



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Update to the Manufacturing Principles for Medicinal Products

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Introduction to updated Manufacturing Principles

- Background
- Legal Requirements
- Operation of the Manufacturing Principles
- Walk through the major changes
- Questions





Background

- Australian Code of GMP, 2002
 - Significant change, based on PIC/S Guide
 - Harmonise requirements, mutual recognition agreements
 - Intent to periodically update to maintain consistency
 - Currently 7 years out of date and placing MRA equivalence at risk





Background

- PIC/S Guide to GMP for Medicinal Products
 - PIC/S Role
 - TGA one of 37 member nations
 - Guidance developed through technical committees, Expert Circles
 - Global consultation
 - Endorsement through Committee
 - Regularly reviewed and updated





Background

- Consultation
 - NCCTG endorsed consultation for ANZTPA for manufacturing requirements, based on PIC/S Guide
 - Consultation undertaken in 2007
 - Draft Rule prepared
 - October 2008 OMQ-Industry workshop & TICC
 - Meetings with GMP committees
 - Announcements at Seminars





Legal Requirements

Section 36 of the Act

(1) The Minister may, from time to time, determine written principles to be observed in the manufacture of therapeutic goods for use in humans.





Legal Requirements

Section 40 of the Act

(4) ... each licence is, except as otherwise specified in the licence, subject to the conditions that the holder of the licence will:

(a) ensure that:

- (i) the goods conform to any standard applicable to the goods; and*
- (ii) the **holder of the licence observes the manufacturing principles** in carrying out any steps in the manufacture of the goods under the licence*





Legal Requirements

*Therapeutic Goods (Manufacturing Principles)
Determination No. 1 of 2007*

- human blood and tissues and therapeutic devices

*Therapeutic Goods (Manufacturing Principles)
Determination No. 2 of 2007*

- active pharmaceutical ingredients (ICH adoption)

*Therapeutic Goods (Manufacturing Principles)
Determination No. 1 of 2009*





Operation of MP 1/2009

Manufacturing Principles (No. 1 of 2009)

- Commenced 30 July 2009 (registered on FRLI)
- Defines the Code as “PIC/S Guide to GMP for Medicinal Products PE 009-08, dated 15 January 2009”
- No automatic updates – requires Australian review and consultation**





Operation of MP 1/2009

Manufacturing Principles (No. 1 of 2009)

- Amends MP 1/2007
- Removes all references to medicinal products
- Revokes the specific Australian Sunscreens Code 1994
- Continues to be operational for Blood and Tissue and Therapeutic Devices





Operation of MP 1/2009

Manufacturing Principles (No. 1 of 2009)

- Revokes MP 2/2007
- Part 2 of the PIC/S Guide adopts the ICH GMP Guide for API manufacturers
- Excises Annex 4 & 5 – Veterinary Products
- Excises Annex 14 – Blood and Plasma





Operation of MP 1/2009

Manufacturing Principles (No. 1 of 2009)

- Must = Should
- Compliance requirement
- Failure to follow a requirement:
 - Not increase risk of harm or injury
 - Not contrary to a standard or condition of listing/registration
 - Not compromise record keeping requirements of the Code





Operation of MP 1/2009

Manufacturing Principles (No. 1 of 2009)

- Transitional period to 1 July 2010
- Manufacturer may elect to adopt early
- Observations concerning new requirements





