Background on PIC/S

(Pharmaceutical Inspection Cooperation Scheme)

Korea, March 2011

Mr Bob Tribe

Canberra, Australia

Background on Bob Tribe

- Former Chief GMP Auditor, TGA (1980-2003).
- Former Chairman PIC/S (2000-2001).
- Expert GMP Advisor to WHO.
- Expert GMP Advisor to regulatory authorities seeking PIC/S membership.
- GMP Consultant to manufacturers of medicinal products (eg. pre-TGA audits).
- ISPE Asia-Pacific Regulatory Affairs Advisor.
- Executive Consultant to PharmOut Pty Ltd, Australia.
- Initiated the preparation of ICH Q7A (API GMP).

Overview

- Introduction to PIC/S
- Current membership
- Benefits of PIC/S membership
- PIC/S approval process
- Experience of other countries joining PIC/S
- PIC/S GMP Guide & related documents
- PIC/S training for inspectors

PIC/S Goal

"To lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products".

Achievement of the PIC/S Goal

PIC/S Goal is achieved by:

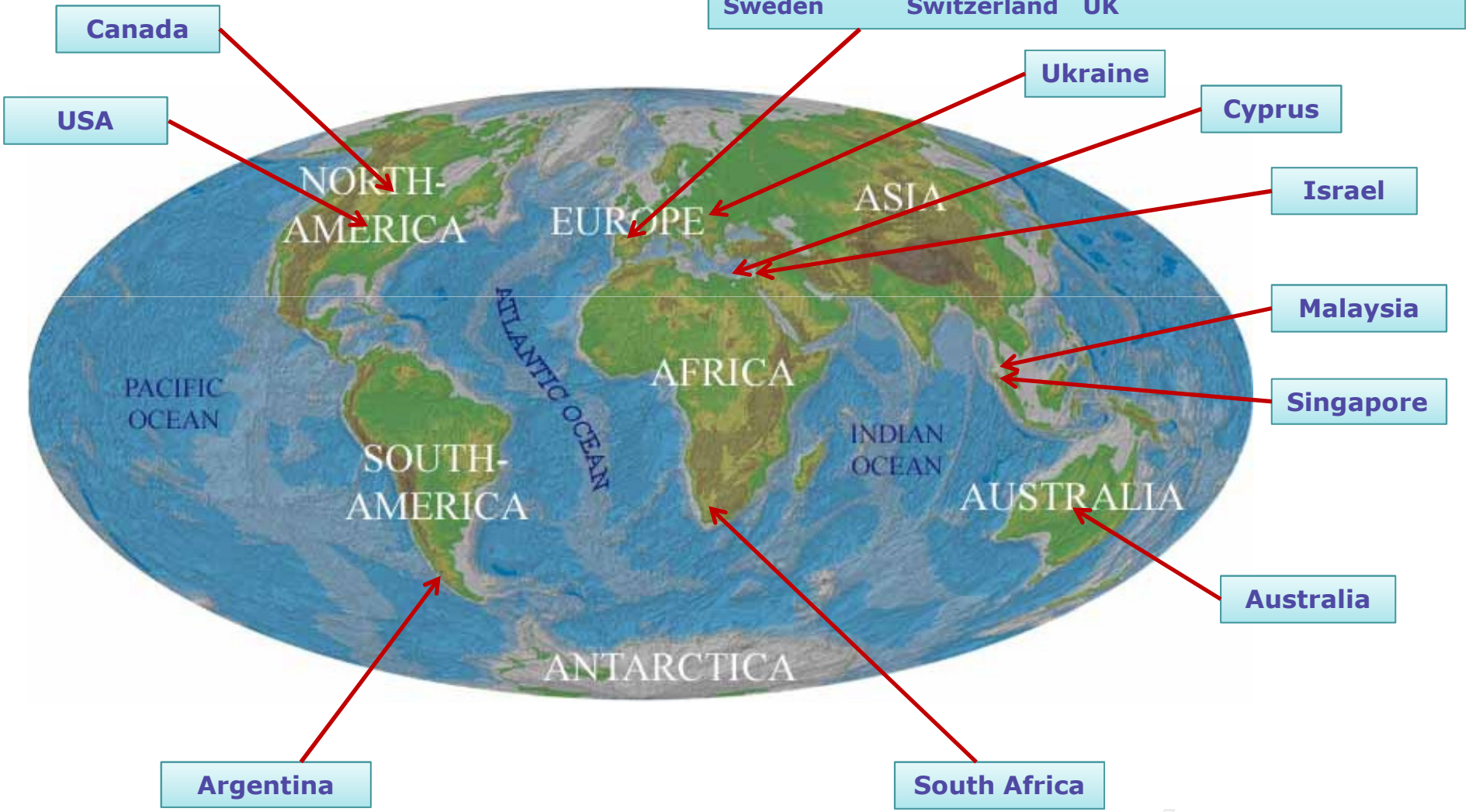
- Developing and promoting harmonised GMP standards and guidance documents.
- Training GMP inspectors of competent authorities.
- Assessing (and reassessing) GMP Inspectorates.
- Facilitating the co-operation and networking for competent authorities and international organisations.

