New TGA Requirements for Microbiology

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ARCS: Topics to cover

- What’s new in TGO 77
- Sponsor obligations under TGO 77
- Relationship between TGO 77 and ARGPM Appendices 16 & 17
- Common deficiencies with applications in the field of microbiology
- What could industry do better in relation to microbiology
Therapeutic Goods Order No. 77

Microbiological Standards for Medicines
Requirements for finished products (effective January 1, 2010):

- Sterile medicines
- Multidose medicines
- Non-sterile medicines

TGO 77: Sterile medicines

- **Requirements:**
  - Must comply with Test for Sterility*
  - Must comply with Bacterial Endotoxin Test*

* Harmonised pharmacopoeial tests
TGO 77: Multidose medicines

- Requirements:
  - Must comply with BP/Ph. Eur. preservative efficacy test and acceptance criteria
  - Liquid oral antacids can comply with USP preservative efficacy test and acceptance criteria
TGO 77: Non-sterile medicines

- Requirements for non-sterile medicines:
  - Must comply with relevant harmonised acceptance criteria for microbiological quality (BP/Ph. Eur./USP)
  - **Exception** – complementary medicine oral dosage forms containing raw material of natural (animal, vegetal or mineral) origin
Requirements for non-sterile medicines:

- Complementary medicine oral dosage forms containing raw material of natural (animal, vegetal or mineral) origin:
  - dosage forms to which boiling water **IS NOT** added before use must comply with acceptance criteria in Schedule 1
  - dosage forms to which boiling water **IS** added before use must comply with acceptance criteria in Schedule 2
TGO 77: Non-aqueous preparations for oral use

- Harmonised criteria:
  - TAMC $10^3$ CFU/g/mL
  - TYMC $10^2$ CFU/g/mL
  - *E. coli* absent 1g/mL

- TGAL Guidelines:
  - TAMC $\leq 10^3$ CFU/g/mL
  - Y & M $\leq 10^2$ CFU/g/mL
  - Enterobacteria $\leq 10^2$ CFU/g/mL
  - *E. coli* absent 1g/mL
  - *Salmonella* absent 10g/mL
TGO 77: Aqueous preparations for oral use

- **Harmonised criteria:**
  - TAMC $10^2$ CFU/g/mL
  - TYMC $10^1$ CFU/g/mL
  - *E. coli* absent 1g/mL

- **TGAL Guidelines:**
  - TAMC $\leq 10^3$ CFU/g/mL
  - Y & M $\leq 10^2$ CFU/g/mL
  - Enterobacteria $\leq 10^2$ CFU/g/mL
  - *E. coli* absent 1g/mL
  - *Salmonella* absent 10g/mL
TGO 77: Rectal use

- Harmonised criteria:
  - TAMC $10^3$ CFU/g/mL
  - TYMC $10^2$ CFU/g/mL

- TGAL Guidelines:
  - No specific category
TGO 77: Oromucosal, gingival, cutaneous, nasal & auricular use

- Harmonised criteria:
  - TAMC $10^2$ CFU/g/mL
  - TYMC $10^1$ CFU/g/mL
  - St. aureus absent 1g/mL
  - Ps. aeruginosa absent 1g/mL

- TGAL Guidelines:
  - TAMC* $\leq 10^2$ CFU/g/mL
  - Pseudomonads absent
  - St. aureus absent
  - *TAMC $\leq 10$ CFU/g/mL
    antiseptics/corticosteroids
TGO 77: Vaginal use

- Harmonised criteria:
  - TAMC $10^2$ CFU/g/mL
  - TYMC $10^1$ CFU/g/mL
  - *St. aureus* absent 1g/mL
  - *Ps. aeruginosa* absent 1g/mL
  - *C. albicans* absent 1g/mL

- TGAL Guidelines:
  - No specific category
TGO 77: Transdermal patches
(one patch, adhesive layer & backing)

- Harmonised criteria:
  - TAMC $10^2$ CFU/patch
  - TYMC $10^1$ CFU/patch
  - *St. aureus* absent per patch
  - *Ps. aeruginosa* absent per patch

- TGAL Guidelines:
  - No specific category
TGO 77: Inhalants
(special conditions apply to liquid preparations for nebulisation)

