

# Assigning expiry dates to compounded medications

First published in the *Australian Journal of Pharmacy*, Vol. 99, No.1169, February 2018, pp.72-76. Reproduced and distributed by the Medisca group of companies with the permission of the publisher.

▲ Patricia Ullmann BPharm, Training and Technical Services Manager, Medisca Australia

The objective of an expiry date of a medication is to provide a degree of certainty that the medication's stability, efficacy and safety will not be compromised if the medication is used as directed within that period.

The Therapeutic Goods Act (1989) (Commonwealth) requires that therapeutic goods marketed in Australia are of acceptable quality. Preliminary Chapter 1 Section 3 of the Act defines 'quality' as follows:<sup>1</sup>

*quality, in relation to therapeutic goods, includes the composition, strength, potency, stability, sterility, purity, bioburden, design, construction and performance characteristics of the goods.*

The Act makes no distinction in its requirement for quality, between therapeutic goods which are bulk-manufactured and those that are compounded.

Based on this definition of quality, it follows that from a legal perspective the expiry date of all medicines, including compounded medicines, is an important aspect of quality.

The purpose of this article is to provide an understanding of how expiry dates are assigned to medicines compounded by (non-hospital) pharmacies in Australia and to highlight the regulatory instruments which underpin the process.

Industry assigns expiry dates to bulk manufactured therapeutic goods based on the results of rigorous analytical and performance testing. The studies are specific for a particular formulation in its container and at stated exposure conditions of illumination and temperature.<sup>2</sup> They reflect every aspect

of the therapeutic good that is dispensed to the patient, including the strength of the active, excipients, total volume or weight in the package, packaging material(s) and temperature.

The expiry date of a compounded formulation is a challenge for compounding pharmacists.<sup>3</sup> In the community pharmacy setting, various objectives are considered including:

- 1. Patient centred care**—convenience, cost, duration of treatment;
- 2. Scientific**—physical, chemical, microbial, therapeutic and toxicological stability of the formulation;
- 3. Regulatory**—compliance with Acts, Regulations and Professional Practice Standards; and
- 4. Commercial**—pressure from competition; profitability.

Alongside these objectives, pharmacists consult and apply drug-specific and general stability documentation and literature where available, to assign expiry dates considering the following criteria:<sup>4</sup>

- the nature of the drug and its degradation mechanism;
- the dosage form and its components;
- the potential for microbial proliferation in the preparation;
- the container in which it is packaged;
- the expected storage conditions; and
- the intended duration of therapy.

## AFTER COMPLETING THIS ACTIVITY, THE LEARNER SHOULD BE ABLE TO:

- describe factors that affect the assigning of expiry dates to compounded products;
- describe resources used to give guidance on assigning expiry dates;
- list processes and properties that verify the quality of non-sterile compounded medications.

The 2010 Competency Standards addressed by this activity include: 1.1, 1.4, 5.1, 5.2, 5.3

The 2016 Competency Standards addressed by this activity include: 1.3, 1.5, 3.2, 3.4



Accreditation Number: A1802AJP1

This activity has been accredited for 1.0 hour of Group One CPD (or 1.0 CPD credit) suitable for inclusion in an individual pharmacist's CPD plan which can be converted to 1.0 hour of Group Two CPD (or 2.0 CPD credits) upon successful completion of relevant assessment activities. Accreditation expires: 01/02/2020

When preparing medications for individual patients immediately prior to use, product-specific experimental studies undertaken by industry are clearly not feasible for compounding pharmacies to achieve. In contrast, compounded medicines are usually assigned conservative expiry dates predicted theoretically, based on first principles.

## Guidance on assigning expiry dates

*Australian Pharmaceutical Formulary and Handbook, 23rd edition*

The *Australian Pharmaceutical Formulary and Handbook* (APF) states:<sup>5</sup>

*All compounded products must be assigned and labelled with an expiry date. This should be 28 days or less, unless otherwise specified.*