Main features of PIC/S

- Commenced operating in November 1995.
  - Previously existed as "PIC" (Pharmaceutical Inspection Convention) from Oct 1970 to Nov'95.
- Is a "Cooperative Arrangement" **between GMP regulatory authorities**; ie. not a legal treaty.
- A forum for:
  - networking and confidence building
  - Exchange of information and experience on GMP
  - Focus on Quality Systems for Inspectorates
  - Focus on training of GMP inspectors
  - International harmonisation of GMP
- No obligation for member authorities to accept inspection reports of other members.

39 PIC/S Member Authorities (at 1.1.2011)

Austria	Belgium	Czech Rep.	Denmark
Estonia	Finland	France	Germany
Greece	Hungary	Iceland	Ireland
Italy	Latvia	Liechtenst.	Lithuania
Malta	Netherlands	Norway	Poland
Portugal	Romania	Slovak Rep.	Spain
Sweden	Switzerland	UK	



How PIC/S Operates

- Secretariat (Geneva based)
- Executive Bureau (Chairman, two Deputy Chairmen, two Members of PIC/S Committee)
- PIC/S Committee (usually the Chief Inspector of each Agency)
- Small Budget (members pay annual membership fee)
- Good relationships and collaboration (family atmosphere)
- Training opportunities (eg. Seminars, Joint visits)
- Information exchange (eg. inspection reports, Rapid Alerts)
- Development of GMP Guides & guidance documents

Benefits of PIC/S Membership

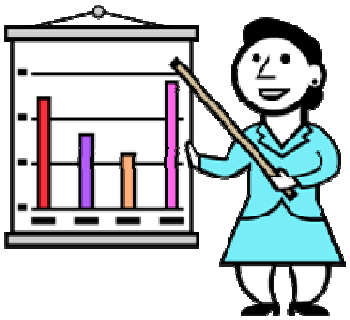
For Regulatory Authorities:

- Accession forces improvements – ie. Discipline.
- Cost savings – more effective use of resources.
- Inspector training (Seminars, Joint Inspections, coached inspections).
- Promotion of harmonisation of GMP inspections.
- Maintaining a consistently high standard of inspections.
- Involvement in developing international GMPs.
- Sharing of information & experiences.
- Participation in Rapid Alert System (for quality defects).
- Networking & personal contacts.