- Harmonised criteria:
  - TAMC $10^2$ CFU/g/mL
  - TYMC $10^1$ CFU/g/mL
  - *St. aureus* absent 1g/mL
  - *Ps. aeruginosa* absent 1g/mL
  - BTGN bacteria absent 1g/mL

- TGAL Guidelines:
  - No specific category

BTGN – bile tolerant gram negative
TGO 77: Complementary medicine oral dosage forms containing raw material of natural (animal, vegetal or mineral) origin:

- Dosage forms to which boiling water **IS NOT** added before use:
  - Must comply with acceptance criteria in Schedule 1
  - Schedule 1 consistent with 2009 BP/Ph. Eur. special provision criteria

- TAMC $\leq 10^4$ CFU/g/mL
- Y & M $\leq 10^2$ CFU/g/mL
- BTGN bacteria $\leq 10^2$ CFU/g/mL
- *E. coli* absent 1 g/mL
- *Salmonella* absent 10 g/mL
- *S. aureus* absent in 1 g/mL

Similar to TGAL Guidelines with exception of *S. aureus*
TGO 77: Complementary medicine oral dosage forms containing raw material of natural (animal, vegetal or mineral) origin:

- Dosage forms to which boiling water IS added before use (herbal teas):
  - Must comply with acceptance criteria in Schedule 2

- Schedule 2 – hybrid of TGAL Guidelines & 2009 BP/Ph. Eur special provision criteria
  - TAMC ≤ 10^7 CFU/g/mL
  - Y & M ≤ 10^5 CFU/g/mL
  - BTGN bacteria ≤ 10^2 CFU/g/mL
  - E. coli absent 1 g/mL
  - Salmonella absent 10 g/mL
TGO 77: Microbial limits test methods

Requirements:

- Mandates harmonised pharmacopoeial test methods only for referee testing by official laboratory

- Does not mandate harmonised pharmacopoeial test methods for routine QC testing

- Sponsors must determine risk to product from other objectionable organisms not just specified organisms
What is an objectionable organism?

- Potential to cause infection when a medicine is used as per label directions
- Capable of growth in a medicine
- Cause spoilage/reduce efficacy of a medicine
- Many organisms can be objectionable under right circumstances
Why the increased interest in objectionable organisms?

- International harmonisation of pharmacopoeial chapters* for microbiological quality of pharmaceutical preparations:
  - Might need to test for other organisms
  - Evaluate significance of “other organisms” (if recovered)
  - Assess risk from contamination of medicine with “other” organisms

- Adoption of TGO 77 Microbiological Standards for Medicines
  - Draws heavily on harmonised pharmacopoeial chapters

* Term “objectionable” not used in final version
Objectionable organisms - what do the harmonised pharmacopoeial chapters state?

- The list (specified organisms) is not necessarily exhaustive and for a given preparation it may be necessary to test for other microorganisms depending on the nature of the starting materials and the manufacturing process.

* BP/Ph. Eur., USP, JP
Objectionable organisms - what do the harmonised pharmacopoeial chapters state?

- In addition to specified organisms the significance of other microorganisms recovered is evaluated in terms of:
  - Route of administration (hazard varies)
  - Formulation (ability to support growth, preservation, $a_w$ etc)
  - Method of application
  - Intended recipient (neonates, elderly, compromised)
  - Use of immunosuppressive agents, corticosteroids
  - Presence of disease, wounds, organ damage
Objectionable organisms - what do the harmonised pharmacopoeial chapters state?

- Where warranted, a risk-based assessment of relevant factors is conducted by personnel with specialised training in microbiology and in the interpretation of microbiological data.
Are objectionable organisms a concern?
Organisms recovered from non-sterile medicines – what do I do?

- Evaluate their significance in the medicine to determine whether they are objectionable or not

- Need to thoroughly understand your product

- Remember - medicine must be safe for use

Not a new concept!!