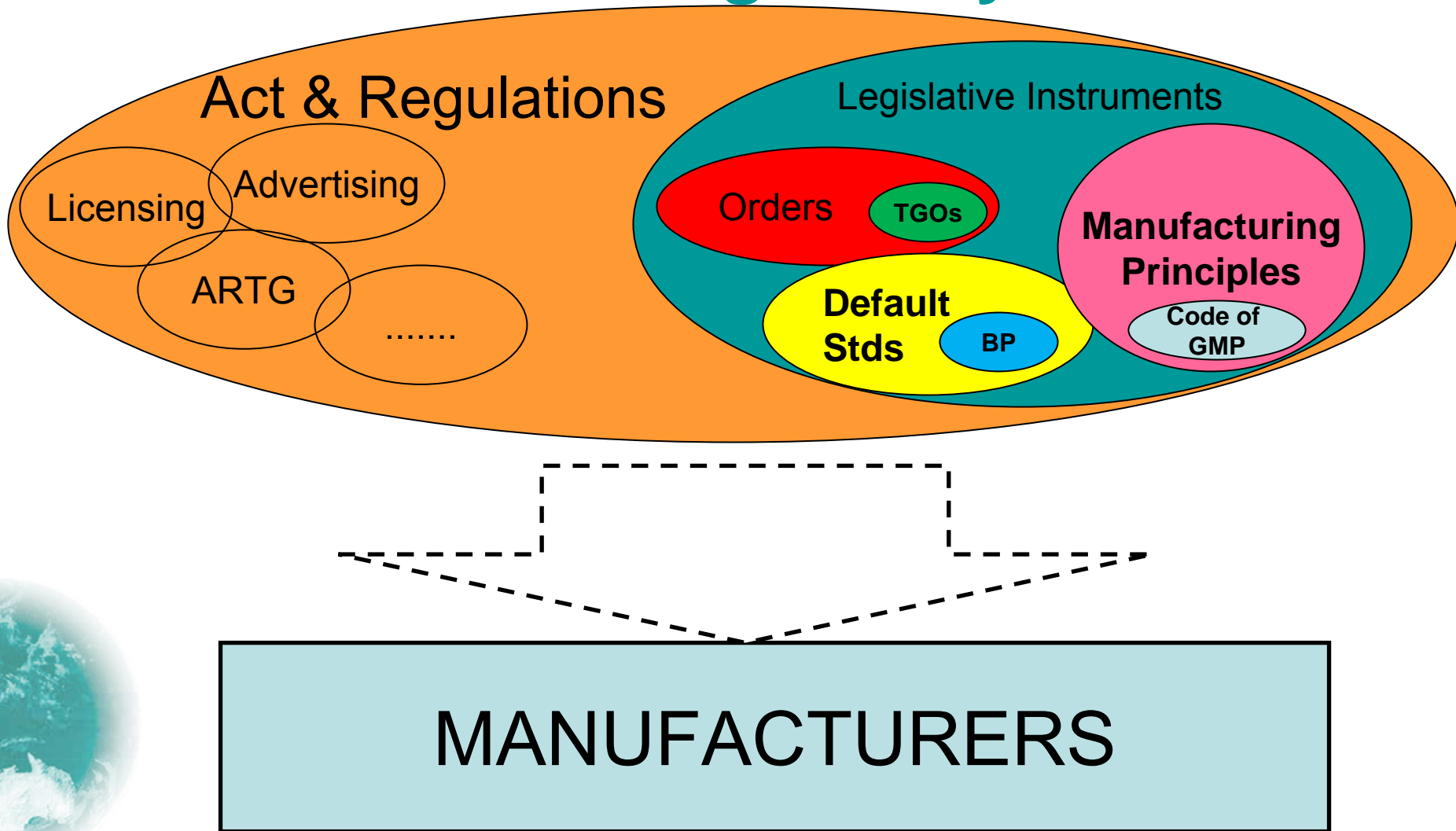
Australian Government
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www.tga.gov.au





1 – Regulatory framework.





1 – Keeping-up-to-date.

The screenshot shows the TGA website homepage with the following structure:

- Header:** Australian Government, Department of Health and Ageing, Therapeutic Goods Administration. Includes a search bar and links for 'A-Z guide', 'Sitemap', and 'Search the product register (ARTG)'.
- Main Title:** TGA - safeguarding public health & safety in Australia by regulating medicines, medical devices, blood & tissues
- Navigation Columns:**
 - Safety information:** Alerts/advisories, Product recalls, Report a problem, Safety monitoring.
 - About the TGA:** What the TGA does, TGA corporate information, Contact the TGA, Employment/job vacancies, International activities.
 - Information for:** Consumers, Health professionals, Manufacturers, Laboratories, Travellers, Importers/exporters, Media.
 - Regulation:** Regulated by the TGA (Medical devices, Complementary medicines, OTC medicines, Prescription medicines, Blood & tissues, IVDs & other therapeutic goods); Related information (Advertising, Clinical trials, Committees, Cosmetics, eBusiness services, Fees/payments, Labelling/packaging, Legislation, Regulatory reform, Scheduling medicines/poisons).
 - News:** What's new, Media centre, Subscribe to email updates, Consultations/reviews, Events/training, Hot topics (Nil).
- Footer:** Site last updated: 11 September 2009, URL: http://www.tga.gov.au/index.htm, Enquiries/feedback: Contact the TGA, www.australia.gov.au, Australian Government Department of Health and Ageing.

