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Commercially available products: To compound or not to compound?

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AFTER COMPLETING THIS ACTIVITY, PHARMACISTS SHOULD BE ABLE TO:

1. Discuss the codes and regulations applicable in determining if a compounded medicine should be prepared
2. Discuss some common instances where a medicine should and should not be compounded
3. Describe the process that pharmacists can follow regrading whether it is appropriate to compound a medicine or not.

The 2010 Competency Standards addressed by this activity include: 1.1, 1.2, 1.4, 3.3, 5.1, 6.3

To comply with regulations and guidelines compounding pharmacies need to understand circumstances that restrict compounding commercially available products.

The Therapeutic Goods Act (1989) requires that therapeutic goods sold in Australia be:

1. registered on the Australian Register of Therapeutic Goods (ARTG) and
2. (produced in facilities that comply with the Code of Good Manufacturing Practice (cGMP)

Prior to registration of Schedule 3, 4 and 8 products, the sponsor has provided sufficient evidence of stability, safety and efficacy to the Therapeutic Goods Administration (TGA).

Compounded therapeutic medications to treat specific patient needs are prepared by

pharmacists in order to fulfill an important role, for which there are exemptions from the above requirements in The Therapeutic Goods Regulations (1990). Personalized medicines for patients are based on medical needs that cannot be met by commercially available drug products, and may be compounded. According to the Therapeutic Goods Act (1989), the exemption is for when the medicines are prepared by pharmacists for specific patients, for therapeutic application on or to that person and supplied by means other than by wholesale.

As per The Guidelines on Compounding of Medicines [1], The Pharmacy Board of Australia, a

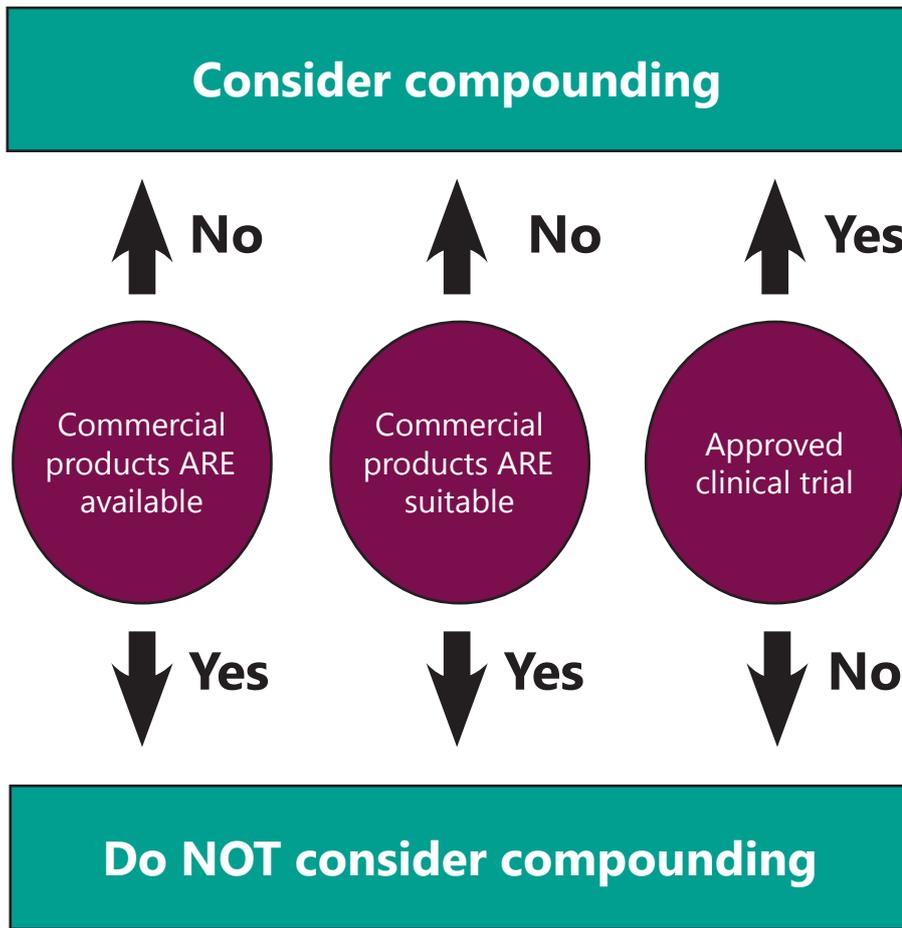


Figure: The compounding circumstances decision-making cascade

risk assessment of a compounded formula includes a requirement for evidence of clinical efficacy, patient safety and formulation stability (physical, chemical and microbial). In addition, the facility, equipment, environment and training need to be adequate for the risk undertaken.