- Regulatory agencies have always required each batch of medicine to be free from contamination with objectionable organisms (e.g. TGA, US FDA, UK MHRA)
Objectionable organisms & pharmacopoeias

- Pharmacopoeial test methods:

  - Intended for use to detect specified organisms
  - Used to demonstrate a medicine/substance meets monograph requirements
  - Never intended for use as methods to detect all potential pathogens - not rigorous QC tests
Objectionable organisms & pharmacopoeias

Pharmacopoeial acceptance criteria:

- Acceptance criteria might not be suitable as QC specifications
- Acceptance criteria are *minimum requirements* to be met
- Demonstrating absence of specified organisms is not enough to demonstrate microbial quality of non-sterile medicines
Microbial contamination of non-sterile medicines

- Contamination with specified organisms
  (e.g. *Salmonella*, *E. coli*, *Ps. aeruginosa*, *S. aureus*, *C. albicans*)

- Rare
- Attracts a lot of attention
- Public generally aware that *bug is bad*
- Potential for infection is known
Microbial contamination of non-sterile medicines

Contamination with “other” objectionable organisms:

- More common
- Generally less public attention
- Wide variety of opportunist contaminants
  - limited pathogenicity for healthy individuals
  - might be able to replicate readily in formulation
  - can present a hazard to compromised individuals
  - infective dose necessary to initiate infection unknown for most opportunists
  - can cause spoilage/reduce efficacy of medicine
TGA consumer level recalls: Non-sterile medicines since 2004

- Specified organisms:
  - 2007: Salmonella (herbal teas)

- Other” organisms:
  - 2006: Creams, lotions - *B. cepacia*, *S. maltophilia*, *Ps. putida*, *Acinetobacter* & *Enterobacter* species
  - 2005: Antiseptic lotion - *B. cepacia*
  - 2004: Antiseptic mouth rinse & gel - *B. cepacia*
  - 2004: Oral liquid - Enterobacteria
  - 2004: Oral liquid - Mould
Recent recall: non-sterile dosage form

- Two batches multidose topical product recalled to retail/hospital level March 2009:
  - >10³ CFU/g Gram negative bacteria (*Klebsiellae*, several unidentified pseudomonad type bacteria – not *Ps. aeruginosa*)
  - >10³ CFU/g yeast (mixed “unusual” yeasts - not *C. albicans*)
  - One batch - suspect link to nosocomial colonisation

NB Medical device – Essential Principles apply not TGO 77
EPs do not specify limits – use TGO 77 only as a guide
Objectionable organisms: Important points

Company is responsible for:

• Quality and safety of their products
• Determining the absence of “other” objectionable organisms from their products
• Determining risk/s associated with their product from “other” organisms to ensure product is free from objectionable organisms (not just specified organisms)
• Ensuring access to competent microbiology group

Risk documentation to be available to TGA for review if required (eg. could be requested for review - product registration/listing, post-market testing, GMP audits)
Objectionable organisms: Important points

- Regulatory agencies and pharmacopoeias are not responsible for:
  - Developing/providing test methods to detect all potential pathogens
  - Providing a list of objectionable organisms for different dosage forms
  - Providing a list of objectionable organisms for different consumer groups
Contamination with objectionable organisms: Where do I start?

Consider the finished product and risks of infecting the consumer:

- **What dosage form is it?**
  - solid oral dosage form with low $a_w$ - lower risk
  - topical dosage form with high $a_w$ - higher risk

- **How will it be used (route of administration)?**
  - e.g. intact skin - lower risk
  - e.g. broken skin - higher risk
Contamination with objectionable organisms: Where do I start

• Who is going to use it?
  - healthy individuals - lower risk
  - compromised/debilitated individuals - higher risk
  - immunosuppressed individuals - higher risk
  - neonates, young children, elderly - higher risk
Contamination with objectionable organisms: Where do I start?

- Consider the organism:
  - What is it?
    - need to know what you are dealing with
    - some level of identification is necessary
    - consider identification to at least genus level
    - solid oral dosage forms – ?? identify contaminants present in high numbers
    - other dosage forms – ?? identify all contaminants
Contamination with objectionable organisms: Where do I start?

- Consider the organism cont’d:
  - Does it cause illness?
    - if so, under what conditions?
    - is the infective dose known?
  - Can it survive or grow in the product?
  - Can it spoil/reduce efficacy of product?
  - What is relationship of organism to other organisms?
    - could its presence indicate potential for other more objectionable organisms to be present?
Points for consideration:

• Some opportunists have simple nutritional needs:
  - can survive in a wide range of medicines
  - can be resistant to preservatives, biocides
  - can be present in very high numbers
  - might be no visible signs of contamination
  e.g. pseudomonads, *Klebsiella*, *Serratia*, *yeasts*
Contamination with objectionable organisms

Know what is “normal” for your product:

- numbers and types of organisms usually present
- deviations from “normal” – should ring alarm bells
- try and find root cause not just quick fix – thorough and methodical
It is important to know your product

- Is product high, medium or low risk for microbial contamination?

