, which give manufacturers very little discretion in terms of what to report, provided FDA with a body of safety data that more accurately reflected the reality of the emerging NSF safety issue. The European requirements, with their greater discretion to determine whether and when an adverse experience is reportable, may result in less unhelpful “noise.” FDA may fear that the loss of all such “noise” may mean it misses signals.

III. DIVERGENT APPROACHES TO NAMING MEDICINAL PRODUCTS: BIOLOGICAL PRODUCTS

Another threat to global harmonization of safety reporting is arising because of divergent approaches to the naming of medicinal products. Brand names can vary from jurisdiction to jurisdiction, as can prescribing and dispensing practices, so most reporting systems and standards rely on a product’s WHO INN, rather than its brand name. This approach works, provided manufacturers and regulators apply the WHO’s naming recommendations in a consistent manner. There are, however, signs that the EC is diverging from the WHO recommendations when applying innovator product INNs to biosimilar medicinal products, even where there are structural differences between the products. This would pose a significant threat to the harmonization of global pharmacovigilance, particularly if other member states follow the WHO recommendations.

The products in question are the follow-on biological products, Epoetin alfa Hexal52 and Abseamed,53 with the same epoetin alfa INN as the innovator product, Eprex/Erypro.54 The follow-on biologics both contain an erythropoietin active ingredient referred to as HX 575 and used the Janssen-Cilag epoetin alfa product, Eprex/Erypro, as the reference medicinal product. HX575 differs in glycosylation pattern to that found in Eprex/Erypro and should, according to the WHO recommendations discussed further below, have used a different INN. Erythropoietins are associated with instances of pure red cell aplasia, a rare but serious blood disorder. The fact that the follow-on biological products use the same INN means that traceability and safety monitoring may be a problem. This problem is compounded by the fact that the majority of physicians prescribe and report medicinal products by INN.

52 Epoetin alfa Hexal (INN: epoetin alfa), marketed by Hexal AG.
53 Abseamed (INN: epoetin alfa), marketed by Medice Arneeimittel Pütter GmbH & Co KG.
54 Eprex/Erypro (INN: epoetin alfa), marketed by Janssen-Cilag.
The sections below discuss the naming requirements for medicinal products in Europe, the solutions proposed by the EC as to the pharmacovigilance and traceability issues, and why these proposals are at odds with WHO policy and global harmonization.

A. Regulation of Similar Biological Medicinal Products


The Directive sets out the general regulatory framework for medicines, including the form and content of marketing authorization applications and the subsequent labeling of products. The body of the Directive itself sets out the basic dossier requirements; more detail is contained in its Annex I (the Annex).

B. Similar Biological Medicinal Products

The Directive provides a formal mechanism for the approval of similar biological medicinal products, which took effect on October 30, 2005. Article 10.4 of the Directive provides that “where a biological medicinal product that is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the similar biological medicinal product and the reference biological medicinal product, the results of appropriate preclinical tests or clinical trials relating to these conditions must be provided.” The authorities determine the nature of these additional data on a case-by-case basis, but these data must be supplied in accordance with the requirements of the Directive, its Annex, and detailed guidelines adopted by the CHMP.

C. CHMP Guidelines on Similar Biological Medicinal Products

The CHMP has adopted a number of guidelines on biosimilar products, the first of which is called “Guideline on Similar Biological Medicinal Products.”

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57 Amendments to the Annex to Directive 2001/83/EC introduced by Directive 2003/63/EC (O.J. (L 1509), p. 46-94) provided a mechanism for the approval of similar biological medicinal products, as of Oct. 31, 2003. The relevant provisions were less than entirely clear. It can also be argued that the EC acted ultra vires by making these amendments outside the scope of the formal European Parliament and Council legislative process. The authors therefore refer to Oct. 30, 2005, as the date on which the European Parliament and Council definitively adopted legislation permitting the approval of similar biological medicinal products.
58 Manufacturers of follow-on biologics are not legally precluded from seeking approval as standard generic medicinal products. This would, however, require that the innovator biological medicinal product be so well-characterized that the follow-on applicant can demonstrate that its product and the chosen reference product have the “same qualitative and quantitative composition in active substances.” Directive 2001/83/EC, Art. 10.1. Few, if any, follow-on versions of biological substances would qualify for ordinary generic approval procedures, and European regulators are therefore unlikely to accept such an application for any but the simplest biotechnology-derived proteins, where there is no possibility that differences in the manufacturing processes and formulation of the products might result in differences in safety or efficacy.
There are other more general guidelines, covering quality issues and non-clinical/clinical issues. These are complemented by product-specific annex guidelines, including those for recombinant erythropoietins, recombinant granulocyte-colony stimulating factor, human growth hormone (somatropin), and recombinant human insulin. These four products were selected because the originator drugs no longer benefit from data exclusivity protection and because generic drug manufacturers had requested pre-submission scientific advice with respect to them.