The decision to treat a specific patient with a specific compounded formula should also consider the specific patient, their medical history, comorbidities, other medications and all the factors considered before dispensing any medication compounded or commercially available.

The Guidelines on Compounding of Medicines, (The Guidelines) also limits the circumstances when

compounding may be considered, to when:

1. an appropriate commercial product is unavailable
2. (a commercial product is unsuitable
3. undertaking research sanctioned by a recognised human research ethics committee.

Circumstance 1: Unavailable products- discontinuation, never registered, short supply

Discontinuation

A commercial product may be unavailable in scenarios where it was discontinued from the Australian market at the sponsor’s discretion. This may be based on financial grounds and does not include discontinuations due

to concerns regarding safety or efficacy or at the request of the registering authority. The product may still be available in larger markets as determined by the sponsor.

Examples of such discontinuations include ergotamine products such as Cafergot™ and Ergodryl™ for the treatment of migraine, which were discontinued in Australia, yet are still available in the USA.

The TGA publishes the publicly available ARTG (currently standing at approximately 87,000 products). [2] Pharmacists may search the ARTG to confirm whether there are other approved commercial products containing the same active pharmaceutical ingredient (API) as the product prescribed.

However, sponsors are not required to officially withdraw products that they have discontinued voluntarily for reasons unrelated to safety or efficacy. Given that in these circumstances the TGA is not officially advised of the discontinuation, the ARTG may contain commercial products that may no longer be available in Australia.

Never Registered

In other instances, the product may be unavailable as the sponsor did not register or list the product in Australia in the first instance. The reasons may relate to the perceived lack of financial gain or even delays in the registration process.

An example of this is the anabolic androgen dehydroepiandrosterone (DHEA), which although available

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in North America for many years, is not available in Australia other than as a homeopathic product.

Another example is melatonin for which until November 2009 there was no registered product in Australia. Currently, the only non-homeopathic melatonin product registered on the (ARTG) is Circadin™ 2mg prolonged release tablets. The approved indication of Circadin™ is monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over. [3] In specific patient circumstances discussed later, a compounded melatonin formulation may be warranted.

Short supply

A registered commercial product may also be considered unavailable when it is in short supply. The TGA publishes the Medicines Shortage Information Initiative [4] (MSII) that pharmacists may search to ascertain whether there is a shortage of a specific approved therapeutic product. Again, as this is a voluntary system, the MSII may not include all approved products that are in short supply.

In these circumstances, a pharmacist may search the ARTG to confirm whether there are other available commercial equivalents such as generic brands, which contain the same APIs [5] as the product that is out-of-stock. An example of this is the Bactroban™ range of products which have been

in short supply since the second half of 2016.

Before deeming a commercial product as being in short supply, it may be best practice for a compounding pharmacist to also consider whether there are alternative pharmaceutical wholesalers that have stock of the specific therapeutic product. If the product is seemingly out-of-stock at their preferred wholesaler, it is reasonable that the pharmacy or patient try to obtain the product from elsewhere. [5]

When the decision to compound is based on short supply, it is advisable that documentation of the evidence of short supply be part of the standard operating procedures. This may be in the form of a screen shot of the MSII or printed advice from a reliable source such as the manufacturer.

Circumstance 2: Commercial Product Unsuitable

The second circumstance permitting compounding is when the commercial product is unsuitable for the specific patient. This includes situations where:

- the specific patient has an allergy or intolerance to an excipient in the commercial product such as a filler or dye
- the route of administration of the commercial product is unsuitable for the specific patient. A topical preparation may be required for a patient with a mental health condition

refusing the oral medication; a liquid dosage form instead of a solid oral dosage form is required for a baby or for an elderly person with swallowing difficulties

- the strengths of the commercial products are unsuitable for the patient eg for veterinary or paediatric use.

It is noteworthy that the patient's financial situation is not covered by this circumstance. When a patient does not purchase the ARTG-registered product due to lack of affordability, the absence of treatment results in medical consequences. Yet the patient may be able to afford the compounded version, if it is less expensive.

However, the current guidelines do not make this link to patient health outcomes, in order to permit compounding in such circumstances. Hence in Australia, financial deliberations affecting treatment options are not considered as circumstances that permit compounding over commercially available products.

It is advisable that the unsuitability of the commercially available product that supports the decision to compound for a specific patient, be documented as part of the standard operating procedures. It is best practice to document the specific purpose of the compounded preparation eg to avoid allergic response to (component X) in the commercial product.