TABLE 1 : SUMMARY OF EXPIRY DATES OF COMPOUNDED MEDICINES FROM APF<sup>5</sup>

DOSAGE FORM	EXPIRY DATE <i>from the date of preparation, unless otherwise specified</i>	STORAGE CONDITIONS, <i>unless otherwise specified in APF</i>	NOTES
Applications, topical (emulsions, suspensions, solutions)	28 Days	<25°C	
Capsules	Up to 6 months	<25°C	The expiry date of up to 6 months applies only if the ingredients are stable in air and not hygroscopic.
Creams	28 Days	<25°C	
Ear drops/installations	28 Days	<25°C	
Emulsifying waxes	28 Days	<25°C	
Eye drops/lotions	28 Days	<25°C	
Gels	28 Days	<25°C	Gels containing tragacanth are particularly prone to bacterial contamination and should be discarded 28 days after the manufacture, unless shorter period is indicated.
Inhalations	28 Days	<25°C	In this formulary, 'inhalations' do not refer to nebuliser solutions (also known as nebulas or respules), metered dose inhalers, dry powder inhalers or nicotine inhalers, but rather are liquid preparations containing volatile substances that upon vaporization are brought into contact with the respiratory tract.
Insufflations	28 Days	<25°C	
Irrigations	28 Days	<25°C	
Liniments	28 Days	<25°C	
Liquids, oral	28 Days	<25°C	
Lotions	28 Days	<25°C	
Mucilages	28 Days	Refrigerate 2–8°C, unless otherwise specified, to prevent decomposition	Unless contains tragacanth.
Nasal installations	28 Days	<25°C	
Ointments	28 Days	<25°C	
Paints	28 Days	<25°C	
Pastes	28 Days	<25°C	
Powders	6 months	Not specified	If any component is hygroscopic or volatile, supply in airtight containers. When supplied as single doses, the powder should be double-wrapped, the inner wrapper being waxed paper.
Shampoos	28 Days	<25°C, unless otherwise specified	
Suppositories	28 Days	Refrigerate 2–8°C, unless otherwise specified	

Assigning an expiry date longer than 28 days should be based on reliable literature, but under no circumstances should an expiry date of longer than 6 months be assigned for compounded products.

The shelf life of a product is dependent on the conditions of storage. Stability and efficacy can be compromised if the product is kept for any prolonged period outside the

labelled temperature range, when the expiry date marked on it has been passed, or if it is repackaged.

Table 1 is a summary of the expiry dates of compounded preparations, as per APF. Specific formulas within the APF may have storage conditions and expiry dates which deviate from those listed in Table 1.

### Professional Practice Standards Version 5 2017

The *Professional Practice Standards* (PPS) provides guidance on expiry dates for both Simple and Complex Compounding in various sections of Standard 5. It is a requirement that the pharmacist:

- implements and maintains SOPs, which include the application of expiry dates

- to compounded products (PPS 5.3.2);
- adheres to evidence-based information sources to optimise storage and stability requirements of raw ingredients and compounded preparations, including when assigning expiry dates (PPS 5.8.1); and
- ensures that all ingredients are correct, stable, compatible, within expiry date (for the expected duration of use of the compounded preparation), and appropriately stored before compounding (PPS 5.10.6).<sup>6</sup>

### Guidelines on Compounding of Medicines<sup>7</sup>

The *Guidelines on Compounding of Medicines*, which was developed by the Pharmacy Board of Australia (PBA) under section 39 of the Health Practitioner Regulation National Law, is in force in each state and territory under national law. Failure by pharmacists to comply may result in action by the PBA including disciplinary proceedings.

Several sections in the Guidelines provide detailed requirements regarding expiry dates:<sup>8</sup>

- When compounding medicines, pharmacists must ensure that there is good clinical and pharmaceutical evidence to support the quality, stability (including appropriate expiry periods), safety, efficacy and rationality of any extemporaneous formulation.
- For guidance on assigning an appropriate expiry date to a compounded medicine, pharmacists should refer to the section *Extemporaneous dispensing in the current edition of the Australian Pharmaceutical Formulary and Handbook*.
- A pharmacist should document... evidence of the efficacy, pharmacokinetic and clinical data, and the basis for the assigned expiry date of the intended formulation.
- Written information should be provided by the pharmacist to assist in the communication of the following counselling points to facilitate the safe and effective use of the compounded product... the appropriate storage requirements and expiry date of the product.

Therefore considering the APF, PPS and *Guidelines on Compounding of Medicines*, in Australia the expiry date of a non-sterile preparation is:

- a maximum of 28 days as per APF, or
- consistent with a specific formula published in APF, or

## In Australia, expiry dates of non-sterile preparations which are not assigned according to specific stability studies, shall be assigned as per the guidance of the APF, not USP <795>.

