Unit-dose packaging of pharmaceutical products: comments of the International Network of Safe Medication Practice Centres on French Health Products Safety Agency specifications draft.

Committed to preventing medication errors and to contributing to safer care, the International Network of Safe Medication Practice Centres (INSMPC) aims to achieve the essential objectives stated in the "*Salamanca Declaration to promote safe medication practices globally*", and to encourage and further the development of safe medication practice centres in all countries and to facilitate cooperation amongst them (1).

The prevention of medication errors related to medication labelling and packaging requires both pre- and post-marketing strategies and involves drug regulatory agencies, pharmaceutical manufacturers, medication error reporting programmes, health care practitioners and patients.

Pre-marketing strategies should be based on human factor principles, in order to ensure complete, correct, and unambiguous identification and safe use, and should provide for assessment/evaluation and user testing for labelling and packaging safety for pharmaceutical products.

Post-marketing strategies should aim at minimising errors occurring with medicines that are already on the market and comprise the change of labelling and packaging prone to errors and the implementation of specific practices that prevent errors that might occur during storage, preparation, dispensing and administration.

On the basis of these principles, the International Network of Safe Medication Practice Centres makes the following comments on French specifications regarding the unit-dose packaging of pharmaceutical products, welcoming this step as it will contribute to improving patient safety (2).

Key points welcomed by the INSMPC

The International Network of Safe Medication Practice Centres, on behalf of its European members particularly, is pleased with the introduction of this guideline focused on improving medication safety.

It heralds not only an increased awareness of medication safety on the part of the French Drug Agency (AFSSAPS) and a swift application of several recommendations from the report of the Council of Europe just a few months after its dissemination (3), but also demonstrates the willingness of the AFSSAPS to promote medication error prevention as it is related to packaging of pharmaceutical products, a step which could serve as a point of reference at the European level, inspiring other countries to follow the lead.

Strong support from AFSSAPS to unit dose drug dispensing systems. By supporting the use of unit-dose packaging, the AFSSAPS contributes to the development of a unit-dose based medication distribution and control system. This is a positive step since the use of unit-dose dispensing has been shown to result in the lowest rates of medication errors (4,5,6). In addition the AFSSAPS provides strong support for health care institutions as they strive to comply with current French regulatory and accreditation standards regarding the provision of medicines to individual patients.

Reduction of the burden of unnecessary repackaging of pharmaceutical products. Direct production of unit-dose packaging by the pharmaceutical companies will decrease the workload and economic burden of hospital pharmacies related to repackaging of pharmaceutical products. This will allow pharmacists more time to provide pharmaceutical care and to prepare unit-of-use individualized doses of high-risk products for patient administration (injectables in particular).

The INSMPC especially welcomes the initiative of pharmaceutical companies to develop unit-dose packaging for normally split doses, a frequent source of dosage and product error (2§IV.3, 2§VIII.3).

Working towards unambiguous labelling identification of each dose to be administered. The stress given to legibility of unit–dose packing is welcome as is the mention of the international non-proprietary name (INN) allowing a redundancy check of the identity of each dose to be administered (2§V.2).

Machine readable codes on medicinal products permit accurate identification during the supply chain and at the stages of storage, dispensing, preparing and administration. Patient safety is improved because this technology allows real-time confirmation of patient identification, medication, dose, time and route of administration and offers a unique opportunity to implement safety checks before the administration of the medicine (3). Even if the "UCD identification code", specifically describing the unit-dose via a data matrix bar code, is not exactly the GS1 Global Trade Identification Number (GTIN), and is only used in the French market (2§VII), it does serve to achieve the standards recommended by the Council of Europe report (3).

Facilitating changes by reducing administrative burden. The AFSSAPS agenda sets an ambitious schedule: as soon as possible for dry oral pharmaceutical forms; 2010 for other pharmaceutical forms. Giving details to pharmaceutical companies regarding the different types of marketing authorisation amendments and variations will be helpful for the sake of reducing the time needed to bring up-to-date unit-dose packaging to the market and to health care settings in a timely manner.

