Sterile Compounding – Regulations, Application & The Future

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Session Overview

- The push for GMP – why?
- Current Regulations
- Future Regulations
- Gone to GMP? Inspection Hot Spots
- The Future of Compounding
The push for GMP – Why?
In 2014, 14 individuals from New England Compounding Center ("NECC") were indicted on federal charges relating to the 2012 fungal meningitis outbreak that traced back to NECC-made methylprednisolone.

The medication had been contaminated with mould due to NECC’s failure to maintain its clean room and use sterile raw materials while mixing the injectable drugs.

The contaminated drugs were administered to over 14,000 patients across 20 states. At least 64 people have died; over 720 were treated for persistent fungal infections.
### Multiple Adverse Events

Six people – including NECC President Barry Cadden and pharmacist Glenn Chin – were indicted under the Racketeering Influenced and Corrupt Organizations Act (“RICO”).

The RICO count alleged 68 overt acts, including 25 counts of second degree murder against Cadden and Chin. They face the possibility of life in prison.

Years earlier, the FDA refused to grant the NECC a GMP manufacturing licence after inspecting the facilities several times. FDA’s cited reasons that were very similar to those that led to the fatal contamination.
Australia is not immune...

- Multiple significant safety issues associated with non-GMP regulated pharmacies in Australia (recent publicly documented events)
  - Glutathione adverse reactions in NSW (2014)
  - Incorrect chemotherapy dosages provided in SA (2014/15)
- Based on information available on these events, it is highly likely they would have been prevented through implementation of GMP principles
FDA response to NECC disaster

**Drug Quality and Security Act**, 27 November 2013 - granted the FDA more authority to regulate and monitor the manufacturing of compounded drugs.

Creation of Section 503B for outsourcing facilities.

Outsourcing facilities that register under section 503B are regulated by FDA:

- must comply with cGMP requirements
- will be inspected
- must meet certain other conditions, such as reporting adverse events

Drugs compounded by an outsourcing facility can qualify for exemptions from the FDA new drug approval requirements and the requirement to label products with adequate directions for use.
Current regulation of compounding pharmacies in Australia

A license from the TGA is **not** required when a pharmacist is practicing:

- In a pharmacy which is open to the public, or on the premises of a private hospital.

**OR**

- In public hospitals or public institutions, and medicines are manufactured for supply in public hospitals or public institutions within the same state or territory.

Must still meet the quality standards set out in the Therapeutic Goods Act 1989

Regulated* by the Pharmacy Board of Australia
Current regulation of compounding pharmacies in Australia

Compounding pharmacies **must** comply with practice standards and guidelines including:

- Pharmaceutical Society of Australia Professional Practice Standards, Standard 10 and 11
- The Society of Hospital Pharmacists of Australia SHPA Standards of Practice
- Australian standards for cleanrooms & OH&S
- State, territory and Commonwealth legislation relevant to the practice of pharmacy and pharmacy supply of medicines
- The section *Extemporaneous dispensing* in the current edition of the *Australian Pharmaceutical Formulary and Handbook*

* In reality, they are largely self-regulated
Why get a TGA license?

**Flexibility**
- Ability to go beyond named patient compounding
- Use own stability data to extend expiry dates
- Larger potential sales base

**Reputation and status**
- Improve commercial opportunities
- Greater perception of quality
- Greater “reality” of quality??

**Government funding**
- A TGA licensed pharmacy may receive up to 50% more per script than an un-licensed pharmacy
Future regulation of compounding pharmacies in Australia

Option A:
• Status quo

Option B:
• Enhance co-regulation and update legislation

Option C:
• Manufacturing license for specified manufacture in pharmacies
Future regulation of compounding pharmacies in Australia

Reform process has slowed (stopped?) since last Community Pharmacy Agreement

• 50% higher fee for compounders with TGA licence compounding chemotherapy drugs

Important development earlier this year when public draft issued

• Pharmacy Board of Australia ‘Guidelines on compounding of medicines’ section
• “Expiry of compounded parenteral medicines”
Future regulation of compounding pharmacies in Australia

Compliance with legislation, guidelines and practice standards

When compounding parenteral medicines (as described above), pharmacists must strictly adhere to all relevant legislation, guidelines and practice standards as outlined in the section Relevant legislation and practice standards in these guidelines, and the principles and procedures outlined in at least one of the following guides/standards, as applicable to the practice setting:

- the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (PE 010-4), or
- the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, as is required by TGA licensed manufacturers (PE 009-8), or
- the USP–NF (797) Pharmaceutical Compounding—Sterile Preparations.
Alternatives to PE009 & Annex 1

USP 797 or PIC/S GMP Guide for Healthcare Establishments (PE010)

- More focussed than PE009. Provide guidance where none is available in medicinal products GMPs
- Typically less stringent – especially in relation to environmental monitoring
- Neither currently provide a suitable alternative if GMP licence is sought (but are a good place to start)
USP 797: Pharmaceutical Compounding – Sterile Preparations

- Revision pending publication (public comment closed in Jan)
- FDA uses 797 for inspecting compounders
- Specific instruction for compounders on a range of issues not covered in GMPs (notably Beyond Use/In Use times)
- EM requirements considerably more lenient than GMPs (and in some cases, less well defined)
- Not recognised as an acceptable GMP standard by TGA. (Very weak on Quality Management by comparison)
PIC/S GMP Guide for Healthcare Establishments (PE010)

- Revised in March 2014
- Some in EU use this for inspecting compounders
- Based on PE009, with modifications for compounders
- EM requirements more lenient (but not as lenient as USP)
- Unfortunately, still not recognised as an acceptable GMP standard by TGA
Gone to GMP? Inspection Hotspots
Top 10 FDA concerns in Sterile Compounding

- Inadequate or lack of environmental monitoring of facility and people
- Inadequate laboratory procedures and controls (definition of a “batch”, sampling and testing controls)
- Lack of Standard Operating Procedures to prevent microbial contamination
- Inadequate deviation/variance controls and lack of adequate investigation
- Stability program non-existent or does not support beyond use dating
Inspection Concerns for Pharmacies

Top 10 FDA concerns in Sterile Compounding

- Inadequate validation of final sterilization (filter or terminal), media fill design
- Inadequate cleaning and disinfecting programs
- Batch release (most done at risk or with no testing for sterility, potency, identity, and pyrogens)
- Control of equipment (preventive maintenance and calibration program inadequate or nonexistent)
- Inadequate facilities designs and controls, inadequate smoke studies
Design issues in the GMPs

Some of the key regulations which can cause design issues:

- Materials and personnel flow – concept of personnel and material airlocks
- Separation of product types & manufacturing stages
- Room grading requirements
- Continuous particle monitoring of critical zones
- Gowning requirements (and therefore gowning facilities)
- Facility finish requirements
- Facility monitoring requirements
- Storage requirements, including segregation
Issues with Implementing PQS

- Appropriate, effective and implemented Document Management Systems
- Understanding and implementation of Quality Risk Management (QRM)
- Appropriate personnel and segregation of responsibilities
- Effective validation program (manual processing)
- Materials traceability
- Third party agreements
The Future of Compounding
Manual Compounding - The Present
“Manual” Compounding - The Future