Taking the guesswork out of supplying multi-compartment compliance aids: do pharmacists require further guidance on medication stability?

As populations age, medications are increasingly being supplied to older individuals in different regions of the world, such as the United Kingdom and Australia, in medication organisers. These compliance aids organise medications according to dosage regimens, and may be referred to as multi-compartment compliance aids (MCAs), monitored dosage systems (MDS) or dose administration aids (DAAs). However, these compliance aids are not air-tight, light resistant, or moisture-impermeable, and therefore light, humidity and temperature may adversely impact on medication stability.[1] Patient risks of medication instability include: active ingredient degradation and loss of potency; changes in the formulation properties resulting in poor dissolution and poor absorption; adverse reactions from potentially toxic degradation product accumulation; and changes in physical appearance, potentially affecting patient adherence.[2] Additionally, medication stability has not been a major focus of recent publications concerning MCAs, where medication repackaging incidents,[3] or knowledge and adherence have been primarily explored. Of the published literature evaluating the stability of medications repackaged into MCAs, concerns regarding altered medication stability, bioavailability and patient acceptability have been raised. For example, 5mg prochlorperazine tablets stored for eight weeks in Multi-Dose Webster-Paks® and exposed to fluorescent lighting experienced discolouration, suggesting the presence of photodegradants that could potentially cause adverse effects.[2] Unacceptable variations in dissolution profiles (British Pharmacopoeia) and changes in weight, have been reported in 100mg sodium valproate tablets repackaged and stored in foil-backed, blister MCAs for 8 weeks at room temperature, refrigerated conditions, and accelerated conditions.[1] Similarly, 100mg generic atenolol tablets repackaged into 28 chamber plastic MCAs with transparent lids failed disintegration tests (British Pharmacopoeia) and dissolution tests (United States Pharmacopoeia) when stored for four weeks in accelerated conditions.[4] The potential for non-equivalence between different types of MCAs has also been reported.[5] Two different brands of 100mg generic atenolol tablet were repackaged for 4 weeks into two different plastic MCAs (Dosett® Maxi and Medidos®).[5] Three factors were tested with each of the two atenolol brands: temperature, MCA type, and co-

storage with aspirin tablets.[5] It was found that storage in MCAs impacted on the physical stability of atenolol at all conditions, where tablet hardness was affected more significantly in the Dosett® Maxi MCA compared to the Medidos® MCA.[5] Further research examining the clinical significance of issues with medication stability when repackaged into MCAs is required.

Pharmaceutical companies do not routinely provide information on the stability of medications repackaged into MCAs, as they are only obliged to submit data on long term and accelerated medication stability when stored in its original packaging. Church and Smith[6] compiled information obtained from pharmaceutical manufacturers about the envisaged stability of medications repackaged into MCAs. Interestingly, of the 392 medications investigated, none had undergone stability testing in MCAs.[6] The following disclaimer was included alongside information provided by the pharmaceutical manufacturers, *"It is important to note that the individual manufacturers do not endorse this practice of transferring medicines from the original packs to compliance aids as it may be outside the terms of their product licence. For the majority of manufacturers any information they provide is based on anecdotal evidence or in-house studies as no formal studies would have been carried out."*[6] A second disclaimer stated that, *"The product information provided in this article has been provided by the marketing authorisation holders for these products. The marketing authorisation holders only recommend that their products are stored in accordance with the summary of product characteristics for each product and that storage of products in any other way is entirely at the pharmacist's own risk."*[6] Additionally, there are limitations associated with the currency and breadth of information covered by resources that are designed to support pharmacists who provide MCAs. Those published in the United Kingdom and Australia, either have not been recently updated[7] or do not provide a comprehensive list of medications that should not be repackaged.[8] Additionally medication management guidelines may not specifically cover MCAs.[9]

These issues highlight a need for long-term solutions to ensure safe and effective use of MCAs, whilst in the shorter term attention can be paid to guidelines for practitioners to minimise potential problems. Several approaches to long-term solutions can be suggested. Firstly, pharmaceutical manufacturers could be advised to conduct medication stability tests with a specific focus on medications that are commonly repackaged, and which have existing stability concerns. Pharmaceutical analysis could be conducted in commonly used MCAs, such as pharmacy-supplied blister/bubble pack MCAs. This information could be included in medication product information. The feasibility of this suggestion would need to be explored as there are many different types of commonly used MCAs and some medications may already have guidance included in their product information. For example, the consumer medication information for hygroscopic sodium valproate (Epilim® and Valpro®) does not include information regarding medication stability in MCAs, however, the consumer medication information for thyroxine (Eutroxsig®) does. Secondly, pharmaceutical bodies could increase pharmacist awareness of evidence-based data from pharmaceutical manufacturers and academic research centres (who could themselves prioritise studies assessing medication stability), by regularly updating guidelines and databases with this information. Thirdly, the stability of medications repackaged into MCAs could be a topic of future continuing professional development events held by pharmaceutical bodies, to increase awareness of this issue amongst pharmacists and prescribers. Although pharmacists may be able to easily identify from original medication packaging or product information if stability issues are associated with medications they are handling. They may however not be aware of the potential adverse impacts of instability associated with repackaging medications into MCAs, they may consider that the benefits associated with MCAs outweigh the risks, or they may be unaware of alternative methods to supply these medications. It has been shown that some pharmacists repackage certain medications into MCAs, despite documented stability concerns. An Australian study examining the accuracy and suitability of repackaging medications into MCAs, supplied to 49 care homes, identified that the majority of inaccurate or unsuitable repackaging incidents involved repackaging potentially unstable medications, including sodium valproate.[3] Lastly, research and development targeted at improving how effectively MCAs can protect their