However, unit-dose packaging is not yet mandatory for supplying health care settings, a condition beyond the scope of AFSSAPS competencies, neither than justification by pharmaceutical companies continuing to provide non unit-dose packaged pharmaceutical products to health care settings.

Some additional tracks to reinforce the AFSSAPS initiative

The INSMPC members would consider it beneficial to include some other key elements of the report of the Council of Europe in these guidelines that have not been taken into account. By adopting them, the AFSSAPS would still reinforce the safety expected from the labelling and packaging of pharmaceutical products.

Assessing labelling and packaging related risks. Ensuring safe medication use requires proactive strategies, and such strategies should be presented and promoted in this document.

Pharmaceutical companies should be required to systematically perform pre-marketing evaluations and user testing that take into account every possible way in which medications may be handled and used. Every stage of the medication use system, such as storage, dispensing, preparation and administration, must be considered to ensure safety of labelling and packaging.

Drug regulatory authorities should review the information provided by pharmaceutical manufacturers. Such a systematic risk assessment would also be done by purchasing groups and hospitals (3: see Appendix 6, 7). This type of risk assessment should be carried out with special attention to injectables and high-risk medications.

Beyond hospitals: promoting unit-dose and ready-to-use packaging for primary care. The current specifications for unit-dose packaging are targeted to health care institutions. Let us not forget, however, they are equally relevant to the whole of the medication use system, including primary care, because of the increased acceptance and prevalence of home-based care, and the provision of medication by community pharmacies to nursing homes, long term care and assisted living facilities.

Therefore, the requirement to dispense pharmaceutical products in unit-dose, ready-to-use packages should be broadened to include community pharmacies, enabling community pharmacists to dispense medications meeting specific patient needs, as is the case with the Australian Dose Administration Aids (DAA) (8). Nonetheless, in terms of patient safety, unit-of use should not be considered the only packaging standard for ambulatory care, as long as the medication is provided with a dispensing label, following the recommendation of the report of the Council of Europe (3).

Beyond oral dry pharmaceutical forms: do not miss high risk pharmaceutical forms. AFSSAPS recommendations for unit-dose packaging primarily target dry oral pharmaceutical forms, such as tablets, capsules, etc., which are the easiest to package in unit-dose containers. In contrast, other pharmaceutical forms are all too frequently packaged in multidose containers.

Ranking of high-risk medications in the priority levels based on their potential for medication errors. On page 6 the highest priority is given to substances that are considered to have a narrow therapeutic margin or classified as toxic (in France). However, it makes more sense from a safety standpoint to give number 1 priority to provide high-risk medications clear, unmistakable labels and unit-dose packaging in every case. The list of high-risk medications should include all

medications given via epidural administration, which were not mentioned in the guidelines.

Missing injectable forms. The development of unit-dose, ready-to-use injectable packaging (either for direct injection, or for use within a medical device, such as an infusion pumps, or an electrical syringe) would protect patients from medication errors with injectables, which typically carry much higher risks than oral pharmaceutical forms.

Beyond complete implementation: uncovered needs should be taken in account

Continuing need for repackaging individual doses. The objective assigned by AFSSAPS to completely avoid repackaging of pharmaceutical products in hospital settings (§ IV), seems unrealistic. There will always remain cases where drugs are not provided by the pharmaceutical companies in unit-dose packages. For these situations and for extemporaneous preparation at the time of administration, good practices recommendations and checklists should be provided to the dispensing pharmacists.

In addition, pharmacopeias (EDQM, as well as the USP) should establish and update the definitions and the technical safety standards for unit-dose packaging of each pharmaceutical form, whether they are manufactured by the pharmaceutical companies or prepared by pharmacists.

Continuing need for bulk packaging. The AFSSAPS guideline seeks to "*prohibit presentations in multidose containers for all oral solid pharmaceutical products (such as tablets, capsules and soft capsules, etc.) that can be packaged in blisters*" (2§IV.1). This elimination of bulk packaging will do away with automated unit-dose repackaging which includes the patient name administration details (called "dispensing label") by pharmacies that incorporate robots. Automated dispensing generates additional safety for patients and should be encouraged. The guidelines should authorize pharmaceutical companies to sell bulk packaging, though only to pharmacies that use dispensing robots, rather than asking these pharmacies to create additional risks of error and of deterioration of manufactured pharmaceutical forms by systematically opening blisters.