- consistent with the stability results of a specific stability-studied formula.

In the latter case, if any aspect of the formulation changes, then the extended expiry date does not apply. An alteration in the concentration of the active, a replacement of any excipient including the base, or a change in the packaging or storage conditions render the extended stability data inapplicable. For example, in the absence of evidence, it cannot be assumed that the same expiry date applies to a lower concentration of the same active pharmaceutical ingredient, even if all else remains the same within two formulations.

Compensatory processing error, calibration, verification, and testing are some of the broader categories of methods employed by the compounding pharmacist to bring active agent quantities, in a blend or mix, to within acceptable margins of error.

### Verification

Verification outcomes should also be considered when assigning expiry dates. Despite the expiry date guidance given above, the results of validation procedures may indicate that:

- the compounded medication passes verification;
- the maximum or extended expiry date should not be assigned to that specific preparation;
- the medication should not be dispensed at all.

Verification may include testing of organoleptic properties which indicate instability,<sup>9</sup> including:

- Consistency*: the condition of cohering or holding together and retaining form; solidity or firmness;
- Appearance*: general visual look;
- Grittiness*: sensation of granular particulate under fingers upon physical touch;
- Colour*: uniformity, transparency, opacity and general acceptance;
- Continuity*: the uniformity in consistency, appearance, texture, and colour;
- Hardness*: the quality or condition of being hard/firm;
- Integrity*: the dosage forms ability to remain intact;
- Aroma*: the lollipops should have a pleasant aroma;
- Homogeneity*: uniformity of distribution of ingredients in the mix.<sup>10</sup>

Verification may also include assays of potency, microbial burden and mixed efficacy of the compounded medication. Although not often utilised in non-sterile compounding, even infrequent subjugation of compounded medicines to such tests may verify the assigned expiry dates. The *Victorian Pharmacy Authority Guidelines 2015*<sup>11</sup> require that frequently prepared medicines are assayed annually by competent analytical laboratories of:

- specialised or novel formulations include high potency substances such as hormones, clobetasol and melatonin;
- tablets and capsules require both disintegration and uniformity of content tests.

Another verification technique is found in USP General Chapter <1163> Quality Assurance in Pharmaceutical Compounding, which requires weight assessment of the compounded medication to fall within +/- 10% of the theoretical weight of one compounded unit (or one unit dose depending on the dosage form). Effectively, this means that the compounded medicine needs to fall within 90 to 100% of the theoretical weight.

USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations, specifies numerous other verifications which are required for sterile compounding, including microbial count and potency testing.

### Risk Assessment

PPS provides the risk assessment tool Appendix 7: Compounding decision support and risk assessment tool. It uses a risk rating matrix to determine the level of risk as being low, medium high or extreme, by considering the likelihood of risk and the consequence(s) of the risk. Such a tool is applicable when assigning expiry dates to compounded medicines.<sup>12</sup>

### United States Pharmacopoeia (USP)

The Beyond-Use Date (BUD) is the date after which a compounded preparation should not be used. It is determined from the date when the preparation is compounded. USP Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations states:<sup>13</sup>

*In the absence of stability information that is applicable to a specific drug and preparation, the following table [refer Table 2] presents maximum BUDs recommended for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature, unless otherwise indicated. Drugs or chemicals known to be labile to decomposition will require shorter BUDs.*

When following a formula published in a jurisdiction outside of Australia, attention must be paid as to the reference used to assign the expiry date or BUD. As demonstrated above, the maximum expiry dates which may be assigned differ between the APF and USP <795>. In Australia, expiry dates of non-sterile preparations which are not assigned according to specific stability studies, shall be assigned as per the guidance of the APF, not USP <795>.

### Specific guidance on assigning expiry dates to sterile compounded preparations

The PBA's guidance *Compounding of Sterile Injectable Medicines*,<sup>14</sup> effective from 1 February 2018, replaces the currently postponed section 'Expiry of compounded parenteral medicines' of the PBA's *Guidelines on Compounding of Medicines*.

Expiry dates for compounded eye preparations are not mentioned in the *Compounding of Sterile Injectable Medicines* guidance, but are detailed in APF. The

TABLE 2 : Reprinted from: USP CHAPTER <795> PHARMACEUTICAL COMPOUNDING—NON-STERILE PREPARATIONS

DOSAGE FORM	BEYOND-USE DATE
Non-aqueous formulations	No later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.
Water-containing oral formulations	No later than 14 days when stored at 2–80°C.
Water-containing topical/dermal and mucosal liquid and semi-solid formulations	No later than 30 days.