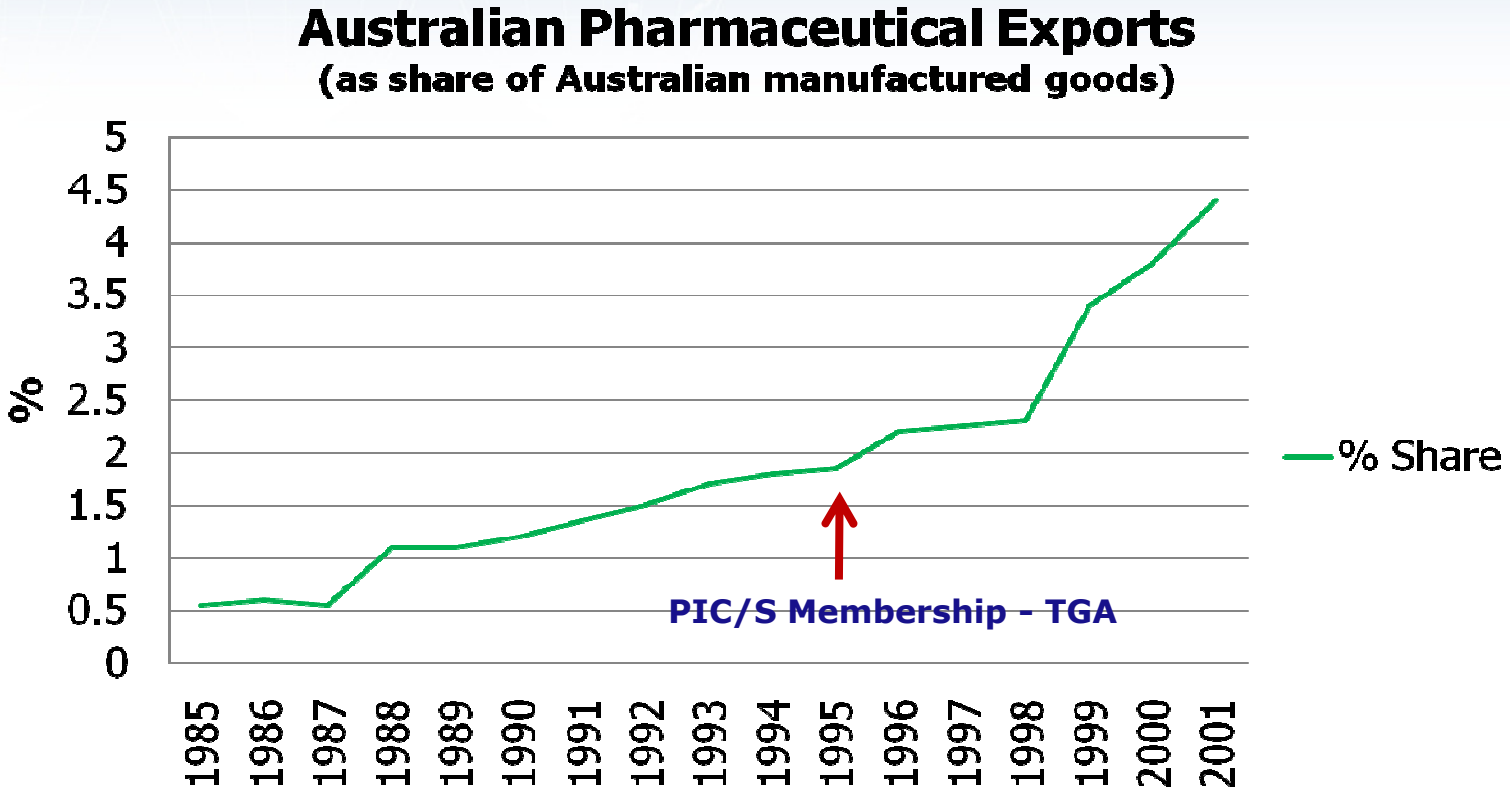
Benefits of PIC/S Membership

For Industry:

- Reduced duplication of inspections (cost savings).
- Export facilitation (including to non-PIC/S countries).
- More competitive internationally.
- Enhanced market access.
- Reputation of industry enhanced.
- Transparent inspection standards.
- Consistency of inspections.
- Reliable quality of medicines available locally and internationally.

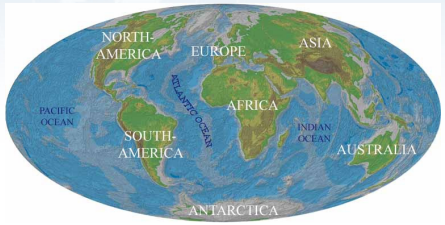


Growth in Australian Exports resulting from PIC/S membership



Source: The Australian Pharmaceutical Industry and its Global Context, Working Paper No. 7, September 2002.
Mr George Messinis, Centre for Strategic Economic Studies, Victoria University of Technology, Melbourne

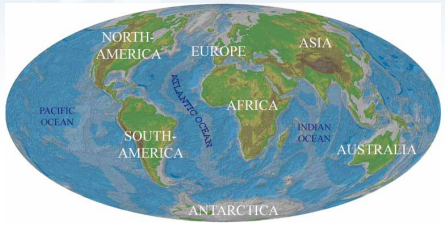
Applicants currently being assessed for PIC/S membership