Beyond complete implementation: technical requirements for safety

Minimum requirements for stating dosage strength on the label. Strength of single dose injectable and single liquid preparations should be expressed as the total quantity of active ingredient per total volume. If the volume in the container is greater than 1 millilitre, the concentration, as amount of the active ingredient per one millilitre, should also be indicated immediately below, either in parenthesis or in less prominent lettering (3).

In terms of safety, it is also important not to use percentages, except in certain specifically justified cases in which the percentage is incorporated in the name of the medicine (for example, in topic products).

Minimum requirements for blister packs. Based on a British research report on blister packs, the report of the Council of Europe recommends to use coloured, non-reflective foils to enhance the readability of the information presented and to allow correct identification of the medicine (3,9). Blister foils should be printed with a sufficiently large, legible, bold or semi-bold sans serif fonts, in order to ensure maximum legibility of the information. Text colours should be chosen carefully in order to contrast text from foil background taking into account that foils are usually reflecting. The text colour should be different for every dosage strength.

Even if colour coding appears as an obvious solution to many authors and professional organisations, there is no clear evidence on the impact of coloured labels in reducing medication errors. Moreover, "blind" trust in colour labels may add new risks of medication errors. Therefore, colour coding should be used only after testing by practitioners (3).

Error-prone devices for oral liquid multi-dose forms. Regarding the proposal of specific measuring and administration devices for oral liquid multi-dose forms, medication error specialists consider that they still threaten patient safety, particularly with regard to the possibility of overdose errors or product error, even when correctly labelled with the brand name of the original pharmaceutical product. If unit-dose packaging is not feasible, then the use of oral syringes specifically prepared by pharmacists should be encouraged. In addition, researchers should consider all possible device failures that could result in improper administration when developing a medicinal product to be administered or delivered by a device (3).

References :

1- International Network of Safe Medication Practice Centres (INSMPC) "Salamanca Declaration to promote safe medication practices globally" November 2006
http://www.intmedsafe.net/SalamancaDeclarationINSMPC.pdf
2- French Health Products Safety Agency (AFSSAPS) "Specification for good practices relating to the unit-dose packaging of pharmaceutical products intended for health-care establishments in particular" 16 August 2007
http://agmed.sante.gouv.fr/htm/3/enq_public/cahier-des-charges-conditionnement-unitaire-def-eng.pdf
3- Council of Europe Expert Group on Safe Medication Practices "Creation of a better medication safety culture in Europe: Building up safe medication practices" Preliminarily version available as from 19 March 2007: 257 pages. http://www.coe.int/t/e/social_cohesion/soc-sp/Medication%20safety%20culture%20report%20E.pdf
4- American Society of Hospital Pharmacists. ASHP statement on unit dose drug distribution. Am J Hosp Pharm 1975; 32(8):835.
5- Kohn LT, Corrigan JM, Donaldson MS. (Ed.) To err is human - Building a safer health system. Report of the Institute of Medicine. Nat. Academy Press 1999; 182-201.
6- National Quality Forum Safe Practices for Better Healthcare. A consensus report. The National Quality Forum, Washington, DC, NQFCR-05-03, May 2003; 53-58.
7- UK National Patient Safety Agency "Patient safety alert 20: Promoting safer use of injectable medicines" 28 March 2007 http://www.npsa.nhs.uk/health/display?contentId=5755
8- Australian Pharmaceutical Advisory Council (APAC) "Guiding Principle 3 - Dose Administration Aids" In: "Guiding principles for medication management in the community" July 2006
http://www.health.gov.au/internet/wcms/publishing.nsf/Content/nmp-guide-medmgt-jul06-contents~nmp-guide-medmgt-jul06-guidepr3
9- NHS National Patient Safety Agency and the Helen Hamlym Research Centre "Information design for patient safety. Design guidance for packaging prescription medicines: secondary packaging (all types) and primary packaging (blister packs only)" London 2007; 74 pages.
http://www.npsa.nhs.uk/site/media/documents/2858_NPSA_Info_design_second_edition.pdf