contents from air, light, humidity and temperature may be a beneficial long-term strategy to address the issue of medication instability when repackaged into MCAs.

The benefits of MCAs may be considered to outweigh their risks and therefore, in the short term, pharmacists need to use their judgment when preparing MCAs, considering the professional and legal implications of this practice. This is important as the pharmaceutical manufacturer's stability guarantee does not apply when medications are removed from their original packaging and stored in MCAs. When a licensed medication is used in a way that is not recommended by the manufacturer (outside its Marketing Authorisation) this is referred to as 'off-label' or 'off-licence' use. In such cases the prescriber should be made fully aware, as the prescriber and pharmacist then assume the responsibility for any associated risks e.g. adverse effects or potential treatment failure. Pharmacists and prescribers should also be supported by their professional organisations when making these decisions. Other recommendations that pharmacists may consider to ensure the optimal stability of medications supplied to patients include considering the product information, supplying medications in their original packaging, and adhering to available guidelines. Pharmacists can avoid repackaging medications that are moisture sensitive, such as effervescent[8] and dispersible tablets;[7] they can limit the time between removing medications from original packaging and placing them into MCAs;[10] and alert patients to monitor MCA integrity and carefully remove tablets, preventing accidental rupture of nearby blisters and environmental exposure.[10] Whilst MCAs are commonly prepared in environments of controlled temperature, they may be subsequently exposed to increased or uncontrolled temperature and humidity in-use.[1] To address these concerns, it is recommended that medications should be stored in MCAs for no longer than eight weeks,[8] in a cool, dry place, and protected from light. Research on in-use conditions should also be undertaken.

Ultimately, decisions concerning the repackaging of medications into MCAs need to be informed by principles of pharmaceutical science, with more detailed and up to date guidance for prescribers and pharmacists, whilst working towards a stronger evidence-base for the use of these aids in the future.

106

107 **References**

108 1. Llewelyn VK et al. Stability of sodium valproate tablets repackaged into dose administration
109 aids. *J Pharm Pharmacol* 2010; 62: 838-843.
110 2. Glass B et al. Prochlorperazine tablets repackaged into dose administration aids: can the
111 patient be assured of quality? *J Clin Pharm Ther* 2009; 34(2): 161-169.
112 3. Gilmartin JF-M et al. Medicines in Australian nursing homes: a cross-sectional observational
113 study of the accuracy and suitability of re-packing medicines into pharmacy-supplied dose
114 administration aids. *Res Social Adm Pharm* 2013; 9(6): 876-883.
115 4. Chan K et al. Pilot study of the short-term physico-chemical stability of atenolol tablets
116 stored in a multi-compartment compliance aid. *Eur J Hosp Pharm Sci Pract* 2007; 13(3): 60-66.
117 5. Donyai P. Quality of medicines stored together in multi-compartment compliance aids. *J Clin*
118 *Pharm Ther* 2010; 35: 533-543.
119 6. Church C, Smith J. How stable are medicines moved from original packs into compliance
120 aids? *The Pharmaceutical Journal* 2006; 276: 75-81.
121 7. Pharmaceutical Society of Australia. Guidelines and standards for pharmacists - dose
122 administration aids service. Australia: Pharmaceutical Society of Australia, 2007.
123 8. Royal Pharmaceutical Society. Improving patient outcomes - the better use of multi-
124 compartment compliance aids Great Britain: Royal Pharmaceutical Society; 2013 [09/2014].
125 Available from: http://www.rpharms.com/support-pdfs/rps-mca-july-2013.pdf.
126 9. General Medical Council. Good practice in prescribing and managing medicines and devices
127 United Kingdom: General Medical Council; 2013 [11/2014]. Available from: http://www.gmc-
128 uk.org/static/documents/content/Prescribing_guidance(1).pdf.
129 10. Perks S et al. Clozapine repackaged into dose administration aids: a common practice in
130 Australian hospitals. *Int J Pharm Pract* 2011; 20(1): 4-8.

131

132