The GMP Regulatory Authorities of:

- Thailand
- Indonesia
- Philippines
- Taiwan
- New Zealand
- Brazil
- Iran
- Slovenia

Agencies showing an interest in joining PIC/S



The GMP Regulatory Authorities of:

- Japan
- Hong Kong
- PR of China
- South Korea
- Saudi Arabia
- Croatia
- Bulgaria

Accession Procedure

Essential Documents:

- Pharmaceutical Inspection Cooperation Scheme (PIC/S 1/95; rev 4).
- Guidelines for Accession to PIC/S (PIC/S 1/98; rev 4).
- Application form and Questionnaire on National Inspection Systems (PS 2/99-3).
- Assessment Checklist (PS W 01/2005).
- Recommendations on quality system requirements for pharmaceutical inspectorates (PI 002-3).

PIC/S Accession Procedure

Steps to Accession

- General interest & commitment, eg. attend Seminars.
- Written application to Secretary + supporting documents.
- PIC/S Committee appoints Rapporteur to evaluate.
- Applicant invited to Committee meeting to answer questions of Rapporteur and Committee.
- PIC/S appoints an Assessment Visit Team.
- PIC/S delegation undertakes assessment visit (assesses Inspectorate's procedures & Quality System, & observes 3 or 4 typical GMP inspections).
- Delegation report issued (to applicant & Committee).
- Committee decides on membership.

PIC/S Accession Procedure

PIC/S Assessment Team:

- The PIC/S assessment team assesses the performance and competence of the GMP inspectors.
- The PIC/S assessment team does NOT assess or inspect the manufacturers being inspected.

Timeframe to become Member:

- In theory, an Agency can become a member in 18 months from application.
- Generally, most applicants take about 3 years to become members of PIC/S.
- Maximum time to become member is 6 years.

Fees:

- Registration fee (not re-fundable): 8,100 Swiss francs
- Annual Membership fee: 8,100 Swiss francs

Experiences of Some Countries

Country	Agency	Years to Join	# of Visits	Main Issues
Australia	TGA	5	1	• Lack of uniform National Legislation • PIC/S inspection report format not used
Singapore	HSA	3	2	• GMP requirement not equivalent to PIC/S • Extensive training of inspectors required • PIC/S inspection report format not used • Categories of products not shown on licences
Malaysia	NPCB	3	2	• GMP requirement not equivalent to PIC/S • Extensive training of inspectors required • PIC/S inspection report format not used • Categories of products not shown on licences • No legal power to enter premises to inspect
USA	US FDA	5	2	• No Quality System for central & regional FDA • "Export Only" drug companies not inspected • Inadequate control of OTC manufacturers • OTC's can be marketed without inspection • OTC's can be recalled without notifying FDA • No procedure for designating inspectors • No inspection performance standards • No risk assessment procedure

Experiences of Some Countries

Country	Agency	Years to Join	# of Visits	Main Issues
Taiwan	TFDA	-	1	Exceeded 6 year deadline & re-applied. Main problems from 1st visit: • GMP requirement not equivalent to PIC/S • Extensive training of inspectors required • PIC/S inspection report format not used • Categories of products not shown on licences • Inspection teams too large • Quality System not covering regional offices • Regional inspectors lacking GMP experience • Quality System not consistent with PIC/S
Thailand	Thai FDA	-	1	• GMP requirement not equivalent to PIC/S • Extensive training of inspectors required • PIC/S inspection report format not used • Categories of products not shown on licences • Inspection teams too large • Quality System not covering regional offices • Regional inspectors lacking GMP experience • Recall of herbals need not be notified to FDA

PIC/S GMP Guide

- PIC/S GMP Guide to GMP for Medicinal Products (PIC/S document PE 009-9, 1 September 2009).
- Virtually identical to EC GMP Guide:

  Main differences:
  - The term "authorised person" used instead of "Qualified Person" (QP).
  - No Annex 16 (QP) in PIC/S GMP Guide.
  - No Annex 18 (APIs) in PIC/S GMP Guide (APIs now in Part II).
- Divided into 3 parts
  - Part I: PIC/S GMP Guide (general provisions).
  - Part II: GMP Guide for APIs (identical to ICH Q7A).
  - Annexes 1 to 20.

