LEADING ARTICLE

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Current Requirements and Emerging Trends for Labelling as a Tool for Communicating Pharmacovigilance Findings

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Abstract

The labelling of prescription drugs is expected to ensure the safe use of medicines and effect changes in use if such changes are required by new safety information. However, withdrawal of drugs from the market and data about medication errors have demonstrated the limitations of labelling as a tool for risk management. Regulatory initiatives in many countries aim at increasing the usefulness and use of labelling by healthcare professionals and patients. These changes in regulations and guidelines, which parallel changes in the approach to premarketing risk assessment and pharmacovigilance, will result in a more relevant and extensive characterisation of a product's safety profile and better international labelling consistency. But despite improvements in the format of labelling in some countries, labelling overall continues to be bound to conventional layout and restricted in its ability to meet the heterogeneous needs of its intended audience. Technological developments such as electronic prescribing and the availability of electronic decision support systems can effectively implement compliance with labelled conditions of use and safety precautions in the prescription process. It will be one of the major challenges to make labelling easily available and suitable for use in such systems. This technology, bar coding of medicines, and preventive evaluation of labelling and packaging for clarity, readability and potential confusion can also help reduce medication errors.

Assessment of a product's risks for disclosure in labelling and as a basis for advice on safe use is one of the main deliverables of drug development and pharmacovigilance. Market withdrawals that occur within a few years after a product has first been approved have nourished concern about the limited amount of safety information available for new products at the time of initial marketing. Such withdrawals, as well as the frequency of medication errors in clinical practice, have also led to increased discussion about the limited effectiveness of labelling in controlling the use of medicines and in changing user behaviour when new risks are identified.

Numerous regulatory and industry initiatives to improve the effectiveness of labelling and its availability for physicians, pharmacists and patients have been recently implemented or are underway. These include the following.

- Proposals/initiatives of the US FDA to: change the format and content of prescription drug labelling in general and of the adverse reactions section in particular;[1,2] require expedited reporting for actual and potential medication errors;[3] require bar coding of prescription medicines and certain over-the-counter (OTC) products and;[4] refine the evaluation procedures for proposed product names and their potential to contribute to product confusion.[5]
- An electronic labelling distribution initiative of the association of the Pharmaceutical Research and Manufacturers of America (the PhRMA Paperless Labelling initiative[6]) and of the FDA (DailyMed initiative[7,8]).
- A review of the guidelines for the Summary of Product Characteristics (SPC) by European Union (EU) regulatory authorities,[9] and the implementation of an expedited review procedure for safety labelling variations at the level of the EU[10] and in some EU member states.
- New regulations on labelling content and format in Brazil.[11]
- New guidelines on the content and format for the Product Monograph in Canada.[12]
- Improvements to container labelling, revision of brand names prone to misrecognition, and plans for bar coding prescription medicines in Japan.[13,14]

At the same time, new technologies have become available that can increase the availability of labelling and its use in medical practice. These include the use of the internet as a tool to deliver and access labelling and, perhaps most importantly, electronic prescribing systems that can automatically connect to drug information databases and decision support systems.

This article reviews regulatory initiatives and trends related to safety labelling, and discusses the impact of new technologies on the effectiveness of labelling. Special emphasis is given to aspects that affect the suitability of labelling as a tool for pharmacovigilance and risk management, and for the prevention of medication errors.

1. Labelling Content

1.1 Adverse Reactions or Adverse Events

Adverse drug reactions are generally understood to be undesirable responses to a drug. However, a causal relationship between an observed type of event and a drug can usually not be established with certainty, and it is not necessary to have proof of a causal relationship in order to have a duty to warn. A reasonable possibility of a causal relationship[15] has, therefore, been defined as the minimum requirement for classifying an item as an adverse reaction for regulatory/labelling purposes.[15] This concept is reflected in the criteria for the inclusion of items in the 'undesirable effects' section of the EU SPC: "This section should provide comprehensive information on all adverse reactions attributed to the medicinal product with at least reasonable suspicion. Adverse events, without at least a suspected causal relationship, should not be listed in the SPC".[16]

It is noteworthy that the SPC guideline does not use an explicit definition of the term 'adverse reaction' to describe the criteria for listing items under 'Undesirable Effects'. The approach of the FDA is different. The current regulation uses a definition of the term adverse reaction to describe the content of the 'Adverse Reactions' section (see table I). In its proposed 'Requirements on Content and Format of Labelling for Human Prescription Drugs and Biologics'[1] (Proposed Labelling Rule) the FDA revises this definition to be consistent with a definition provided in the International Conference on Harmonisation (ICH) E2A guideline (see table I).