*These maximum BUDs are recommended for non-sterile compounded drug preparations in the absence of stability information that is applicable to a specific drug or preparation. The BUD shall not be later than the expiration date on the container of any component.*

sterile injectable medicines to which the *Compounding of Sterile Injectable Medicines* guidance applies, irrespective of scheduling are:<sup>15</sup>

- injections;
- infusions;
- concentrates for injections or infusions;
- powders for reconstitution for injections or infusions; and
- gels for injections.

Pharmacists must adhere to one of the following guidelines/standards, whichever is the most appropriate and relevant to their compounding practice:

- the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010), or
- the PIC/S *Guide to Good Manufacturing Practice for Medicinal Products* (PE 009), or
- the USP-NF <797> *Pharmaceutical Compounding—Sterile Preparations*.

When choosing the appropriate guideline/standard, pharmacists shall consider the:

1. practice setting;
2. types of medicines compounded;
3. risks identified during the risk assessment process for compounded products;
4. risks to the patient;
5. risks to other individuals handling/exposed to the compounded medicines (e.g. staff, caregivers).<sup>16</sup>

To assign a BUD longer than 24 hours, a pharmacist must follow USP-NF <797> and have evidence:

1. that the compounded medicine when stored under the specified storage conditions during its assigned BUD, and during the administration of the medicine to the patient, remains physically and chemically stable in a particular container;
2. that the compounded medicine when stored under the specified storage conditions during its assigned BUD, and during the administration of the medicine to the patient, remains microbiological stability stable;
3. of quality and control (SOPs);

TABLE 3 : RISK LEVEL BEYOND-USE DATES

STORAGE CONDITIONS	LOW RISK	MEDIUM RISK	HIGH RISK
Room temperature: ≥20°C and ≤25°C	48 hours	30 hours	24 hours
Refrigerated: ≥2°C and ≤8°C	14 days	9 days	3 days
Frozen: ≥-25°C and ≤-10°C	45 days	45 days	45 days

2

CPD CREDITS  
GROUP TWO

PRACTICE UPDATE

Assigning expiry dates to compounded medications

This unit attracts up to 2 Group Two CPD credits. Accreditation number: A1802AJP1. Accreditation expires: 01/02/2020. Each question has only one CORRECT answer.

1. Select the TRUE statement. Verification processes that can be conducted in-house by compounding pharmacies to indicate stability include:

- A Potency assay, colour, texture
- B Continuity, mixed efficacy testing, smell
- C Integrity, consistency, hardness
- D Appearance, taste, homogeneity

2. Select the TRUE statement regarding assigning expiry dates in Australia:

- A USP chapter <797> is used as the guidance when assigning expiry dates for all sterile preparations.
- B The APF, USP <795> and PPS Standard 5 may be used when assigning expiry dates.
- C Under no circumstances are expiry dates informed by USP.
- D Expiry dates may be assigned based on the results of studies pertaining to the specific formulation being compounded.

3. Select the best statement regarding assigning expiry dates in Australia:

- A Standard Operation Procedures need

to include assigning expiry dates and counselling the patient or caregiver regarding expiry dates.

- B Expiry dates assigned based on stability studies do apply when the concentration of the active being compounded is less than that which was studied.
- C Commercial and financial issues are considerations which inform the assignment of expiry dates.
- D A and B are both correct.
- E A, B and C are correct.

4. Select the CORRECT statement:

- A Since guidelines on compounding of medicines are not national law, they are not mandatory in Australia.
- B The standard expiry date for the majority of dosage forms according to the APF, is a maximum of 28 days.
- C In Australia, the expiry date of sterile injectable medicines is assigned according to the APF.
- D In Australia, the expiry date of eye drops is assigned according to USP <797>.