Two black arrows originate from the 'Regulatory reform' link in the 'Related information' column and point to a yellow box labeled 'Regulatory reform'. Another black arrow originates from the 'Legislation' link in the 'Related information' column and points to a green box labeled 'Legislation'.

Legislation

Regulatory reform



1 – Keeping-up-to-date.

The screenshot displays the Australian Government Department of Health and Ageing Therapeutic Goods Administration website. The page title is "Australian therapeutic products legislation". The main content area is divided into three columns: "Regulation", "Acts/regulations", and "Legislative instruments".

Navigation and Search:

- Search bar: Search
- Links: A-Z guide, Sitemap, Search the product register (ARTG)
- Tagline: TGA - safeguarding public health & safety in Australia by regulating medicines, medical devices, blood & tissues
- Menu: Safety information | About the TGA | Information for | Regulation | News | Contact the TGA
- Breadcrumbs: Home > Regulation > Legislation

Regulation (Left Sidebar):

- Regulated by the TGA
 - Medical devices
 - Complementary medicines
 - OTC medicines
 - Prescription medicines
 - Blood & tissues
 - IVDs & other therapeutic goods
- Related information
 - Advertising
 - Clinical trials
 - Committees
 - Cosmetics
 - eBusiness services
 - Fees/payments
 - Labelling/packaging
 - Legislation
 - Regulatory reform
 - Scheduling medicines/poisons

Acts/regulations (Middle Column):

- Therapeutic Goods Act 1989
- Therapeutic Goods Regulations 1990
- Therapeutic Goods (Medical Devices) Regulations 2002
- Therapeutic Goods (Charges) Act 1989
- Therapeutic Goods (Charges) Regulations 1990

Legislative instruments (Right Column):

- Excluded goods order No. 1 of 2008
- Groups orders
- Listing notices
- Manufacturing principles
- Medical devices notices & standards orders
- Therapeutic Goods Orders (TGOs)
- Therapeutic Goods Advertising Code
- Definition of British Pharmacopoeia
- Order that goods are therapeutic goods No. 1 of 1999
- Single therapeutic goods order

Related information (Bottom Middle):

- Enforcement guidelines
- Commonwealth of Australia Gazette notices
- Australia-US Free Trade Agreement
- Review of drugs, poisons and controlled substances legislation (the Galbally Review)
- Legislation changes & proposed changes

Footer:

- Web site copyright, security, disclaimer, & privacy statement
- Web page last updated: 3 September 2008
- URL: http://www.tga.gov.au/legis/index.htm
- Legend: Link to another website, Email link



Mfg Principles.

- ❑ On 29 July 2009 the National Manager determined the new **Manufacturing Principles (No1 / 2009)** to be observed by manufacturers of medicinal products, (including APIs and sunscreens) under Section 36(1) of the Therapeutic Goods Act 1989.





Mfg Principles.

	MP1/ 2009	Current standard (revoked)	PE-009-8 - New standard			
			Intro	Pt 1	Pt 2	Annexes
API	#	ICH – Q7 - 2000	#		#	#
Sunscreens	#	Sunscreen code – 1994	#	#		#
Medicines	#	Medicines code - 2002	#	#		#





Changes:

- Chapter 1 - Product Quality Reviews
- Chapter 1 - Quality Risk Management
- Chapter 6 - Ongoing Stability Programme





Product Quality Reviews.

☐ Clause 1.4.

- Regular periodic quality reviews.
- Consistency of the process.
- Appropriateness of specifications.
- Highlight any trends and identify product and process improvements.
- Conducted annually.





Product Quality Reviews.

To include, at least, review of:

- Past reviews (assessment of).
- Materials, in-process controls and finished product results.
- Failed batches, deviations or non-conformities and CAPA.
- Process, equipment or test method changes.
- Marketing authorisation variations, stability results.
- Complaints, returns and recalls.
- Qualification and validation status.
- Contractual arrangements.