FDA states that it is making the change because the current definition has been interpreted to mean "that a reaction should be included merely if there is a temporal association, rather than a reasonable causal association".[1] According to the FDA, "this has resulted in the inclusion of information that is not meaningful to prescribers and which dilutes the usefulness of the clinically meaningful information", whereas "the revised definition would clarify that at least a reasonably plausible causal relationship must exist between a drug and a noxious and

Table I. Definitions of the term 'adverse reaction'

US: Current definition in 21 CFR 201.57
"An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."
US: Revised definition in Proposed Labelling Rule[1]
"An adverse reaction is a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response (i.e. the relationship cannot be ruled out)."
Definitions and Interpretations in ICH Guideline E2A: "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting"[15]
"II. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE A. Basic Terms 2. 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 products' means that 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, a well-accepted definition of an adverse drug reaction in the postmarketing setting is found in WHO Technical Report 498 [1972] and reads as follows: 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. III. STANDARDS FOR EXPEDITED REPORTING A. What Should be Reported? 1. Single Cases of Serious, Unexpected ADRs … All cases judged by either the reporting healthcare professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs. …. The expression 'reasonable causal relationship' is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship."

unintended response for the response to be included as an adverse reaction in the 'Adverse Reactions' section of labelling". [1]

In the description of the rationale for the change, the FDA has not discussed the effect of the text in parentheses in the revised definition, "(i.e. the relationship cannot be ruled out)", on the content of the 'Adverse Reactions' section. In fact, in its rationale the FDA uses a truncated version of the new definition that omits the wording in parentheses.

Interpreting a reasonable possibility of a causal relationship as the inability to rule out such a relationship does not provide a suitable criterion for inclusion of items in labelling under conditions where there is usually insufficient information for a satisfactory evaluation. Under such conditions, this interpretation could require the inclusion as adverse reactions of, for example, the vast majority of events from spontaneous postmarketing reporting, as well as clinical study events for which no proof of another cause is available. Such lists of reactions/events would be largely useless for healthcare professionals and patients in assessing the risk of use of a product, and in deciding if treatment with a product needs to be stopped in case of an event. It would also cause further international labelling disharmonisation. From a labelling viewpoint it would be more practical to interpret the concept of reasonable possibility/suspicion as meaning "that there are facts (evidence) or arguments to suggest a causal relationship".[15] This alternative interpretation is also found in the ICH E2A guideline[15] (see table I).

Important considerations on the level of evidence for listing an item as an adverse reaction can be found in the report of the Council for International Organizations of Medical Sciences (CIOMS) III/V working group.[17] While the report concludes that "it is not possible to specify exactly when an association becomes well established", it lists factors to be considered when weighing the evidence for a causal relationship. The working group also adopted the principle that new safety information should be included in labelling the sooner, i.e. with less evidence, the more relevant it is. This is expressed in the form of a list of criteria for lowering the threshold for inclusion: medical seriousness of the risk;

clinical utility of new information; availability of other treatments; the extent of use; and the fact that a product may commonly be used for relatively trivial conditions, for treatment of symptoms or for prevention.

When adhering to the above principles (i.e. not requiring proof of a causal relationship, requiring at least reasonable suspicion, and including an item the earlier the more relevant it is) and referring to these principles in the supporting rationale provided to regulatory authorities, companies will usually find acceptance of their labelling decision worldwide. Only rarely will regulatory authorities disagree and determine that, in their assessment, the item has not (yet) crossed the threshold for inclusion. Overall, for postmarketing additions to the list of adverse reactions, this approach allows companies to achieve a fairly consistent labelling outcome worldwide.

So far a similar degree of consistency cannot be achieved for the presentation of safety experience from clinical trials for new products or new uses. The US and Canadian regulatory authorities usually have preferred lists of adverse events while most European countries have traditionally requested lists of reactions. This difference in approach affects labelling worldwide since both North American and European labelling, or elements of it, are often used by companies as templates for submission of labelling in other markets.