D. The EC Rules Governing Naming of Medicinal Products

The basic requirements for the naming of medicinal products under European Community law are found in the Directive. The Directive draws a distinction between the invented, or brand, name of the product and the name of the active ingredient(s) it contains. Article 8.3 of the Directive requires that an applicant for marketing authorization include in its dossier the “name of the medicinal product” and the “qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its INN recommended by the WHO, where an INN for the medicinal product exists, or a reference to the relevant chemical name.” This information must also appear in the summary of product characteristics (SmPC), which is the EC counterpart of the package insert. It must also appear in the outer packaging of the medicinal product, the immediate packaging (e.g., blister packs), and the patient information leaflet.

The Directive defines the “name of the medicinal product” as “the name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the

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64 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues—Guideline on Similar Medicinal Products containing Somatropin (EMEA/CHMP/94528/05), adopted Feb. 2006.


68 Id., Art. 8.3(c).

69 The European SmPC is equivalent to U.S. prescribing information.


71 Id., Art. 54(a).

72 Id., Art. 55.2.

73 Id., Art. 59.1(a)(i).
marketing authorization holder.” A product’s “common name” is “the international non-proprietary name recommended by the WHO, or, if one does not exist, the usual common name.”

Although many applicants choose to use an invented or brand name, they are not required to do so. Generic products in particular typically bear only the common name. As far as European regulators and prescribers are concerned, the product’s common name is therefore key both to prescribing and post-approval monitoring of a product.

The Directive makes it clear that the WHO INN is the preferred common name, and that the “usual common name” may only be used if an INN is not available. This is reflected in the Annex, which requires that dossiers include “information on the nomenclature of the active substance … including recommended INN, European Pharmacopoeia name if relevant, chemical name(s).” Volume 2B of the Notice to Applicants states that each active substance should be identified by “only one name … in the following order of priority: INN*, [European Pharmacopoeia name], National Pharmacopoeia [name], common name, scientific name […] * the active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.”

The EC’s Guideline on Summary of Product Characteristics contains consistent advice:

The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant, or the European Pharmacopoeia name if that name represents an established name in Europe. If no INN exists, the European Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given.

In short, the only mandatory name for medicinal products under European Community law is the common name. The common name is the WHO INN for the product but, if none exists, may be the European Pharmacopoeia name, National Pharmacopoeia name, common name, or scientific name, in order of descending preference.

The subsections that follow describe each of these and the procedures for their adoption.

74 Id., Art. 1.20.
75 Id., Art. 1.21.
77 For example, the EMÉAs Pre-Submission Procedural Guidance, supra note 79, at Question 5, recommends that the product’s INN or the common name should be used when referring to properties of the active substance(s) rather than the invented name. The use of pronouns (e.g. “it”) is encouraged whenever possible. Further guidance is provided in the EC’s Guideline on summary of Product Characteristics, supra note 23 at page 1, that the invented name, to the extent that one exists, must appear on the SmPC, but that “when otherwise referring to the medicinal product throughout the text … the INN or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the product.”
79 Notice to Applicants Medicinal Products for Human Use, Volume 2B, Module 1: Administrative Information Application Form, (Feb. 2007), at section 2.1.2.
80 Volume 2C, supra note 23, at page 2.
E. The WHO INN

The WHO INN is a unique name that identifies a particular pharmaceutical substance or active ingredient and is recognized globally. INNs have been designated by the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances since 1953. INNs are usually selected only for single, well-defined substances that can be unequivocally characterized by a chemical name or formula. The WHO does not assign INNs to substances that have a long history of medical use under well-established names (for example, morphine or codeine) or that have trivial chemical names (for example, acetic acid).

The WHO has published guidelines on the selection of INNs, setting out details of the application procedure and the principles that the WHO will follow when selecting an INN. INNs are selected following a request from the manufacturer or inventor of the pharmaceutical substance. The manufacturer must apply for an INN; the WHO does not select INNs on its own initiative. The applicant may suggest up to three possible names for the substance in question. The WHO’s expert committee considers the application and proposes an INN for the substance. That proposed INN will be published in *WHO Drug Information*, followed by a four-month period for objections (most often on the ground that the proposed name would infringe an existing trademark). If no objections are received, or if all filed objections are withdrawn or satisfactorily resolved, the proposed INN will become a recommended INN and will be adopted following its publication as a recommended INN in *WHO Drug Information*.

In some circumstances, despite an application from the manufacturer or inventor, the expert committee may decide not to propose an INN at all. This might occur if there is already a common name in general use for the substance in question and the selection of an INN could cause medication or prescription errors. The expert committee may also refuse to propose an INN when the general criteria for selection of an INN are not met—for example, if the product is a combination of two pharmaceutical substances, or if the substance cannot be fully characterized.