(PIC/S GMP Guide available at www.picscheme.org)

PIC/S GMP Guide
(PE 009-9, 1 September 2009)

- Introduction
- Chapter 1 – Quality Management
- Chapter 2 – Personnel
- Chapter 3 – Premises & Equipment
- Chapter 4 – Documentation
- Chapter 5 – Production
- Chapter 6 – Quality Control
- Chapter 7 – Contract Manufacture & Analysis
- Chapter 8 – Complaints & Product Recall
- Chapter 9 – Self Inspection

(PIC/S GMP Guide available at www.picscheme.org)

PIC/S GMP Guide

Annexes (1 – 9)

1. Sterile Medicinal Products
2. Biological Products for Human use
3. Radiopharmaceuticals
4. Veterinary medicinal products other than immunologicals
5. Immunological veterinary medicinal products
6. Medicinal gases
7. Herbal medicinal products
8. Sampling of starting and packaging materials
9. Liquids, creams & ointments

(PIC/S GMP Guide available at www.picscheme.org)

PIC/S GMP Guide

Annexes (10 – 20)

10. Pressurized metered dose aerosol products
11. Computerised systems
12. Ionising radiation
13. Investigational medicinal products
14. Products derived from human blood or human plasma
15. Qualification and validation
16. [Qualified person and batch release in EC GMP Guide only]
17. Parametric release
18. [GMP Guide for active pharmaceutical ingredients]
19. Reference and retention samples
20. Quality Risk Management (voluntary)
    (identical to ICH Q9)

(PIC/S GMP Guide available at www.picscheme.org)

Recent Changes

- Changes to the PIC/S GMP Guide since 2006:
  - "Product Quality Review" (cl. 1.4).
  - "Quality Risk Management" (cl. 1.5, 1.6; new Annex 20).
  - "On-going Stability Program" (cl. 6.23 - 6.33).
  - "Counterfeiting" (cl. 8.7- 8.8).
  - Significant changes to Annex 1 (Sterile Medicinal Products).
  - New Annex 19 on "Reference Samples & Retention Samples".
  - New Annex 20 on "Quality Risk Management".

Expected Future Changes to the PIC/S GMP Guide

NB: Changes are usually initiated by EMEA and adopted by PIC/S after EU GMP Guide is amended.

- The concepts of ICH Q10 (Quality Systems) to be incorporated into Part 1 of the GMP Guide. New sections will include:
  - Quality Management System
  - Process Performance, Product Quality Monitoring System & Product Quality Review
  - Management of Outsourced Activities and Purchased Materials
  - Management Review on the Quality Management System
  - Monitoring of Internal & External Factors Impacting the Quality Management System
  - Outcomes of Management review and Monitoring

  - A new Annex 21 (being a direct copy of ICH Q10) as a voluntary Annex

Expected Future Changes to the PIC/S GMP Guide

- Clarification of GMP requirements for "certain highly active drugs" mentioned in clauses 3.6 & 5.18 (eg. penicillins, hormones, steroids, cytotoxics).That is, clarification of requirements for "dedicated facilities".
- Changes to Chapter 5 on "qualification of suppliers".
- Changes to Chapter 7 on "contract manufacturing".
- Replacement of clause 3.12 ("air control for production areas") with clause 12.30 of WHO GMP Guide.

Expected Future Change to Clause 3.12 PIC/S GMP Guide

- To be replaced with clause 12.30 of WHO GMP Guide.

  (Words additional to PIC/S clause 3.12 shown in red)

  WHO Clause 12.30:

  "Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity ~~and filtration~~) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications".

Expected Future Changes to the PIC/S GMP Guide

- Revisions currently being undertaken for:
  - Annex 2 (Biological Products for Human Use).
  - Annex 6 (Medicinal Gases)
  - Annex 7 (Herbal Medicinal Products).
  - Annex 11 (Computerised Systems).
  - Annex 13 (Investigational Medicinal Products)
  - Annex 14 (Human Blood and Plasma)
  - Part II (APIs; to include QRM)

Useful PIC/S Aide Memoires

Whilst PIC/S Aide Memoires are written for GMP inspectors, they can be very useful for a company's internal audits.