The revised definition of the term 'adverse reaction' in the Proposed Labelling Rule and FDA's 'Draft Guidance on the Content and Format of the Adverse Reactions Section of Labelling for Human Prescription Drugs and Biologics'[2] (Draft AR Section Guidance) appear to indicate a change in the FDA's approach. The draft guidance states that items should be selected for presentation "based on factors such as frequency of reporting, whether the adverse reaction rate for drug exceeds the placebo rate, extent of dose-response, extent to which the adverse reaction is consistent with the pharmacology of the drug, timing of the reaction relative to time of drug exposure, and whether the adverse reaction is known to be caused by related drugs". This is not compatible with populating clinical study adverse experience tables with mere events, using reporting rate and, in some cases, clinical investigator causality assessment as the only criteria for inclusion. It is also not compatible with defining the inability to rule out a causal relationship as the sole criterion for labelling an item as adverse reaction.

A change-over to reaction lists for clinical study safety experience would be a significant step toward worldwide labelling consistency.

1.2 Frequency of Adverse Reactions

Lists of suspected adverse reactions with best estimates of their expected frequency are an essential element of labelling in countries such as the EU member states where full-disclosure patient information is required to inform the users about the risks involved in taking a medicine.

To generate the best possible information for patients, these estimates should reflect the portion of events that is attributable to the product and not include the 'background noise', which is often included in event reporting rates from clinical trials. Ideally, the excess rates of reported events compared with placebo are used as a starting point for frequency estimates. To accommodate for the low precision of such estimates, frequencies are typically not presented as exact percentages but in categories such as the ones proposed by EU guidelines,[16,18] in the new Canadian Product Monograph guideline,[12] and the CIOMS III/V guidelines.[17]

In US labelling, more common adverse events from clinical studies are typically presented in tables with event reporting rates for product, comparators and placebo, as available and appropriate. It is expected that healthcare professionals use these 'raw data' to estimate the likelihood of an adverse reaction. There is no indication that the FDA is changing this approach. So future US labelling might be characterised by lists of adverse reactions, with the frequency of more common reactions from clinical studies illustrated by event reporting rates. This approach may lead to apparent labelling inconsistencies if such event rates are presented out of context and a reaction is, for example, listed in the US in a 'most common' category (defined by a rate

cut-off of, e.g., 3%) but ranks in the EU under 'uncommon' (<1%) because of its low excess reporting rate over placebo.

1.3 Additional Safety Information

Current labelling regulations and guidelines for prescription medicines are rather unspecific and non-demanding with regard to information to be presented in the adverse reactions section over and above the listing of reactions and their frequencies. In contrast, the FDA's Draft AR Section Guidance[2] expresses very clear expectations about information to be provided. Based on this document, this section should include a discussion of the following:

- The dose response of reactions and a description of how it was investigated.
- The change of adverse reaction rates with continued use, and the emergence of reactions with long-term use.
- For clinically important reactions that are not addressed under 'warnings' and 'precautions': factors that may affect their rate or severity; required interventions; and their nature (if necessary to explain its clinical significance).
- Reliable information about observed differences in reaction rates in various demographic groups and disease subsets, and about the lack of observed differences for certain demographic groups and disease subsets where concerns about differences are greatest (e.g. in patients with renal or hepatic failure, patients receiving concomitant medications) – with a requirement to disclose and explain any absence of reliable information.
- Significant differences in the profile between different indications and formulations, respectively.

This list of topics is to be read in the light of the FDA's concept paper on Premarketing Risk Assessment,[19] which discusses the methodology and feasibility of the analyses necessary to address the points raised in the draft labelling guidance.

The new Canadian Product Monograph guideline provides a very similar list of items for discussion in the adverse reaction section.[12]

EU regulatory authorities have not released any more detailed requirements for the content of the 'undesirable effects' section of the SPC. The summary report of a working group of the heads of EU regulatory authorities on a European risk management strategy[20] discusses, however, the need for a 'Pharmacovigilance Specification' at the time of marketing authorisation – a document also proposed in the draft ICH guideline on Pharmacovigilance Planning (E2E).[21] The characterisation of known risks and areas for further evaluation described in such a Pharmacovigilance Specification can be expected to lead to a more detailed discussion of known risks and the absence of reliable safety information in labelling worldwide, consistent with the information required by the FDA's Draft AR Section Guidance.