Circumstance 3: Clinical Trials

There are two schemes for clinical trials in Australia, both of which involve a review by a Human Research Ethics Committee (HREC). When compounding for clinical trials, the pharmacy must ensure that the research has been sanctioned by a committee that is approved by the Australian Health Ethics Committee of the National Health and Medical Research Council (NHMRC). [6]

The HREC may require that the clinical trial medication be produced in a facility that complies with cGMP. Such compliance is diametrically opposed to compounding, which is structured to prepare individualized medicine immediately prior to use. Since the majority of Australian pharmacies do not comply with cGMP, they may be prevented from compounding clinical trial medication by limitations of the clinical trials ethics committee.

Recent Allegations

Recently, regulators have had complaints against compounding pharmacies allegedly not complying with the restrictions

of the circumstances in which compounding is permitted. Pharmacists may have compounded preparations similar to or the same as commercially available products.

The commercial product Duromine™ and its generic equivalent Metermine™, both sponsored by iNova pharmaceuticals, contain phentermine in an ion-exchange resin complex designed and tested to release the active drug over a period time, which is an important factor in its duration of action. [7,8]

Phentermine hydrochloride capsules have been compounded for weight loss. A compounded formulation cannot claim to emulate the release of the proprietary commercially available product, without evidence. Even if such studies of the compounded formulation were conducted, the commercial product would need be in short supply or unsuitable for the specific patient to meet the permitted compounding circumstances. Such a compounded medication would need be labelled as ``Phentermine Hydrochloride`` and not any

trademarked name.

Phentermine hydrochloride capsules have also been compounded for weight loss with the addition of chromium, 5-hydroxy tryptophan or topiramate as dual-actives. There are no commercial products equivalent to the combination-compounded formulations at this time.

Regulators argue that combining phentermine with other APIs has two issues. Firstly, clinical evidence is required that the dual-active preparation is more efficacious than the single active commercially available phentermine. Secondly, if the evidence exists, then the patient may take two proprietary products instead of one compounded product.

However, the Guidelines do not contain any such restrictions regarding dual-actives. Also controversial, is the level of clinical evidence required to support the decision to compound. Compounding by its nature to fulfill individual patients` needs can not be expected to have Level I high quality randomized trials or prospective studies; double-



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blind clinic trials or groups with large numbers of participants. The acceptable minimum level of clinical evidence required to support compounding decisions remains undefined in Australia. This makes the decision to compound at times difficult to determine.

Lawley Pharmaceuticals produce an ARTG-listed testosterone cream in 5% strength, Androforte®, in a TGA-registered facility. When a prescription is presented for testosterone 5% cream, the default dispensing is the commercial product, unless any of the three circumstances to compound apply.

However other strengths of testosterone cream are not included on the ARTG at this time. [9,10] Consider the question whether the circumstances to compound a progesterone topical cream of strength other than 5% exist. Given there are no commercial products of strengths other than 5% approved for marketing in Australia, following a

thorough risk assessment outlined in the Guidelines, a progesterone cream may be compounded.