Aide Memoire on Inspection of Utilities	Sept'07
Aide Memoire on Inspection of Packaging	Jan'09
Aide Memoire on Inspection of QC Laboratories	Sept'07
Aide Memoire on Inspection of APIs	Jan'09
Aide Memoire on Inspection of Biotech	Sept'07
Aide Memoire on Medicinal Gases	Sept'07

(All available at www.picscheme.org)

Useful PIC/S Guidance Documents

Good Practices for Computerised Systems	Sept'07
Validation (Master Plan, IQ, OQ, Process & Cleaning)	Sept'07
Site Master File Preparation (Explanatory Notes)	Sept'07
Guidance on Parametric Release	Sept'07
Recommendations on Sterility Testing	Sept'07
Isolators for Aseptic Processing and Sterility Testing	Sept'07
Validation of Aseptic Processing	June'09

(All available at www.picscheme.org)

Two New PIC/S Guidance Documents

- *PIC/S Document PI 032-2*
  GMP Annex 1 Revision 2008 – Interpretation of most important changes for the manufacture of sterile medicinal products
- *PIC/S Document PS/INF 1/2010*
  Quality Risk Management – Implementation of ICH Q9 in the pharmaceutical field of methodology from PIC/S

(Both available at www.picscheme.org)

PIC/S Training for GMP Inspectors

- Annual Training Seminars
- Basic Seminar for New Inspectors
- Expert Circles
- Joint Visits Programme (JVP)
- Coached inspections
- PIC/S-Industry Workshops

Recent PIC/S Training Seminars

Biotechnology	France, 2000
Inspection of Utilities	Czech Rep, 2001
Interface between GCP and GMP	Canada, 2002
Inspection of QC laboratories	Slovak Rep, 2003
Inspection of APIs	Spain, 2004
Packaging/Labelling/Prevention of Mix-ups	Romania, 2005
Risk Management	Germany, 2006
Inspection of Solid Dosage Forms	Singapore, 2007
Inspection of GDP	Poland, 2008
Sterile Aseptic Manufacturing	Sweden, 2009 *
Inspection of Traditional/Herbal Medicines	Malaysia, 2011

* 120 participants from 44 different countries

(Booklets/CDs of Seminar proceedings available for purchase)

Representatives from Indonesia and Turkey participating in the PIC Seminar on Computer Systems, Sydney, September 1996

Future PIC/S Seminar

- Good Inspection Practices — South Africa, Nov'2011
- Topic yet to be decided — Ukraine, 2012

(NB: Open to GMP inspectors only, including inspectors from non-PIC/S countries)

Joint Visits Programme (JVP)

- Currently 27 groups operating, with each group comprising 3 inspectors from 3 different countries.
- 1 inspection conducted per year per country.
- Each group can focus on a specific type of inspection, eg. aseptic processing, APIs, GCP, etc.
- Open to inspectors from PIC/S member authorities and applicant authorities (each inspector pays own costs).
- Benefits:
  - for training purposes
  - for uniform GMP interpretation
  - for uniform inspection procedures
  - for mutual confidence
  - Mechanism to report on any differences to PIC/S Committee.

Coached Inspections

- New initiative by PIC/S.
- Expected to commence in near future.
- Extensive list of inexperienced inspectors have applied.
- Presently looking for experienced trainers to volunteer.
- Only small groups of inspectors to be coached.
- Open to inspectors from PIC/S member authorities and applicant authorities.

Expert Circle Groups

- Human Blood and Tissues
- Computerized systems
- APIs
- Quality Risk Management
- Radiopharmaceuticals within Hospitals

Aim: - Develop draft guidance documents
- Training in specialized field

PIC/S Quality System Requirement for GMP Inspectorates (Document PI 002-3)

Reasons for Quality System for Inspectorates

- If industry is being asked to follow QS requirements, so should GMP Inspectorates.
- Helps ensure a uniform approach and structure for all PIC/S Inspectorates (& facilitates mutual recognition).
- Enables relevant PIC/S SOPs to be incorporated into the QS.
- Helps enhance the image of Inspectorates if they can show they follow QS requirements.
- A functional QS is an essential pre-requisite for PIC/S membership.