2. Labelling Format and Delivery

2.1 Finding New Information

Labelling is living information and needs to be reviewed regularly for new information, particularly for new instructions for use (e.g. precautions). A review of US MedWatch reports showed that most drugs had one to six safety-related labelling updates between the annual printings of the Physicians' Desk Reference.[22]

Currently, labelling texts do not generally provide support for finding updated information. Labelling relies on other communication systems to get news out. Labelling changes of exceptional importance are brought to the attention of healthcare providers via 'Dear Healthcare Professional Letters' and/or other special communications such as publication in professional journals, on web sites and in other media. Some countries have systems in place to point out every safety labelling change to healthcare professionals. In Japan, for example, prescribers of a product are informed by companies about all safety changes and their rationale;[23] the US MedWatch system offers the option to subscribe to e-mail notifications of FDA-approved safety changes. In its Proposed Labelling Rule,[1] the FDA also announced plans to require highlighting of recent labelling changes in regular prescribing information texts. A similar proposal has been made for

European patient information leaflets by a joint working group of the European EMEA/CPMP with patients' organisations.[24] While such an approach has its obvious limitations, in a paper labelling system (inability to show changes that pre-date a rolling baseline version), it has great potential on an electronic platform where readers could scroll back in time to get a cumulative view of all changes since they last reviewed the document. The FDA's publishing of labelling histories on its Drugs@FDA web site,[25] or EMEA's posting of 'steps taken after authorisation' as an element of the European Public Assessment Report (EPAR)[26] may be seen as good first steps in this direction.

2.2 Readability

To ensure that labelling is reader-friendly and referred to as the primary source of medication information, its content and format must be easy to read and navigate. Current labelling structures generally work best when populated with limited information. Legibility, understandability, and navigability are the keys to readability. Even if very well written, the presentation of large amounts of information in the usual conservative labelling structure and layout will often reduce readability. This is not only a concern for patient leaflets, and full-disclosure EU patient leaflets in particular, but can also be a problem for HCP information texts. Criticism of their readability have both been voiced for the US prescribing information[1] and for the EU SPC.[27]

The FDA acknowledged these concerns in its Proposed Labelling Rule. The FDA suggests, among other changes, the addition of a table of contents, a reorganisation of the text structure to bring more relevant information forward, and the addition of a very brief 'highlights' section that is intended to show selected information of greatest importance for prescribers.[1] Industry has expressed concern that this 'highlights' section will be relied upon too much by healthcare professionals.[28]

Even when adhering to a one-document approach for prescribing information, there should be other, equally or even more effective means to lead readers to the most important information than excerpting. Information design techniques such as those proposed for patient labelling by the Communication Research Institute of Australia[29] have been successfully used to improve the readability of patient leaflets and could also be applied to prescribing information texts.

An even more fundamental solution for readability problems may lie in progressing from the traditional two-layered labelling systems – with one document for healthcare professionals and one for patients – to three-layered or even multi-layered models, either paper-based or using a combination of paper and electronic media. The new Canadian Monograph guidelines[12] establish three-layer labelling with patient information (focused on most important information), a traditional prescribing information level and a level of scientific information. In 1999 Kahn[30] discussing the implications of the use of MedDRA (Medical Dictionary for Regulatory Activities) for safety reporting and labelling, proposed the development of three-layered labelling, including a prescriber-friendly format and a separate MedDRA-based manufacturer/regulator level used to determine the expectedness of adverse events for regulatory reporting purposes. In 2003, Waller and Evans[27] published a proposal for a three-layered model for EU labelling, with the scientific level of information available via the internet.

Multi-layered labelling could even provide a platform for lists of clinical study events and their reporting rates in addition to lists of adverse reactions with their frequencies, and have room for a detailed discussion of the evidence for postmarketing additions to the list of reactions. It could allow the inclusion of high-granularity lists of reactions at the MedDRA 'Preferred Term' level in addition to lists using terminology flexibly, optimised for informing healthcare professionals. Such features would both increase the credibility of labelling with the medical community and make labelling (and core data sheets) a better reference for the pharmacovigilance dialogue between companies and regulatory authorities.