Product Quality Reviews

Currently:

- Management reviews
- Trending/review:
 - Test results – materials/products
 - Deviations/non-conformances
 - Complaints/recalls
 - Changes – specs, process, materials
 - Validations/revalidation review





Product Quality Reviews

New Code:

- Structured, product-centric or grouped approach.
- Review at least annually.
- Grouped by product type eg solid dose forms, liquid dosage forms, sterile dose forms where scientifically justified.
- Other approaches may be considered with adequate justification:
 - Eg for contract manufacture, low volume products





Product Quality Reviews

Outcome:

- Holistic review of elements impacting upon product quality to assess whether corrective and preventative actions are required or whether revalidation should be undertaken.
- Performed by both manufacturer and marketing authorisation holder.





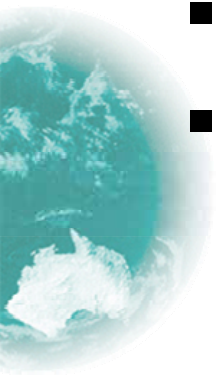
Product Quality Reviews.

If Sponsor \neq Manufacturer, then

- Technical agreement
- Responsibilities defined

The authorised person and sponsor are jointly responsible that the review is

- Timely
- Accurate





Product Quality Reviews.

Things to consider:

- A product centric approach?
- Is it logically & scientifically justified ?
- What is the relationship between sponsor and manufacturer?
- Technical agreements:
 - flow of information
 - final review and assessment





Product Quality Reviews.

July 2010 Expectations:

- The manufacturer has defined and documented the approach to PQRs with justification(s) where relevant.





Quality Risk Management.

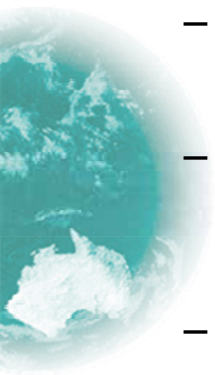
- Strengthened as a systematic process.
- Requirement of Manufacturing Principles (Determination No. 1/2009)...Section 5.clause 5





Quality Risk Management.

- The failure of a manufacturer of therapeutic goods in Australia to follow a particular procedure or requirement set out in an applicable Part of, or Annex to, the Code, constitutes a failure to comply with the Code, unless in relation to that particular procedure or requirement:
- the **manufacturer demonstrates**, to the satisfaction of the TGA, that the failure to adopt that procedure or requirement:
 - will **not increase the risk** of harm or injury to any person or will not potentially have the effect of causing or contributing to such harm; and
 - will **not increase the risk** of the therapeutic goods in question failing to comply with, where applicable, both the standard for that therapeutic goods and to the terms of the listing or registration; and
 - will not compromise the record keeping requirements contained in the Code; or
- where an alternative procedure to the procedure or requirement set out under an applicable Part of, or Annex to, the Code has been adopted, the **manufacturer demonstrates**, to the satisfaction of the TGA, that:
 - the alternative procedure will **not increase the risk** of harm or injury to any person or will not potentially have the effect of causing or contributing to such harm; and
 - the alternative procedure will **not increase the risk** of the therapeutic goods in question failing to comply with, where applicable, both the standard for that therapeutic goods and the terms of the listing or registration; and
 - will not compromise the record keeping requirements contained in the Code.





Quality Risk Management.

To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, and thus Quality Control and Quality Risk Management.





Quality Risk Management.

It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities.





Quality Risk Management

□ Clause 1.5

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product.

It can be applied both proactively and retrospectively.





Quality Risk Management

□ Clause 1.6

The quality risk management system should ensure that :

- The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.





Quality Risk Management.

□ Annex 20

- Corresponds to ICH Q9 guideline on QRM
- Is voluntary.
- Provides guidance on a systematic approach to quality risk management facilitating compliance with GMP and other quality requirements.





Quality Risk Management.

□ Annex 20

The degree of rigor and formality of QRM should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.





Quality Risk Management.

□ Annex 20 clause 34.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.



Quality Risk Management.

□ Annex 20 clause 35.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools





Quality Risk Management.



Annex 20

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.
- (AS/NZS ISO 31000:2009)





Quality Risk Management.