Essential Copies

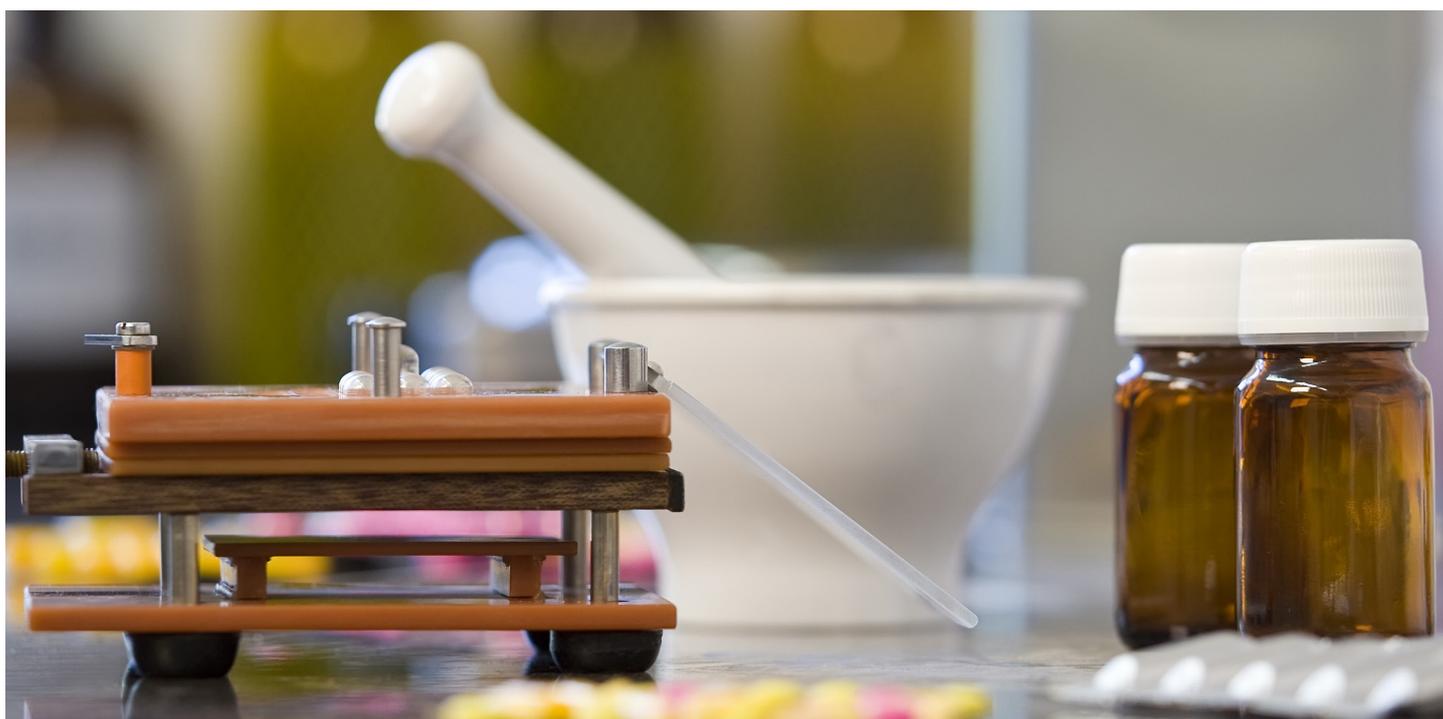
Although other than in the above three circumstances compounding of commercially equivalent products is not permitted, Australian regulations and guidance documents currently do not clarify what is commercially equivalent. When the strength of the compounded formulation varies from that of a commercially available product only slightly, the pharmacist needs to consider whether the compounded preparation would essentially be a copy of a commercially available product.

The Guidelines state that “compounding of a medicine (whether prescribed or not) that would be a close formulation to an available and suitable commercial product, and would not be likely to produce a different therapeutic outcome to the commercial

product, should not take place”. [1]

In July 2016, the United States Food and Drug Administration (FDA) released the document *Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance for Industry*. The Guidance was open for comment and is currently under industry discussion. It’s current version clarifies that a compounded preparation is not considered essentially a copy of a commercially available drug product in circumstances where the compounded preparation has “a change made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug.” [11]

In this Guidance, the FDA explains that restrictions on



compounding intend to protect “the integrity and effectiveness of the new drug and abbreviated new drug approval processes”. [12] By inference, the restrictions aim to protect patients from unsafe, ineffective, or poor quality drugs. Moreover, the Guidance aims to support sponsors, who “may be less likely to invest in and seek approval of innovative, life-saving medications if a compounder could, after a drug is approved, compound “substitutes” that have not had to demonstrate safety and effectiveness and are not produced in accordance with CGMP requirements or labeled with adequate directions for use.” [11] Similarly, the Guidance aims to support the current approval seeking process of generic medications.

In Australia the process of ARTG registration of generics, requires the inclusion of data to demonstrate that, compared to the approved drug, the generic drug:

- has the same active ingredient
- has the same quantity of active drug substance
- is bioequivalent, including evidence of dissolution profiles
- has the same size, weight and coating
- has a well-described dose-response curve
- the tests have been validated, so that the results are both accurate and precise. [11]

Authorities such as the TGA also conduct inspections of manufacturing facilities, not of compounding pharmacies. Compounded medications and pharmacies are not required to undergo the same level of scrutiny as commercially available products whether the

original brands or the generics.

“FDA intends to consider a compounded drug product to be essentially a copy of a commercially available drug product if:

- the compounded drug product has the same active pharmaceutical ingredient(s) (API) as the commercially available drug product;
- the API(s) have the same, similar, or an easily substitutable dosage strength; and
- the commercially available drug product can be used by the same route of administration as prescribed for the compounded drug, unless a prescriber determines that there is a change, made for an identified individual patient, which produces for that patient a significant difference from the commercially available drug product.” [11]

Easily Substitutional Strength

What constitutes an easily substitutional strength has not been defined in Australia nor specifically excluded by guidelines as a circumstance to prohibit compounding. However it is inferred in the Guidelines that a compounded medication would “not be likely to produce a different therapeutic outcome to the commercial product”. [1]

FDA has defined that drugs “have a similar dosage strength if the dosage strength of the compounded drug is within 10% of the dosage strength of the commercially available drug product. ” [11] This is currently being debated by the industry in

that jurisdiction.

