

1 **Taking the guesswork out of supplying multi-compartment compliance aids: do pharmacists** 2 **require further guidance on medication stability?**

3 As populations age, medications are increasingly being supplied to older individuals in different
4 regions of the world, such as the United Kingdom and Australia, in medication organisers. These
5 compliance aids organise medications according to dosage regimens, and may be referred to as multi-
6 compartment compliance aids (MCAs), monitored dosage systems (MDS) or dose administration aids
7 (DAAs). However, these compliance aids are not air-tight, light resistant, or moisture-impermeable,
8 and therefore light, humidity and temperature may adversely impact on medication stability.^[1] Patient
9 risks of medication instability include: active ingredient degradation and loss of potency; changes in
10 the formulation properties resulting in poor dissolution and poor absorption; adverse reactions from
11 potentially toxic degradation product accumulation; and changes in physical appearance, potentially
12 affecting patient adherence.^[2] Additionally, medication stability has not been a major focus of recent
13 publications concerning MCAs, where medication repackaging incidents,^[3] or knowledge and
14 adherence have been primarily explored. Of the published literature evaluating the stability of
15 medications repackaged into MCAs, concerns regarding altered medication stability, bioavailability
16 and patient acceptability have been raised. For example, 5mg prochlorperazine tablets stored for eight
17 weeks in Multi-Dose Webster-Paks® and exposed to fluorescent lighting experienced discolouration,
18 suggesting the presence of photodegradants that could potentially cause adverse effects.^[2]
19 Unacceptable variations in dissolution profiles (British Pharmacopoeia) and changes in weight, have
20 been reported in 100mg sodium valproate tablets repackaged and stored in foil-backed, blister MCAs
21 for 8 weeks at room temperature, refrigerated conditions, and accelerated conditions.^[1] Similarly,
22 100mg generic atenolol tablets repackaged into 28 chamber plastic MCAs with transparent lids failed
23 disintegration tests (British Pharmacopoeia) and dissolution tests (United States Pharmacopoeia)
24 when stored for four weeks in accelerated conditions.^[4] The potential for non-equivalence between
25 different types of MCAs has also been reported.^[5] Two different brands of 100mg generic atenolol
26 tablet were repackaged for 4 weeks into two different plastic MCAs (Dosett® Maxi and Medidos®).^[5]
27 Three factors were tested with each of the two atenolol brands: temperature, MCA type, and co-

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

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

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

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

82 The benefits of MCAs may be considered to outweigh their risks and therefore, in the short term,
83 pharmacists need to use their judgment when preparing MCAs, considering the professional and legal
84 implications of this practice. This is important as the pharmaceutical manufacturer's stability
85 guarantee does not apply when medications are removed from their original packaging and stored in
86 MCAs. When a licensed medication is used in a way that is not recommended by the manufacturer
87 (outside its Marketing Authorisation) this is referred to as 'off-label' or 'off-licence' use. In such cases
88 the prescriber should be made fully aware, as the prescriber and pharmacist then assume the
89 responsibility for any associated risks e.g. adverse effects or potential treatment failure. Pharmacists
90 and prescribers should also be supported by their professional organisations when making these
91 decisions. Other recommendations that pharmacists may consider to ensure the optimal stability of
92 medications supplied to patients include considering the product information, supplying medications
93 in their original packaging, and adhering to available guidelines. Pharmacists can avoid repackaging
94 medications that are moisture sensitive, such as effervescent^[8] and dispersible tablets,^[7] they can limit
95 the time between removing medications from original packaging and placing them into MCAs,^[10] and
96 alert patients to monitor MCA integrity and carefully remove tablets, preventing accidental rupture of
97 nearby blisters and environmental exposure.^[10] Whilst MCAs are commonly prepared in
98 environments of controlled temperature, they may be subsequently exposed to increased or
99 uncontrolled temperature and humidity in-use.^[11] To address these concerns, it is recommended that
100 medications should be stored in MCAs for no longer than eight weeks,^[8] in a cool, dry place, and
101 protected from light. Research on in-use conditions should also be undertaken.

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

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107 **References**

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