WHO guidelines explain that, wherever possible, the INN for a substance belonging to a group of related substances should reveal that relationship. Group relationship is shown by use of a common stem, and the guidelines contain at Annex 3 a list of common stems. The guidelines also acknowledge the difficulty of naming certain new types of pharmaceutical substances, including biological products. Annex 4 sets out the scheme that the WHO has adopted for naming such products. The WHO has adopted schemes for a large number of biological products, including erythropoietins, growth factors and hormones, hormone release stimulating peptides, interleukins, pituitary hormones, and monoclonal antibodies.

The fact that the relevant Annex does not contain a specific scheme for a particular type of protein does not mean that there is no INN or procedure for deriving one. There are a number of product classes to which the WHO’s general...
approach is applied—INNs are developed based on historic common names. In addition, for some product classes, names are developed in cooperation with other international bodies.

The WHO’s general approach for naming peptides and proteins is as follows:

- A stem is selected for the main compound (e.g., -poetin for erythropoietin derivatives and -cog for blood coagulation factors).
- Subgroups are designated by expanding the stem (e.g., -eptacog, -octacog).
- A random prefix is selected for compounds with differences in amino acid sequence.
- For glycosylated compounds with identical amino acid sequences, a Greek letter is selected as the second part of a two-word name to indicate different glycosylation patterns.

For example, erythropoietins that have the same amino acid sequence as human erythropoietin are called epoetin, together with a Greek letter to differentiate between compounds which vary in the glycosylation pattern (epoetin alfa, epoetin beta, etc.). If the erythropoietin has a different amino acid sequence from human erythropoietin, a random prefix will be used (e.g., darbepoetin alfa). The Greek letter prefixes are used exclusively to show differences in glycosylation, not differences in manufacturing process. Thus, two human erythropoietins would have the same INN so long as their glycosylation pattern could be shown to be identical, even if they were produced in different cell substrates. For example, the EC has approved Stada’s erythropoietin product, Silapo, a similar biological version of Eprex, with the INN epoetin zeta. As with the HX 575 products mentioned above, Silapo appears to differ from Eprex in its glycosylation patterns and the presence of O-glycan chains. However, its INN contains the different Greek suffix “-zeta” rather than “-alpha.”

F. European Proposals

During the legislative and administrative proceedings leading to the establishment of the regulatory framework for similar biological medicinal products in Europe,

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84 This scheme does not apply to insulin, primarily because insulin has been used for many years and predates the adoption of this naming scheme. For example, insulin that has the same amino acid sequence as naturally occurring human insulin is called insulin human, irrespective of whether it is manufactured by recombinant DNA technology or by enzymatic modification of porcine insulin. Insulins that have a different amino acid sequence are named insulin followed by another word (e.g., insulin glargine, insulin lispro).

85 The official INNs for interferons, as published in the WHO’s 11th Cumulative List of International Nonproprietary Names for Pharmaceutical Substances, are limited to interferon alfa, interferon beta and interferon gamma. In the early 1980s the Interferon Nomenclature Committee, a committee established jointly by the WHO, the U.S. National Institute for Health and the U.S. National Institute of Allergy and Infectious Diseases, issued recommendations on the naming of interferons. This committee recommended that sub-species of the interferon proteins be designated by the hyphenated addition of a number (e.g., interferon alfa-2). Drug nomenclature agencies have further qualified this number by an arbitrary letter to indicate variations in amino acid residues (e.g., interferon alfa-2a). Although these alphanumeric qualifications do not constitute distinct official INNs, they are recognized in United States Adopted Names and are used throughout the world as if they were part of the INN. For example, the EMEA website states that the INN of Viraferon® is interferon alfa-2b.

the EC’s Committee for Medicinal Products for Human Use (CHMP) recognized that such products may cause rare but serious side effects, including immunologically-mediated effects, that can only be detected through programs of post-market surveillance and testing. Effective postmarket surveillance will depend in part on mechanisms to identify the product that each patient receives, and one such mechanism is a requirement that each product bear a distinctive name.

The EC has proposed guidelines and legislation to address the issue of traceability with follow-on biological products that have the same INN as the reference product. The proposed new guidance states that marketing authorization holders and competent authorities should encourage reporters to provide the invented name of the product. The EC has also proposed new Article 101a of the Directive, which states that “… Member States shall ensure that any biological medicinal product prescribed and dispensed in their territory which is the subject of an adverse reaction report is identifiable.”

To comply with this new provision, Member States may need to require adverse reaction reports for biological medicinal products to distinguish between products by reference to the brand name and/or the manufacturer, rather than merely to use the INN.

There are a number of significant potential issues with these proposals. Not least of these is that manufacturers of biosimilar medicinal products are not required to give their products a brand or invented name. The implementation of a system requiring prescribing, dispensing, and safety reporting by brand name would also require Member States to make significant changes to their systems for the prescribing, dispensing, and reimbursement of medicines. This is because prescribing and dispensing practices are integral to such schemes.