If labelling is not redesigned, other sources of product information will grow even more important

and reduce the effectiveness of labelling for risk management. These sources include pocket guides for healthcare professionals, medication books for patients, information offered on the internet and for electronic office, pharmacy and hospital information systems, which may not be fully consistent with labelling, and not current.

3. Labelling and Medication Errors

Labelling information design and labelling/packaging design have been identified both as factors causing or contributing to medication errors, and as instruments to reduce the likelihood of medication errors.

An analysis of 265 reports of medication errors performed in 2001 by the FDA attributed 20% of the reported errors to labels/labelling (including 1.9% attributable to the package insert and printed or electronic reference material). Three percent of the errors were attributed to packaging or design, and 13% to name confusion (including 10.3% to proprietary name confusion). The remaining 64% were attributed to other factors such as communication problems (19%) and human factors (42%, including knowledge or performance deficits, miscalculations, and transcription errors).[31]

Currently, there is no internationally accepted regulatory definition of the term medication error. The following definition of the US National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) has, however, been adopted by the European Foundation for the Advancement of Healthcare Practitioners, and has been used by the FDA in its proposed rule on Safety Reporting Requirements for Human Drug and Biological Products[3] (Proposed Safety Reporting Rule): "A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use".

This definition stresses that medication errors can occur at any level of the medication system. Medication errors do not only result from factors that are under the control of manufacturers, regulatory authorities, repackagers and distributors, such as similarities of product names, product/package/container design, and the clarity/readability of labels and instructions for use. Medication safety also depends on the quality of verbal and written communication between healthcare professionals, and between healthcare professionals and patients, and on staffing, training, equipment and the quality of, and compliance with, procedures. To what extent these factors contribute to or help to prevent medication errors and/or harm depends on the individual setting.

The complexity of situations and factors leading to specific medication errors is well illustrated by the medication error analyses published on the web site of the FDA's Division of Medication Errors and Technical Support.

Both (proactive) testing and the evaluation of spontaneous error reports can help identify the need for a redesign of a product's information, labelling and packaging to reduce the likelihood of medication errors.

In January 2004, the US Institute for Safe Medication Practices (ISMP) listed only seven countries with established specific medication error reporting programmes.[32] However, medication error information that may indicate a chance or need for labelling/packaging improvements may also be obtained through traditional adverse event reporting programmes. In its Proposed Safety Reporting Rule, the FDA reports that it receives approximately 3000 reports of medication errors annually through regular adverse event reporting programs. The FDA remarks that event reports in most cases do not, or not explicitly, identify associated medication errors. Therefore, the FDA sees a need to ask pharmaceutical companies to report both 'actual' and 'potential' medication errors as part of their postmarketing safety reporting obligations.[3]

Since medication errors are preventable, the FDA proposes that they be subject to expedited reporting. The requirements would, however, only cover domestic (US) error reports and appear to be limited to reports related to marketed products.

The FDA's main criterion of differentiation between actual and potential errors is the existence of an identifiable patient who is, or would have been, affected by the error. A potential medication error would be defined as an "individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a patient". This definition would oblige companies to report only those potential errors that are related to factors under their and/or the FDA's control.

For both error types, a full data set would be required (with the exception of data not asked for by definition, i.e. existence of a suspected adverse reaction or of an identifiable patient, respectively). If this is not available for initial reporting, an active query would need to be initiated to complete the data set for follow-up reports.

A labelling-related question that these requirements raise is about the basis on which erroneous use would be defined if the original notification by a healthcare professional or patient does not explicitly classify an event as associated with an error, but describes a use that does not conform with approved labelling. In this case, since an important characteristic of an error is its unintendedness, assumptions would need to be made about the intentions of a medication user. When categorising such cases, companies might be bound to assume that the use of the product was always intended to be compliant with approved labelling, while its labelledness is not necessarily a binding condition for actual clinical use. In this context, it is interesting to note that the NCC MERP definition of medication errors does not even include the concept of unintendedness.