PIC/S Quality System Requirement for GMP Inspectorates

PIC/S Quality System Document – PI 002-3

- Based on the requirements of ISO 9001 & ISO 17020 (EN 45004), but modified for GMP Inspectorates.
- Certification of the Inspectorate's QS not mandatory as long as the principles of PI 002-2 are followed.
- About 50% of PIC/S Inspectorates have their QS certified – usually to ISO 17020 or ISO 9001.

PIC/S Quality System Requirement for GMP Inspectorates

Contents of Document PI 002-3

- Introduction, Purpose, Scope & Definitions
- Quality Manual
- Administrative Structure
- Organisation and Management
- Documentation and Change Control
- Records
- Inspection Procedures
- Inspection Resources
- Internal Audit

PIC/S Quality System Requirement for GMP Inspectorates

Contents of Document PI 002-3

- Quality Improvement and Corrective/Preventative Action
- Complaints (against inspectors & Inspectorate)
- Issue & Withdrawal of Licences and GMP certificates
- Handling of Suspected Quality Defects and Rapid Alert System
- Liaison with the Official Medicine Control Laboratory (OMCL)
- Sub-contracting and Assessing
- Publications

PIC/S Relationship with EMEA

- EMEA representative attends PIC/S Committee meetings as an observer
- PIC/S-EU liaison officer attends EU Inspectors' meetings at EMEA as an observer
- A harmonised consultation procedure:
  - EU & PIC/S usually adopt each other's GMP Guides & guidance documents
- An "Associated Partnership" in place

Liaison with other organisations

- WHO Co-operation with PQ (Prequalification of Medicines) and IVB (Immunization, Vaccines and Biologicals)
- EDQM (The European Department for the Quality of Medicines) – An "Associated Partnership" in place
- ICH (participation in the development of ICH Guidelines)
- UNICEF – An "Associated Partnership" in place
- European Commission (DG SANCO, DG Enterprise)

PIC/S Executive Bureau (2011)

- PIC/S Executive Bureau:
  - Chairman — T Gråberg (MPA, Sweden)
  - 1st Dep. Chairman — H Baião (INFARMED, Portugal)
  - 2nd Dep. Chairman — J Gouws (MCC, South Africa)
  - Member — V Revithi (EOF, Greece)
  - Member — P Hargreaves (MHRA, UK)
  - Member — M Boon (HSA, Singapore)
  - Member — J Holy (ISCVBM, Czech Republic)

www.picscheme.org

PIC/S contact details

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Fax: +41.22.7389217
Email: info@picscheme.org
Web site: www.picscheme.org

PIC/S GMP Guide

Korea, March 2011

Mr Bob Tribe
Canberra, Australia

ENGINEERING PHARMACEUTICAL INNOVATION

Overview

- Comparison of PIC/S, EU, WHO & FDA GMPs.
- Overview of the important areas of Part 1 and Annex 1 of the PIC/S GMP Guide.
- Provide summaries of "possible inspection issues" often observed by GMP inspectors.

Comparison of Different GMPs

- US FDA — Unique
- EU
- PIC/S
- WHO

  } Broadly similar

- Others
  - SFDA, China — Combination of EU, WHO & FDA
  - India (Schedule M) — ?

PIC/S GMP Guide
(PE 009-9, 1 September 2009)

- Introduction
- Chapter 1 – Quality Management
- Chapter 2 – Personnel
- Chapter 3 – Premises & Equipment
- Chapter 4 – Documentation
- Chapter 5 – Production
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- Chapter 8 – Complaints & Product Recall
- Chapter 9 – Self Inspection

(PIC/S GMP Guide available at www.picscheme.org)

Reference to PIC/S GMP Guide → Principle & clause 1.1

Quality Management

- Determines and implements the "quality policy" or "quality objectives" so as to ensure that":
  - products are fit for their intended use,
  - comply with requirements of marketing authorization, &
  - do not place patients at risk due to inadequate safety, quality or efficacy.
- The basic elements are:
  - an appropriate infrastructure or "quality system" encompassing suitable procedures, processes, and resources.
  - the systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for "Quality".

