Packaging too often ill-suited to dose prepararation

"Dose preparation" means that a patient's doses of medication are prepared in advance and sorted according to their order of administration. It involves removing the drugs from their original packaging, and sometimes repackaging them in a container other than their authorised packaging (**a**). The process can be manual, where doses are inserted into the compartments of a pill organiser for example, or automated, where a machine is used to repackage individual doses into relabelled transparent pouches. It is mainly used for oral solid forms (tablets, capsules), but some automated systems can repackage a variety of pharmaceutical forms, including liquids (1-4).

The health professionals involved in dose preparation are hospital pharmacists and nurses, nurses who care for dependent patients in the community or in residential care, and community pharmacists who prepare treatments for care homes (1-4). Drugs may also be prepared in this way by patients themselves, or their carers.

All health professionals, regardless of whether they perform dose preparation, should be aware of its risks and limitations.

Dose preparation is not suitable in all cases. Given the uncertainties surrounding dose preparation (see below), the first question to address is which patients may benefit from this practice despite the risks. This entails verifying that the pharmaceutical form and the drug concerned are suitable for dose preparation, estimating the drug's shelf life once it is removed from its original packaging, and ruling out dosing schedules that are conditional or variable (e.g. "as needed") and therefore incompatible with advance preparation (1,3). Most drugs are taken every day. With those that are not, such as once-weekly *methotrexate*, the consequences of mistaking them for a daily treatment when preparing a weekly pill organiser could potentially be very serious.

The dangers of non-unit-dose blister packs. In the early 1980s, hospital pharmacists in France spearheaded a call for drug packaging that would enable safe, reliable dose preparation for individual patients, rather than an entire ward (5,6). It is impossible to reliably identify a drug when most are not available in unit-dose packs and so many tablets and capsules look alike. Our drug packaging analyses in the intervening 30-odd years show that most products are not marketed in unit-dose packaging. This has led some health professionals in the community, hospitals and nursing homes to remove drugs from their original packaging and repackage and relabel them in a unit-dose format, and to automate this process.

Removal of drugs from their original packaging: identification and stability issues. The introduction of dose preparation raises several issues (1-3,7). What is the drug's shelf life once removed from its original packaging? How can this shelf life be determined? Are some substances or pharmaceutical forms incompatible with dose preparation? What container should be used when repackaging them? What information should be included on the new label? How many days' worth of treatment can be prepared in advance? Which hygiene rules should be followed? Guidelines exist, but little evaluation has been conducted (1-3). Another issue, beyond the scope of this article, concerns liability if an error occurs.

When drugs are placed in a pill organiser (or relabelled pouches), the new container must offer the same security as the original packaging, by ensuring that the drugs remain identifiable, protected and traceable right up until they are administered to the patient. Additional checks are required for any information added to the new label that was not present on the manufacturer's packaging, such as the patient's name and the time at which the drug should be taken.

Once tablets and capsules are removed from their packaging, exposure to humidity, heat, light and dust may reduce the quantity of active ingredient they contain and generate degradation products, possibly resulting in toxicity or loss of efficacy (2-4). Degradation is not always apparent. Some oral forms are particularly friable or sensitive to humidity, such as effervescent tablets, lyophilisates and orodispersible tablets.

The shelf life of drugs after removal from their original packaging is not generally stated in the summaries of product characteristics (SPCs) or patient leaflets. When questioned about this, the ANSM confirmed that pharmaceutical companies are only required to provide data on the storage conditions of their drugs in their original packaging. According to the European Pharmacopoeia, health authorities should encourage pharmaceutical companies to conduct stability studies on drugs without their immediate packaging. But when such data are not available, drugs should be kept for the shortest possible time outside their original packaging (1). A guideline issued by a French Regional Health Agency recommends preparing no more than 7 days' worth of treatment in advance (2). Other sources recommend a maximum of 10 days to 180 days, depending on the conditions (3,7). These different recommendations reflect the fact that accurate evaluations are lacking.

Risk of cross-contamination. Cross-contamination occurs when particles from unpackaged drugs are deposited along the pathway they take through an automated dose preparation system (hoppers and chutes) before reaching their pouch, and are then transferred onto other drugs that subsequently pass through the system (2). This can also happen with multi-patient pill organisers. Cross-contamination with cytotoxic drugs is particularly dangerous, but contamination with other drugs, such as psychoactive agents, hormones, antibiotics or antivirals can also cause problems, not to mention tablets and capsules being contaminated with potential allergens. Thorough cleaning procedures for automated dose preparation equipment, which should also be applied to pill organisers, and protective measures for operators are recommended (2-4).