Same Route of Administration

Where the route of administering a drug to a site in a patient differs, FDA does not intend to consider a compounded drug preparation to be essentially a copy of a commercially available drug product. The expectation is that the change in route of administration would produce a significant difference for an identified individual patient relative to the commercially available drug product. It is notable that the difference lies in the route of administration, not the drug label. Where a commercially available product is labelled for intramuscular use, a compounded preparation of the same (or similar) drug labelled for subcutaneous use is essentially a copy, unless other criteria apply. [11]

Multiples and Fractions

The FDA has defined that drugs are essential copies which can be easily substituted, if the same or similar dosage strength can be achieved by administration of fractional or multiple doses of a drug product. Such examples include when two tablets of a commercially available drug can be taken, instead of one compounded capsule. [11]

Same Characteristics as Two or More Commercially Available Drug Products

Compounding may assist in situations of poor patient compliance, where by combining multiple actives into one compounded formulation, patient

compliance is increased. Similarly, fractioning the dose may assist in situations of poor patient compliance. Australian regulations do not identify multiples or fractions as circumstance to prohibit compounding. FDA considers that compounded preparations of two or more commercially available drug products are essential copies of commercial products, unless other criteria apply. [11] FDA does not consider factors such as a lower price, as sufficient to establish that the compounded drug product is not essentially a copy of the commercially available drug product. [11]

Summary

Compounding provides the

clinician with pharmacotherapeutic options that are not commercially available, the patient with suitability-related and compliance-related improvements and the pharmacist with professional satisfaction and possibly financial reward. All of these factors are underpinned by the purpose of compounding, which is improved patient outcomes.

References

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CPD MULTIPLE CHOICE QUESTIONS

1. Which regulations and guidelines provide the limits of compounding?

- A. The Therapeutic Goods Act (1989) and Therapeutic Goods Regulations (1990)
- B. The guidelines on compounding of medicines (Pharmacy Board of Australia)
- C. The Medicines Shortage Information Initiative
- D. A and B
- E. All of the above

2. Under which circumstances is compounding permitted in Australia?

- i. The commercial drug is unavailable due to a drug shortage
 - ii. The commercial drug is unavailable due to it being withdrawn for reasons of safety
 - iii. The commercial drug is unsuitable for the specific patient
 - iv. In clinical trials sanctioned by the pharmacy's ethics committee
 - v. The patient cannot afford the commercial product
- A. All of the above
 - B. i and iii
 - C. i, ii and iii
 - D. i, ii, iii and iv
 - E. i, ii and iv

3. Which circumstances are identified in the Guidelines on Compounding of Medicines as ones where compounding may NOT occur?

- A. Digoxin 12.5mcg oral liquid for a cat. Commercial tablet products containing digoxin 62.5mg or 250mcg are available.
- B. Bactroban™ is in short supply and there is no commercial equivalent
- C. Thyroxine tablets in all brands are out-of-stock at all the wholesalers
- D. The prescription is for a scheduled drug, for which you cannot find any supporting clinical evidence for the intended clinical indication
- E. The local university is conducting a clinic trial for oxytocin nasal spray which has been sanctioned by an approved ethics committee

4. Where a commercial drug appears to be out-of-stock at the pharmacy's preferred wholesaler, the pharmacist should:

- A. Explain this to the patient and offer to source it from another wholesaler
- B. Offer to compound the medication as soon as possible to avoid delaying treatment
- C. Offer to access the drug through the Special Access Scheme
- D. Confirm with the Medicines Shortage Information Initiative and other wholesalers before offering to compound it
- E. Confirm with the ARTG for generic alternatives, confirm the shortage on the Medicines Shortage Information Initiative and with other wholesalers before offering to compound it

5. Five month-old Reece who is blind has been discharged from hospital with a compounded prescription for melatonin oral liquid. You haven't compounded this preparation. In determining whether you are permitted to compound it, you would consider:

- i. the circumstances to compound
 - ii. whether the facility, equipment, environment and training are appropriate for the risk
 - iii. the evidence of safety, efficacy and stability of this medication
 - iv. the medical history of the patient
 - v. whether the patient can afford the medication
- A. All of the above
 - B. i and iii
 - C. i, ii and iii
 - D. i, ii, iii and iv
 - E. i, ii and iv



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