For instance, in many countries physicians are encouraged, or even required to prescribe by INN, rather than brand name. Moreover, many Member States permit, or require, generic substitution, or do require records of the product actually dispensed or administered to patients.

Therefore, where different biological products use the same INN, patients may be switched back and forth against the wishes of, or without the knowledge of, their treating physicians. This not only interferes with the practice of medicine and may have significant health consequences for the patient, but also makes it difficult, if not impossible, for the reporting physician to know for certain which product a patient has used.

Therefore, whatever the EC recommends, physicians may simply be unable to prescribe by brand name without changes in their national laws and health service requirements. In any event, it is far from clear that the EC has the power to require such changes to national health service rules.

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89 In the UK, for example, the British National Formulary, an authoritative source on prescribing, states: “Where non-proprietary (generic) titles are given, they should be used in prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the health service.” BNF, 54 (2007) at page 1.

90 The European Communities have always made it clear that the pricing and reimbursement of medicines is a national matter that the Community does not have competence, or desire, to regulate (with the exception of the requirement that pricing and reimbursement decisions be made in a trans-
Putting aside whether the EC’s proposals will have the desired effect or are lawful, one must also bear in mind that they will only have the desired effect if other jurisdictions take the same approach. In essence, all other jurisdictions would need to ignore the WHO recommendations on the naming of erythropoietins with different glycosylation patterns, and also amend their prescribing, dispensing, reimbursement and reporting rules to require use of brand name. Moreover, this assumes that all manufacturers of similar biological medicinal products will choose to brand their products. A simpler and more effective measure would be to require that all marketing authorization applicants obtain a distinct INN for their product whenever WHO guidelines require that.

IV. Conclusion

There have been several opportunities over the past decade for countries to bring their safety reporting regulations into line with recognized international standards such as ICH. However, not everyone has implemented such standards consistently. The degree of association between a drug and an adverse event necessary to trigger a reporting obligation has been a difficult issue for FDA. FDA’s proposed definition of adverse reaction does not reflect the most common understanding of what constitutes a suspected adverse reaction, as presented in the ICH E2A guideline. If the FDA Proposed Rule requires that a causal relationship be regarded as existing simply because “the relationship cannot be ruled out” then the consequence would be that any adverse event occurring after drug administration should usually be treated as a suspected adverse reaction, given that a temporal relationship inevitably means that the role of the investigational product in the causation of an adverse event cannot be totally excluded.

In practice, this would mean that almost all adverse events would then be regarded as suspected adverse reactions, arguably negating any value in the distinction drawn between an adverse event and an adverse reaction.

These different interpretations can have adverse consequences for pharmaceutical companies marketing products in several jurisdictions as regulators can, and will, adopt different and inconsistent solutions to potential safety issues. To avoid such consequences, international standards such as ICH should be implemented consistently into national laws.

See, for example, Regulation (EC) No. 726/2004, Art. 1, which states:

The provisions of this Regulation shall not affect the powers of Member States’ authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions. In particular, Member States shall be free to choose from the particulars shown in the marketing authorisation those therapeutic indications and pack sizes which will be covered by their social security bodies.

Directive 2001/83/EC, Recital 33, also states:

The provisions dealing with the classification of medicinal products for the purpose of supply do not infringe the national social security arrangements for reimbursement or payment for medicinal products on prescription.

These subsidiarity principles have been confirmed by the European Court of Justice. For example, see Case 238/82 DUPIHAR (1984) E.C.R. 523.
The use of INNs for similar biological products is also of fundamental importance, as it presents potential safety issues that result from inevitable difficulties with the traceability of the products and the fact that the majority of physicians prescribe and report by INN. In some cases, national social security rules require or recommend prescription by INN and may require or recommend that products are dispensed by INN.

The EC considers that encouraging the prescribing and reporting of biological products by brand name should address this issue. Although such encouragement is praiseworthy, we do not think it goes far enough to ensure that the public is protected against the potential safety risks that may result from inappropriate application of INNs. Although many applicants choose to use an invented or brand name, they are not required to do so. Generic products in particular typically bear only the common name. Although the EC has the power to implement changes in Community safety reporting requirements to address concerns surrounding biosimilar medicinal products these will only work if they are applied throughout the European Economic Area. Further, effective pharmacovigilance requires global harmonization of nomenclature, standards, and definitions and we consider it unlikely that an approach relying on brand name reporting would be adopted internationally in the short term, because ICH safety reporting standards rely on the appropriate use of INNs.

Meaningful global pharmacovigilance requires global harmonization. Many prescribing, dispensing and pharmacovigilance systems are not adapted to deal safely with similar biological medicinal products unless they are allocated a distinct INN.