- Annex 20 Appendices
- Risk Management Methods and Tools
 - Overview of common approaches.
- Potential Applications for QRM eg.
 - Process development.
 - Quality defects.
 - Change management/control.
 - Computer systems/controls.
 - Materials management.





Quality Risk Management.

Considerations:

- Part of a systemic approach within the quality system.
- The approach and documentation should be consistent with the complexity and criticality of the issue.
- General premise is that QRM should be used to demonstrate how the principle of a Code requirement is achieved rather than to obviate the need to follow a requirement!





Quality Risk Management.

July 2010 Expectations:

- The manufacturer has defined and documented the approach to QRM with in accordance with the new requirements.





Quality Risk Management.

- Presentation: “Risk Management - TGA perspective” - A. Gould TGA web site

<http://www.tga.gov.au/manuf/presentation-qrm.pdf>

- PIC/S Aide Memoire – 2010





On-going stability.

- **On-going stability clauses 6.23-6.33**
 - Explicit requirements
 - The content of protocols
 - The number of batches
 - How results are to be handled.





On-going stability.

- Continuous appropriate program.
- Consideration for bulk/intermediates in studies.
- On-going protocol may be different from initial.
- No. batches/frequency of testing to allow trending.
- Bracketing/matricing if justified.
- Written agreement if studies performed at other than manufacturing site.





On-going stability.

Results should be available:

- To key personnel, and in particular the Authorised person.
- **At the site of manufacture for review by the competent authority.**
- Included in the Product Quality Reviews.





On-going stability.

July 2010 Expectations:

- The manufacturer has defined and documented the approach to the stability program relevant to the products manufactured in accordance with new requirements.





Sponsor-Manufacturer

Define responsibilities of each party

For example:

Sponsor

Marketing authorisation

PQR

Stability testing

Change control

Complaints

Recalls

Returns

RFS

MA

PQR results

Stability results

Batch Review

Manufacturer

MA

Deviations & OOS

CAPA

Validation/Qualification

Testing methodology

Rejection of product

Materials





PE-009-8 Part 2.

Incorporates ICH Q7 Guidelines for APIs into the Guide.

- Some rewording.
- Radiopharmaceutical APIs included.
- Annex 1 for Sterile APIs.
- Other annexes may apply also.





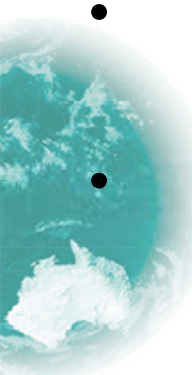
PE-009-8 Annexes.

Changes:

- Annex 1 – Sterile Products
- Annex 19 – Reference & Retention Samples
- (Annex 20 – QRM)

Excluded:

- Annex 4 & 5 - Manufacture of Veterinary Medicinal Products
- Annex 14 - Manufacture of Products Derived From Human Blood or Human Plasma.





Annex 1- sterile manufacture.

Changes include:

- Particulate levels in clean rooms, monitoring and classification.
- Garments in Grade A&B.
- Acceptance limits for Media Fills.
- Bioburden monitoring.
- Requirements for capping vials.





Annex 1- sterile manufacture.

Increase in the permitted number of particles in clean rooms and specific requirements for **how** clean rooms are monitored and classified.





Annex 1- sterile manufacture.

Maximum permitted number of particles/m ³ equal to or greater than the tabulated size				
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3,520 (3,500)	20 (0)	3,520 (3,500)	20 (0)
B	3,520 (3,500)	29 (0)	352,000	2,900 (2,000)
C	352,000 (350,000)	2,900 (2,000)	3,520,000 (350,000)	29,000 (2,000)
D	3,520,000 (3,500,000)	29,000 (20,000)	not defined	not defined



Annex 1- sterile manufacture.

Classification vs monitoring.

Classification:

- as per ISO 14644-1.
- Grade A = ISO Class 4.8 as per 5 micron counts.
- Monitoring locations/acceptance of results as per 14644-1.
- Effectiveness of current monitoring should be assessed (cf precipitation of particles in long lengths tubing).
- ISO 14644-2 on re-qualification periods or justified.





Annex 1- sterile manufacture.

Classification vs monitoring.

