Navigating the TGA's Requirements for Combination Products

Combination products are integral to the healthcare system and play an increasingly important role in patient safety and medicinal usability, enhancing therapeutic benefits and improving outcomes.

According to analysis, the drug-device combination market was valued at US$127.8 billion in 2022 and it is predicted to grow at a compound annual growth rate of 8.9% between 2023 and 2030.[1]

While combination products have been available for many years, advances in technologies, as well as the need for 'user-friendly' delivery of medicines, have led to an increase of these types of products globally and to a new generation of combination products.

Today, combination products have gone well beyond simple drug-release delivery systems, such as drug-eluting stents, to now offering intelligence and analytical capabilities that have the potential to reshape medicine.[2] These include wearable sensors, 3D-printed implantable modules and digital drugs offering real-time monitoring.

Australia's Combination Pathway

Australia's Therapeutic Goods Administration (TGA) recently published its updated guidance on combination products and what it refers to as "boundary" products as a means to give sponsors and manufacturers greater clarity on the category and pathway for their therapeutic goods.[3]

The 2023 guidance updates the 2005 guidance, providing more context around what combination products are as well as additional considerations, given that much has changed in the market in the past 18 years.

In its guidance, the TGA defines combination products as those with components that have more than one therapeutic effect, for example, medicine-medical device combinations and medical devices that incorporate or are used to administer a medicine. Boundary products are defined as those that have characteristics from two or more categories and for which the appropriate regulatory pathway is not necessarily obvious.

In addition to the guidance, in April 2024 the TGA provided a further update with examples of boundary and combination products and their product category.[4] This provides manufacturers and sponsors with information on how the agency is likely to regulate common boundaries and combination products. As the TGA makes further determinations on these products, it is likely that examples will continue to be updated.

How the agency regulates boundary products will depend on their principal therapeutic effect, therapeutic claims and stated intended use. Boundary products can include products that contain medicinal substances that work in an ancillary way, which, depending on their therapeutic effect, may be regulated as medicines. Examples include alcohol swabs and disinfectants with antiseptic claims that may be classified as medicinal products, and nasal decongestion products and eye lubricants that, depending on the mode of action, may be a medical device or a medicinal product.[3]

In Australia, the way combination products are regulated depends on the primary mode of action (PMOA) for achieving their therapeutic effect, as well as the primary intended purpose. Drug device combinations may be regulated as either medicines or medical devices and would therefore be registered as such. Examples include:

- Devices that administer medicine, such as syringes and droppers – are regulated as medical devices
- Co-packaged medicines with devices where the medicine is the main component and the device is used to measure or administer the medicine – regulated as a medicinal product
- Integral combination products, where the device and medicine form a single, non-reusable unit, such as pre-filled inhalers – registered as a medicine
- Devices incorporating a medicine where the medicine's action is considered secondary, such as a heparin-coated catheter – registered as a medical device

Medical device companies must have their product in the Australian Register of Therapeutic Goods (ARTG) database unless "the product is exempt from ARTG inclusion, excluded from regulation by TGA or otherwise approved". Where a device is a component of a medicinal product, it follows the Essential Principles from the Therapeutic Goods (Medical Devices) Regulations 2002 and, as such, does not need a separate ARTG entry, unless supplied separately.[5,6] The Essential Principles are safety and performance requirements that determine whether the product has been designed according to safety principles and risk mitigation, that solutions are best practices, and that the benefits outweigh the risks.[7]

The medicinal component of a combination product is evaluated against appropriate TGA regulatory requirements, to assess the product's safety, quality, and efficacy.

There are, however, innovative combination products that are harder to classify if there is no clearly defined PMOA, for example, customised 3D-printed scaffolds with incorporated medicinal products and bioprinting material that is classified as part of a medical device.[8,9]

Streamlining the Combination Product Pathway

In the devices space, there have been recent changes which now allow abridged pathways for drug-device combinations, permitting overseas manufacturers to avoid the expensive and extensive TGA full conformity assessment process under certain circumstances.