Additional information for patients and carers. Patients who receive drugs through dose preparation systems

require additional information, such as how to use their pill organiser or explanations about the information on relabelled drugs. A general drawback of repackaging is that the drug becomes separated from the patient leaflet, which means that the information it contains is no longer available at the time and place it is most needed. It is advisable to make sure that such patients or their carers have the information they require (8).

a- *Both removing a drug from its primary packaging (blister, bottle) and repackaging it in a transparent pouch with a new label constitute off-label use because, unlike reconstitution of an oral or injectable suspension for example, neither procedure is described in the summary of product characteristics or was intended when the drug was authorised. It is sometimes possible to repackage a drug without removing its immediate packaging, for example by placing a detached portion of a blister pack in a bag.*

1- Council of Europe-EDQM "Automated dose dispensing (AAD). Guideline on best practice for the AAD process, and care and safety of patients" 2018: 40 pages.
2- ARS Provence-Alpes-Côte d'Azur "Guide pour la préparation des doses à administrer (PDA) en Ehpad et autres établissements médico-sociaux" 2017: 15 pages.
3- Lagrange F "Recommandations de bonnes pratiques en pharmacie automatisée: préparation des doses à administrer des formes orales sèches" *Le Pharmacien hospitalier et clinicien* 2015; (50): 448-455.
4- Pharma Système Qualité "État des lieux de la PDA: valeur ajoutée de la certification ISO 9001 QMS pharma" 1 May 2017: 44 pages.
5- Schmitt E "La présentation unitaire des médicaments destinés aux établissements hospitaliers. Cahier des charges, aspects techniques, septembre 1984" *Le Pharmacien hospitalier* 1984; (79): 5 pages.
6- "Circulaire n° 666 du 30 janvier 1986 relative à la mise en application des pratiques de bonne dispensation des médicaments en milieu hospitalier" 30 January 1986: 8 pages.
7- FDA "Expiration dating of unit-dose repackaged solid oral form drug products: compliance policy guide" August 2017: 7 pages.
8- Prescrire Rédaction "Savoir où trouver une notice sur internet et identifier la dernière version". www.prescrire.org, updated 2019.

Unsuitably packaged paediatric drugs

Children continue to be endangered by the practice of failing to adapt a product's formulation and packaging for paediatric use when a product initially intended for adults is subsequently authorised in children.

The indications for *sevelamer* powder for oral suspension (Renvela°) have been extended to include the treatment of children aged 6 years and older, requiring doses of 0.8 g or 1.6 g and the ability to adjust the dose by increments of 0.4 g or 0.8 g respectively, which the SPC states should be measured with a 1-ml measuring scoop or measuring spoon. But in France, as of early 2019, no dosing device is provided with the 2.4 g sachets, the 0.8 g and 1.6 g dose strengths are not available, and a 0.4 g dose strength has not been authorised in the European Union.

Vimpat° syrup (*lacosamide* 10 mg/ml) used to be authorised for use in adults and children weighing more than 50 kg, and the box contained a 30-ml measuring cup. When its indications were extended to include children weighing less than 50 kg, a 10-ml oral delivery syringe was added. As of 2019, the "adult" pack of Vimpat° syrup therefore also serves as the "child" pack, by including two different dosing devices, which could cause confusion. As both devices are graduated in millilitres, users must systematically calculate how many millilitres of syrup to measure in order to administer the number of milligrams prescribed, with a risk of ten-fold dosing errors. Most dosing devices examined by *Prescrire* in 2018 were graduated in millilitres, such as those provided with Celsentri° (*maraviroc*), Kaletra° (*lopinavir* + *ritonavir*) and Tamiflu° (*oseltamivir*).

It would be more prudent to provide a 50 mg dose strength of *hydroxycarbamide* (Siklos°) for children with sickle-cell disease than a 100 mg divisible tablet. This would avoid the risk of cutaneous cytotoxicity and contamination of the environment with debris generated when splitting the tablets. It would also be safer if the labelling made it easier to distinguish between the 100 mg and 1000 mg dose strengths of *hydroxycarbamide*.

The indication for Étiléfrine Serb° (*etilefrine*) in France has been changed from orthostatic hypotension in adults to priapism, which also occurs in children with sickle-cell disease. Its packaging, however, has not changed: the dose strength is inappropriate for children (half of the contents of an ampoule must be withdrawn); no equipment for preparation or injection is supplied; and the patient leaflet contains too little information about self-injection.

As in previous years, several drugs of varying toxicity, mainly oral liquid preparations, were supplied in bulk bottles without a child-proof cap in 2018: Théralène° (*alimemazine*), Mucoplexil° (*carbocisteine*), *fluconazole* products (e.g. Fluconazole Biogaran°), *fluoxetine* products (including Prozac°), Panfurex° (*nifuroxazide*), Efferalgan° orodispersible tablets and Dolko° (*paracetamol*), and A 313° (*vitamin A*). Yet packaging solutions are available to prevent children from tasting or swallowing drugs without their carers' knowledge: bottles of Noyada° (*captopril*), Vimpat° (*lacosamide*) and Triflucan° (*fluconazole*), for example, are equipped with a child-proof cap; Orobupré° (*buprenorphine*) blister packs are covered with a child-proof film; and boxes can incorporate a safety catch, such as the one used for Galafold° (*migalastat*).

Handling oral antineoplastics in the home: the dangers should be taken more seriously

A new programme is due to be introduced in France in 2019, whereby community pharmacists will receive payments from the national health insurance system