- Set suitable microbial limits (release & expiry specifications):
  - TGO 77 minimum specifications (not comprehensive)
  - assess risk from “other” objectionable organisms
  - not unusual for specifications to include limits for additional organisms not specified in TGO 77

- Use suitable test methods:
  - TGO 77 only mandates test methods for referee testing

- Demonstrate reliable “product history”:
  - product manufacture complies with GMP
  - consistent microbial content established
  - no requirement to batch release test all batches
Contamination with objectionable organisms

- Gram negative contamination of topical, nasal and inhalant preparations is a potential moderate to serious health hazard:
  - risks of infecting user are higher
  - prudent to include screening test for Gram negatives, including pseudomonads, non-fermenters
Contamination with objectionable organisms

- Examples of infections from use of contaminated topical medicines:
  - Burn patients – pseudomonad infection – antiseptic solutions
  - Ear piercings – *Ps. aeruginosa* infection – antiseptic solution
  - Infants (eczema) – Gram negative infections – creams
  - ICU patients – pseudomonad/*Acinetobacter* infections – mouthwashes
  - Neonates (ICU) – pseudomonad infection/colonisation – lubricant gel
TGO 77: Current action items

- TGO 77 effective January 1, 2010:
  - Update Australian Regulatory Guidelines:
    - Prescription medicines (sterility, ML, PE)
    - OTC medicines (sterility, ML, PE)
    - Complementary medicines (ML, PE)
Common Deficiencies:

Prescription Medicine Applications
Cat. 1 Applications: Aseptic manufacture

- Prefiltration bioburden limit exceeds $\leq 10$ CFU/100 mL
- Media fill studies inadequate:
  - Maximum hold and fill times not stated
  - Acceptance criteria not consistent with ISO 13408-1:2008
  - Not all aseptic manipulations validated (e.g. aseptic pooling sterilised APIs, transport of sterilised APIs/bulks between sites)
- Sterilising filter/s:
  - Bacterial retention studies - not supplied (or not performed)
  - Integrity testing - information not supplied
- Sterilisation processes - equipment, containers, closures:
  - Validation – information not supplied
Cat. 1 Applications: Terminal sterilisation

- Inadequate PPQ and MPQ studies:
  - Presterilisation bioburden limit not specified
  - Extended hold times for bulk/filled product prior to terminal sterilisation not microbiologically validated
  - If master load used for validation, inadequate information supplied to demonstrate that master load represents worst case
  - Evidence to demonstrate SAL of $10^{-6}$ throughout load not supplied
  - SAL calculations from validation studies not supplied
  - Radiation sterilisation – does not comply with ISO 11137 (as BIs used to validate process)
Cat. 1 Applications: Multidose preparations

- Ophthalmics and injectables for use in a single patient:
  - No, or inadequate data to support open shelf life period
  - Should include results of either:
    - repeated microbiological challenge testing; or
    - tests for presence of microorganisms in product containers used by patients for full open shelf life
Cat. 1 Applications: Labelling of injections in vial (no preservative)

- Does not comply with TGO 69, 3(5)(b)(ii):
  - Use in one patient on one occasion only. Contains no antimicrobial preservative

- PI not consistent with ADEC Resolution 7507:
  - Product is for single use in one patient only. Discard any residue

- PI for reconstitutable/dilutable product not consistent with ARGPM Appendix 14:
  - To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°-8°C for not more than 24 hours…
Cat. 1 Applications: Test for Sterility

- Batch release sterility test:
  - Application states *compliance with Ph. Eur./BP/USP*
  - No statement of compliance with *current* (harmonised pharmacopoeial) Test for Sterility (Ph. Eur., BP, USP)
Cat. 3 Applications: Increase in sterile medicine batch size

- No, or inadequate information about microbiological validation of associated changes:
  - Increased batch size might mean:
    - different equipment, e.g. additional filling line
    - longer holding and/or filling times
    - larger sterilisation loads
Cat. 3 Applications: Increase in sterile medicine batch size

- Aseptic manufacture – should include:
  - Media fill studies to validate increased batch size conducted under worst case conditions:
    - should include maximum permitted holding and filling times
  - Confirmation that integrity of sterilising filter is verified before use and tested after use
  - Prefiltration bioburden limit (≤ 10 CFU/100 mL)
Cat. 3 Applications: Increase in sterile medicine batch size