The complexities and problems associated with medication error reporting requirements should be discussed in the light of available alternative or additional approaches to identify options for the improvement of labelling/packaging, i.e. testing of critical elements of labels and labelling (e.g. dosage and administration sections) – an approach chosen, for example, for patient labelling in the EU and in Australia. Other measures to reduce the likelihood of medication errors should also be taken into account, including differentiating colour schemes for packs and labels to reduce confusion between different strengths and dosage forms; the use of pharmacy labels even on patient packs to identify the patient, the indication and prescribed dosage; a more intensive review of product names for potential confusion before approval; bar coding; and the use of electronic prescribing in conjunction with electronic patient records and decision support systems.

The implementation of such measures should allow medication error reporting requirements to focus on events that are explicitly classified by healthcare professionals or patients/consumers as errors or potential causes for error. In the presence of such measures, there may also be no need to require expedited reporting for all actual and potential errors.

4. New Technologies

Paper-based labelling and compendia, web publishing and electronic distribution of labelling documents constitute 'pull systems' requiring an active step to access labelling and, therefore, unable to guarantee attention to safety information. This important weakness of labelling as a risk-management tool can only be overcome by forcing labelling information to be acknowledged during the prescription process. This can be achieved by more conventional administrative measures like those listed by the FDA in its concept paper on risk-management programmes[33] or, at least partially, by utilising electronic prescribing technology. This technology, in conjunction with electronic patient records, has the potential to greatly improve the effectiveness of labelling.

Many of the current electronic prescribing systems include, or can connect to, decision support modules that can compare patient data against information in a drug information database to identify inappropriate dosing, the presence of contraindica-

tions, the potential for interactions, etc.[34] In such decision support systems, product information does not (only) reside in the form of conventional text but as 'computer readable' bits of information. An example of how information is represented in a decision support system can be found on the web site of the German Institute of Medical Documentation and Information.[35]

The use of electronic prescribing systems – with various levels of sophistication – is rapidly increasing in physician offices, pharmacies and hospitals. This technology is even available for wireless handheld devices that can be networked with office systems. The use of portable patient records residing on, or accessible through, 'patient cards' (chip-equipped plastic cards the size of a credit card) can offer the opportunity for automated medication safety checks in any pharmacy or at any other point of care.

The significance of such developments for labelling and its potential role in risk management is 3-fold. First, these technologies have the potential to establish a 'push system', incorporating labelled conditions of use and safety advice in the prescription process without requiring an unrealistic level of attention by time-pressured healthcare professionals. Secondly, such systems can, or will be able to, provide many of the functions and features necessary for effective risk management: the capability for automatic notification of both patients and healthcare professionals about new information to be reviewed, verification of the availability of laboratory and other monitoring results as a pre-condition for prescription or continued prescription, and much more. Electronic prescribing systems also help to reduce medication errors.[36,37] Thirdly, the reference drug information currently used by such systems for safety checks is not necessarily original labelling. Labelling may be only one of many sources for this type of drug information.

Pharmaceutical companies and regulatory authorities must be interested in a rapid and complete uptake of new safety labelling information in these systems. Otherwise, labelling will loose even more of its influence on the usage of medicines. The FDA's DailyMed initiative[7,8] appears to lay the conceptual and technical foundation for the necessary link between original labelling and decision support systems in the US. Similar technology-based or conventional regulatory efforts may be expected in other countries.

5. Conclusions

Regulatory initiatives in many countries will increase the usefulness and use of labelling by healthcare professionals and patients. These initiatives parallel changes in the approach to pre-market risk assessment and pharmacovigilance, and appear to aim at a more relevant and extensive characterisation of a product's safety profile, at an earlier point in a product's life cycle. The possible change-over to lists of adverse reactions to describe clinical study experience in the US would help to improve international labelling consistency. But despite better delivery of labelling through use of electronic media and improvements of labelling format in some countries, labelling overall continues to be bound to conventional layout and restricted in its ability to meet the heterogeneous needs of its intended audience. This limits its attractiveness when compared with alternative sources of product information. Perhaps most importantly, official labelling systems have not yet been effectively linked to electronic prescribing and clinical decision support technology. Making use of these technological developments could greatly improve the effectiveness of labelling for risk management and in reducing medication errors.