Monitoring:

- Rooms/devices monitored in operation.
- Locations based on formal **risk analysis** of classification results.
- **Continuous** in Grade A zones – frequency/ sample size appropriate to detect issues.
- Similar for Grade B – monitoring importance to A/B separation.
- 5.0µm monitoring as diagnostic tool of early detection of failure.
- Grade C/D monitoring based on risk assessment.





Annex 1- sterile manufacture.

Single use sterile protective garments in Grade A&B.

- Change every working session.
- “or at least once a day” deleted.





Annex 1- sterile manufacture.

Changes to acceptance limits for media fills.

- Harmonised with FDA aseptic guide.
- Previously, less than 0.1% (with 95% confidence).
- Now:
 - < 5000 units, no contaminated units.
 - 5,000 – 10,000 and > 10,000
 - One contaminated unit, consider revalidation.
 - Two contaminated units, revalidation.





Annex 1- sterile manufacture.

Bioburden monitoring:

- Assay per batch for both aseptically filled and terminally sterilised immediately prior to final step.
- Working limits related to efficiency for terminal sterilisation.
- Overkill parameters may justify periodic monitoring.
- Parametric release of finished product → incorporated as an in-process test.





Annex 1- sterile manufacture.

Increased requirements for partially stoppered freeze drying vials, capping and crimping.

- Partially stoppered freeze drying vials maintained in Grade A zone (basically equivalent to previous Cl.12).
- Aseptic process capping using sterilised caps or clean process capping outside aseptic core.
- Clean process – vials protected by Grade A zone up to leaving aseptic core, then Grade A air supply until caps are crimped.





Annex 1- sterile manufacture.

Provisional interpretation:

- Grade A air supply required:
 - In transfer tunnels from aseptic processing to crimping equipment in a “clean process”.
 - For transport of freeze-dried vials from freeze-drier to crimping equipment.
 - At the crimping equipment.





Annex 1- sterile manufacture.

Provisional interpretation:

- Grade A air supply classification:
 - Definition of “at rest”
 - **Crimping equipment** - with air supply operating, equipment off, no interventions.
 - **Tunnels** – with air supply operating, conveyor off, no interventions.
 - Non-viables/micro as per Grade A requirements. Active sampling probes located by risk assessment.
 - Smoke studies (at rest/in operation). Effective protection of vials should be demonstrated.
 - Limits for air velocity should be defined and justified.





Annex 1- sterile manufacture.

July 2010 Expectations:

- The manufacturer has incorporated new and changed requirements for sterile manufacture

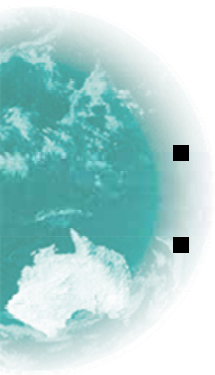




Reference and Retention Samples

□ Annex 19 - New annex – more detail

- Records of traceability required.
- Reference samples representative of the batch.
 - Additional samples to monitor process stress points.
 - Split packaging should be reflected in samples.
- Agreements to set out:
 - Authorised person to ensure reference and retention samples accessible.
 - Arrangements for samples – taking/location.
 - Closedown of a manufacturer.





Reference and Retention Samples

- Close down of manufacturer
 - Unexpired batches may remain on the market.
 - Detailed arrangements to be made for transfer of samples (and relevant documentation) to an authorised storage site.
 - Suitable storage and access maintained.





Mfg Principles.

□ PE-009-08

- Brings Australian in-line with current international practices.
- Maintains equivalence under MRAs with international regulatory partners,
- Continued recognition of certification of Australian companies.





Transition

- Industry information seminars in 2009
 - Stimulate awareness of changes in requirements
 - Answer initial questions
 - Initiate / progress organisational review
 - Identify areas requiring additional guidance
- Additional seminars in 2010 to cover Quality Risk Management





Transition

- Update Q&As
- Review current interpretive Guidance
 - Complementary medicines
 - Medicinal gases
 - (new) Product Quality Review
 - (new) Ongoing Stability Programs
- TWG's assessing other guidance





Conclusions

- Manufacturing Principle 1/2009 will become mandatory from 1 July 2010
- OMQ updating current interpretive guidance
- Developing further guidance for product quality reviews and ongoing stability program requirements
- Assess any issues being identified and publish Q&As





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