- Terminal steam sterilisation – should include:
  - PPQ and MPQ if changes to sterilisation load size or configuration - to show an SAL of $10^{-6}$ throughout load
  - Data to show microbiological quality of bulk not adversely affected by any increase in processing time
  - Presterilisation bioburden limit
Cat. 3 Applications: Change in site/new site for manufacture of sterile medicine

- No, or inadequate information about microbiological validation of sterile manufacture at the new site

- Type and extent of information required is the same as for a Category 1 application (i.e. initial application)
Cat. 3 Applications: Change in site/new site for manufacture of sterile medicine

- Aseptic manufacture – should include:
  - Confirmation that PPQ and MPQ for equipment sterilisation processes performed
  - Confirmation that PPQ and MPQ for container/closure sterilisation and depyrogenation processes performed (brief outline of studies performed)
  - Sterilising membrane:
    - Confirmation that bacterial retention studies performed (if filter type different to that used at original site)
    - Confirmation that integrity of sterilising filter is verified before use and tested after use
Cat. 3 Applications: Change in site/new site for manufacture of sterile medicine

❖ Aseptic manufacture – should include (cont’d):
  • Maximum permitted holding and filling times

  • Prefiltration bioburden limit (≤ 10 CFU/100 mL)

  • Media fill studies to validate aseptic manufacturing process conducted under worst case conditions:
    - should include maximum permitted holding and filling times
Cat. 3 Applications: Change in site/new site for manufacture of sterile medicine

- Terminal steam sterilisation – should include:
  - PPQ and MPQ if changes to sterilisation load size or configuration - to show an SAL of $10^{-6}$ throughout load
  - Data to show microbiological quality of bulk not adversely affected by any increase in processing time
  - Presterilisation bioburden limit
Cat. 3 Applications: Change in batch release sterility test site

- Application states *compliance with Ph. Eur./BP/USP*
  - No statement of compliance with *current* (harmonised pharmacopoieal) Test for Sterility (Ph. Eur., BP, USP)

- Should include statement of compliance with *current* Test for Sterility (current editions of Ph. Eur., BP, USP)
Cat. 3 Applications: Change in container/closure

- No information supplied about testing performed to demonstrate container/closure integrity:
  - e.g. change from vial/stopper to prefilled syringe

- Should include information about container closure integrity tests, e.g:
  - dye penetration testing
  - microbial ingress testing
Cat. 3 Applications: Extension to closed shelf life for multidose medicines

- No, or inadequate preservative efficacy (PE) data.

- Should include:
  - Results of Ph. Eur./BP PE testing performed at end of proposed shelf life – demonstrate compliance with Ph. Eur/BP PE test
  - Numbers of organisms inoculated and subsequent $\log_{10}$ reductions
Common Deficiencies:

Device Conformity Assessment Applications
Device CA applications

- Radiation sterilisation (ISO 11137):
  - Inadequate justification for defining product families
  - Inadequate justification for assigning new product to an existing product family
  - Insufficient information about frequency and method of dose auditing
Device CA applications

- Ethylene oxide sterilisation:
  - Inadequate justification for new product to be defined as equivalent to previously validated product, package or loading pattern
  - Inadequate justification for use of process challenge device (PCD):
    - equivalent or more challenging to process than most difficult to sterilise part of the product
  - Inadequate justification for use of worst case
    - especially validation of mixed loads
  - Insufficient information about biological indicator (BI):
    - type, spore count, D-value
Disinfectant and sterilant applications:

- Some applications are of a poor standard:
  - poorly organised
  - level of disinfectant not specified
  - documentation inadequate

- Labelling, product information, advertising material etc:
  - all efficacy claims must be supported by data
Device CA applications

- Disinfectant and sterilant applications (cont’d):
  
  - Test results provided do not support requirements for efficacy:
    - e.g. $4 \log_{10}$ reduction for Mycobacteria when $6 \log_{10}$ reduction required
    - little point in submitting data that clearly does not comply with requirements

  - Claims against blood borne viruses:
    - data submitted which does not comply with Australian requirements
    - tests must be conducted using a minimum 50% whole blood and for HIV and HCV, cell associated virus
Questions?