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References

1. US Food and Drug Administration. Requirements on content and format of labelling for human prescription drugs and biologics; requirements for prescription drug product labels; proposed rule 65. Fed Regist 2000 Dec 22; 247: 81082-131

2. US Food and Drug Administration. Draft guidance for industry: content and format of the adverse reactions section of labelling for human prescription drugs and biologics [online]. May 2000. Available from URL: http://www.fda.gov/cder/guidance/1888dft.pdf [Accessed 2004 Feb 14]
3. US Food and Drug Administration. Safety reporting requirements for human drug and biological products; proposed rule 68. Fed Regist 2003 Mar 14; 50: 12405-97
4. US Food and Drug Administration. Bar code label requirements for human drug products and biological products; final rule 69. Fed Reg 2004 Feb 26; 38: 9119-71
5. US Food and Drug Administration. Evaluating drug names for similarities: methods and approaches [online]. Public Meeting June 26, 2003. Meeting transcript and presentations available from URL: http://www.fda.gov/cder/meeting/drugNaming.htm [Accessed 2004 Feb 15]
6. PhRMA Paperless Labelling Task Force. User requirements for paperless labelling [online]. 2000 Mar 17. Available from URL: http://srpub.phrma.org/reports/03.17.00.user.reqs.pdf [Accessed 2004 Feb 15]
7. Levin R. DailyMed Initiative: enhancing patient safety through accessible medication information [online]. Presentation at DIA Electronic Document Management Plenary Session, February 2003. Available from URL: http://www.fda.gov/cder/regulatory/ersr/2003_02_13_ dailymed/2003_02_13_dailymed.PPT [Accessed 2004 Feb 14]
8. US Food and Drug Administration. The Food and Drug Administration's Strategic Action Plan: protecting and advancing America's health: responding to new challenges and opportunities [online]. August 2003. Available from URL: http://www.fda.gov/oc/mcclellan/strategic.html#healthcare [Accessed 2004 Feb 14]
9. European Agency for the Evaluation of Medicinal Products. Work programme for the European Agency for the evaluation of medicinal products 2004 [online]. Available from URL: http://www.emea.eu.int/pdfs/general/direct/emeawp/005803en. pdf [Accessed 2004 Feb 13]
10. European Commission Directorate General III. Notice to applicants, Vol. 2A. Procedures for marketing authorisation [online]. Chap. 5. Variations. February 2004. Available from URL: http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm [Accessed 2004 Feb 14]
11. National Health Surveillance Agency, Brazil. Resolução - RDC nº 140, de 29 de maio de 2003 [online]. Available from URL: http://www.anvisa.gov.br/legis/resol/2003/rdc/140_03rdc.htm [Accessed 2004 Feb 15]
12. Minister of Health, Canada. Guidance for industry: product monograph [online]. Available from URL: http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/product_monograph_e.html [Accessed 2004 Feb 15]
13. Japan Pharmaceutical Manufacturers Association. Pharmaceutical industry action to prevent medical accidents [online]. Available from URL: http://www.jpma.or.jp/12english/topics/topics030629_6.html [Accessed 2004 Feb 14]
14. Japan. Bar codes to stop medicine errors [online]. Medical News Today 2004 Jan 27. Available from URL: http://www.medicalnewstoday.com/index.php?.newsid = 5549 [Accessed 2004 Feb 14]
15. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonized tripartite guideline: clinical safety data management: definitions and standards for expedited reporting – E2A. October 1994 [online]. Available from URL: http://www.ich.org/MediaServer.jser?.@_ID=436&@_MODE=GLB [Accessed 2004 Feb 14]
16. European Commission Enterprise Directorate General. Notice to Applicants, Volume 2C - regulatory guidelines [online]. Guideline on Summary of Product Characteristics. December 1999. Available from URL: http://pharmacos.eudra.org/F2/eudralex/vol-2/C/SPCGuidRev0-Dec99.pdf [Accessed 2004 Feb 14]
17. Council for International Organizations of Medical Sciences. Guidelines for preparing core clinical-safety information on drugs. 2nd ed. Report of CIOMS Working Groups III and V. Geneva: Council for International Organizations of Medical Sciences, 1999
18. European Commission Directorate General III. Notice to applicants. Vol. 2C. Regulatory guidelines: guideline on the readability of the label and package leaflet of medicinal product for human use [online]. September 1998. Available from URL: http://pharmacos.eudra.org/F2/eudralex/vol-2/C/gl981002.pdf [Accessed 2004 Feb 14]
19. US Food and Drug Administration. Concept paper: premarketing risk assessment [online]. March 2003. Available from URL: http://www.fda.gov/cder/meeting/riskManageI.htm [Accessed 2004 Feb 14]
20. Heads of Agencies Ad Hoc Working Group. Establishing a European risk management strategy: summary report of the heads of agencies ad hoc working group [online]. Available from URL: http://heads.medagencies.org/heads/docs/summary.pdf [Accessed 2004 Feb 14]
21. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Draft consensus guideline: pharmacovigilance planning (PVP) – E2E [online]. Available from URL: http://www.ich.org/MediaServer.jser?.@_ID=1195&@_MODE=GLB [Accessed 2004 Feb 14]
22. Goldman SA. Letter to the editor. JAMA 2002; 288 (8): 956-7
23. Japan Pharmaceutical Manufacturers Association. Pharmaceutical administration and regulations in Japan. March 2003 [online]. Available from URL: http://www.jpma.or.jp/12english/parj/index. [Accessed 2004 Feb 14]
24. EMEA. EMEA/CPMP Working Group with patient Organizations. Outcome of discussions, recommendations and proposals for action [online]. London, Apr 24, 2004. Doc. ref. EMEA/CPMP/5819/04/Final Available from URL: http://www.emea.eu.int/pdfs/human/patientgroups/581904.pdf [Accessed 2004 Apr 30]
25. Drugs@FDA web site [online]. Available at URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ [Accessed 2004 Feb 14]
26. European Public Assessment Report (EPAR) for products [online]. Available from URL: http://www.emea.eu.int/index/indexh1.htm [Accessed 2004 Feb 14]
27. Waller PC, Evans SJW. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003; 12: 17-29
28. Pharmaceutical Research and Manufacturers of America. Comments of the pharmaceutical research and manufacturers of America on the food and drug administration's proposed rule on requirements on content and format of labelling for human prescription drugs and biologics; requirements for prescription drug product labels. June 2001 [online]. Available from URL: http://srpub.phrma.org/fda.responses.html [Accessed 2004 Feb 14]