This paves the way for more innovative combination products that have been approved in some major markets to be brought into Australia more expeditiously.

For example, devices that incorporate a medicine can leverage certification through the European Union's Medical Device Directive or Medical Device Regulation (MDR) for ARTG

application.[10] If this is not available, they must undergo a TGA conformity assessment first, then subsequent ARTG application.

The abridged pathway can be a huge time saver since these are Class III medical devices in Australia and, without appropriate overseas evidence, can face a lengthy conformity assessment process with the TGA. This process includes in-depth assessment of the manufacturer's compliance with the Quality Management System requirements, as well as review of the technical documentation to establish compliance of the device with the applicable Essential Principles.

The regulator requires companies to supply a significant amount of documentation including device verification and validation information, supplier agreements, storage and packaging, sterilisation and other device documents. In addition, manufacturers may be subject to an onsite audit by the TGA prior to certification.[11] Similarly, once certification is received, the TGA conformity assessment requires ongoing maintenance. For example, manufacturers are required to notify the TGA of any 'substantial changes' to the QMS, manufacturing processes or device design, and such changes must be assessed and approved by the TGA prior to implementation. This process is also lengthy and expensive.

In comparison, most changes to ARTGs supported by overseas evidence will not require notification to, or assessment by, the TGA, and can be implemented once the overseas body has assessed and approved the change.

It is important to note that while TGA does recognise overseas evidence from a number of countries for medical devices, that recognition is restricted to the EU when it comes to devices incorporating a medicine.[9] That is because the conformity assessment process is similar to that carried out by a notified body in the EU – a requirement for the assessment and certification (or recertification) of most medical devices and *in vitro* diagnostic devices placed on the EU market.[12]

Similarly, when it comes to medicinal products, the TGA will, where possible, use assessments from comparable overseas regulators (COR). This will depend on whether there is enough similarity between the TGA and a COR, as is the case with the European Medicines Agency, and whether other key criteria are met, such as that the indication proposed is equivalent.[13]

Patient Benefits of Abridged Pathways

Australia faces the same health challenges as many other markets, specifically a rising prevalence of chronic diseases such as cardiovascular disorders, diabetes, respiratory illnesses and cancer.

To address these issues, patients and physicians are looking to products that are designed to provide a more integrated and effective approach to patient care by combining drugs and medical devices, thereby controlling and targeting the release of the drug product and delivering minimally invasive treatment.[1] The benefits of such an approach include improved treatment effectiveness, enhanced patient compliance, and simplified healthcare delivery.

In all major markets, streamlined regulatory pathways and the addition of clearer guidelines for combination products have facilitated faster approval processes.[14]

And the marketplace for combination products continues to evolve, as more innovative technologies emerge, paving the way for improved patient care.[15] Regulatory authorities, including the TGA, are responding to these cutting-edge technologies through more streamlined pathways. Ultimately, the goal is to provide patients with products, including combination products, that can more effectively treat and diagnose life-threatening or debilitating diseases, while continuing to demand manufacturers and sponsors meet safety, quality and efficacy requirements.

The information provided during this presentation does not constitute legal advice. PharmaLex Pty Ltd and its parent Cencora, Inc., strongly encourage readers to review available information related to the topics discussed herein and to rely on their own experience and expertise in making decisions related thereto.

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Piety Rocha

Piety Rocha is the Director, Head of Regulatory Affairs & Country VDC Head at Pharmalex, Australia. She has more than 20 years of experience in the Australian and New Zealand pharmaceutical industry. Piety is a seasoned regulatory affairs professional, with extensive knowledge and expertise covering innovative and generic prescription medicines across multiple therapeutic areas.

Heyam Kalla

Heyam Kalla is Associate Director, Team Lead Medical Devices / IVD at Cencora Pharmalex, Australia. As a regulatory affairs and quality assurance professional in the medical devices industry, Heyam has extensive experience in pre-market activities and post-market surveillance for medical devices in Australia and New Zealand.