5. Select the CORRECT statement.

In the absence of stability studied formulas with additional evidence of microbial stability:

- A sterile infusions stored in refrigerator temperature conditions between 2°C and 8°C, prepared from a non-sterile active pharmaceutical ingredient, have a maximum expiry date of 3 days in Australia.
- B sterile eye drops stored in refrigerator temperature conditions between 2°C and 8°C, prepared from a non-sterile active pharmaceutical ingredient, have a maximum expiry date of 3 days in Australia.
- C sterile injections stored in freezer temperature conditions below -10°C and -25°C, prepared from a non-sterile active pharmaceutical ingredient, have a maximum expiry date of 3 days in Australia.
- D all capsule formulations composed solely of powders have a maximum expiry date of 6 months in Australia.

- 4. of the quality of the components, e.g. container-closure integrity;
- 5. that the processes followed were appropriate for the medicine being compounded;
- 6. of the competence of the personnel performing the compounding; and
- 7. that the environmental conditions under which the compounding is performed are appropriate.<sup>17</sup>

- sterility of ingredients, products, components, and devices; and
- garbing and gloving of personnel.

Table 3 illustrates the relationship between risk classifications of CSPs and Beyond-Use Dates (BUDs).<sup>18</sup>

When any starting material, whether active pharmaceutical ingredient

or an excipient, is used in sterile compounding, the compounded medication is classified as High Risk.

For completion it is important to note that the Society of Hospital Pharmacists of Australia provides guidance on expiry dates for hospital pharmacies in its publication *Manufacturing Standards* June 2010. ●

USP <797> Pharmaceutical Compounding—Sterile Preparations classifies compounded sterile preparations (CSP) into three categories: Low, Medium and High Risk, depending on the:

- number of manipulations or entries into packaging;
- the duration of the compounding procedure;
- the length of time after compounding before the commencement of administration to the patient;

1. www.legislation.gov.au/Details/C2012C00355  
 2. http://app.uspnf.com  
 3. Allen L. The art, science, and technology of pharmaceutical compounding. 4th edn. Washington, DC: American Pharmacists Association, 2012; 15.  
 4. http://app.uspnf.com General Chapter <797>  
 5. Sansom, LN. Australian pharmaceutical formulary and handbook. 23rd edn. Canberra: Pharmaceutical Society of Australia, 2015; 28-31.  
 6. www.psa.org.au/practice-support-and-tools/psa-professional-practice-standards  
 7. www.pharmacyboard.gov.au/Codes-Guidelines.aspx  
 8. Guidelines on Compounding of Medicines. Pharmacy Board of Australia. Published 2 March 2015.  
 9. United States Pharmacopeial Convention. <1163> Quality Assurance in Pharmaceutical Compounding. United States Pharmacopeia 40—National Formulary 35. Rockville, MD, 2017.  
 10. The Science of Pharmaceutical Compounding: Non-Sterile Training. LP3 Network 2015.

11. Victorian Pharmacy Authority Guidelines 2015, s. 4.6.4; 20.  
 12. Pharmaceutical Society of Australia, Professional Practice Standards v5 2017; 103-4.  
 13. United States Pharmacopeial Convention. <795> Pharmaceutical Compounding—Nonsterile Preparations. United States Pharmacopeia 40—National Formulary 35. Rockville, MD, 2017.  
 14. Compounding of sterile injectable medicines. Pharmacy Board of Australia. Published 1 August 2017.  
 15. www.pharmacyboard.gov.au/Codes-Guidelines.aspx  
 16. Modified from www.pharmacyboard.gov.au/Codes-Guidelines.aspx  
 17. Pharmacy Board of Australia, Compounding of sterile injectable medicines, Aug 2017.  
 18. Modified from United States Pharmacopeial Convention. <797> Pharmaceutical Compounding—Sterile Preparations. In United States Pharmacopeia 40—National Formulary 35. Rockville, MD, 2017.



# Are you part of the picture?

***By the end of 2018, all Australians will have a My Health Record, unless they decide not to have one.***

The My Health Record provides a picture of an individual's medical history, compiled from their existing healthcare records.

Meaningful clinical use of the My Health Record system will support timely access to important health information by both patients and their treating healthcare providers, and improve patient health outcomes.

When it comes to your patient's health information, make sure you are in the picture.

The Pharmaceutical Society of Australia (PSA) is supporting pharmacists to integrate use of the My Health Record system into patient care.

For guidelines, practice support and education materials, and to find your local digital health leader, visit the PSA Digital Health hub at [www.psa.org.au/digitalhealthhub](http://www.psa.org.au/digitalhealthhub)

*This project is funded by the Australian Digital Health Agency.*