29. Sless D, Wiseman R. Writing about medicines for people. 2nd ed. Canberra: Pharmaceutical Benefits Branch, Department of Health and family Services, 1997
30. Kahn SN. Can MedDRA be used for labelling? Should it? Presented at the Drug Information Association (DIA) Annual Meeting, Jun 1999, Baltimore (MD)
31. Thomas MR, Holquist C, Phillips J. Med error reports to FDA show a mixed bag. FDA Safety Page [online]. Drug Topics 2001 Oct 1; 145 (19): 23-4. Available from URL: http://www.fda.gov/cder/drµg/MedErrors/reports.htm [Accessed 2004 Feb 15]
32. Institute for Safe Medication Practices. International Medication Error Reporting Programs [online]. Available from URL: http://www.ismp.org/Pages/mederr_intl.html#errlist [Accessed 2004 Feb 15]
33. US Food and Drug Administration. Concept paper: risk management programs [online]. March 2003. Available from URL: http://www.fda.gov/cder/meeting/riskManageII.htm [Accessed 2004 Feb 14]
34. Buckley M. Improving drug prescribing practices in the outpatient setting: a market analysis. California HealthCare Foundation [online]. October 2002. Available from URL: http://www.chcf.org/documents/ihealth/ImprovingDrugPrescribing.pdf [Accessed 2004 Feb 14]
35. ABDA Interactions Data Base - Datasheet. German Institute of Medical Documentation and Information [online]. Available from URL: http://www.dimdi.de/de/db/dbinfo/dbmemo/ai00ger.html#datenfelder [Accessed 2004 Feb 14]
36. Oren E, Shaffer ER, Guglielmo J. Impact of emerging technologies on medication errors and adverse drug events. Am J Health Syst Pharm 2003; 60 (14): 1447-58
37. Covert-Kimmel K, Sensmeier J. A White paper: technological approach to enhancing patient safety. healthcare Information Management and Systems Society 2002 [online]. Available from URL: http://www.himss.org/content/files/whitepapers/patient_safety.pdf [Accessed 2004 Apr 30]

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