The totality of these actions is termed "Quality Assurance"

Quality Management

Quality relationships

Quality Management

Quality Assurance

GMP

Production & Quality Control

The Authorised Person

Main Responsibility covered in "*clause 1.1, vii*"

- The system of Quality Assurance appropriate for the manufacturer of medicinal products should ensure that:
  - Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products.

Quality Management

Product Quality Review

- Requires regular quality reviews of all products to verify the consistency of the existing process to highlight trends & to identify the need for product/process improvements.
- Normally on an annual basis.
- Quality reviews may be grouped by product type.
- Requires (for each product) reviews of:
  - Starting & packing materials, especially from new sources.
  - Critical in-process controls and finished product results.
  - All batches that failed to meet specifications.
  - All significant deviations.
  - All changes to processes and analytical methods.
  - Marketing Authorisation variations.
  - Stability monitoring and any trends.
  - Recalls, complaints and returns.
  - Qualification status of equipment & utilities.
  - Technical agreements.

Quality Management

Quality Risk Management

- Requires quality risk management to be an integral part of a manufacturer's quality system.
  - Use scientific knowledge & experience with the process to evaluate the risk to quality.
  - Level of effort, formality & documentation of the risk management process to be commensurate with the level of risk.
- Reference to Annex 20 (quality risk management), which is a copy of the ICH Q9 guideline on quality risk management. Annex 20 is voluntary (as it provides examples tools to use).

(Note that there is an expectation from GMP regulators that risk assessments will be undertaken for critical areas of GMP, eg. validation, deviations, OOS, change control, complaints, etc.)

Quality Management

Possible Inspection Issues – (1)

- Quality Management manual not established in writing.
- Limited human resources.
- Lack of qualified people.
- Processes not properly validated.
- Poor SOPs or standard batch documentation.
- More consideration to cost than quality.
- Family members in key positions of authority.

Quality Management

Possible Inspection Issues – (2)

- Substandard materials deliberately purchased.
- Technical staff not involved in purchasing.
- Product Quality Reviews not undertaken.
- Owner insists on selling rejects.
- Corruption & fraud.
- No commitment to training.
- No SOP in place for conducting risk assessments.

Quality Risk Management

Bungy Jumping Video

How do we practically use this risk based approach?

Dr. H. Gregg Claycamp

Director, Division of Compliance Risk Management and Surveillance, FDA, CDER Office of Compliance.

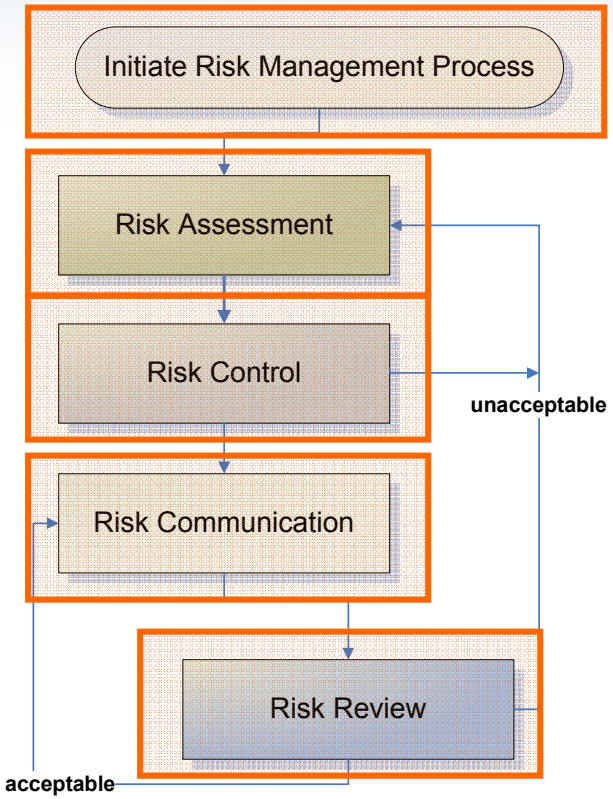
"There is no magic bullet!

It is a multi disciplinary team applying an agreed methodology, making an educated and experienced judgement and then seeking ways to mitigate the risk.

This obviously must be documented".

ICH Q9 Risk Management Model

- **Initiate the Risk Management Process**
- ***Risk Assessment*** consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. The steps include risk identification, risk analysis and risk evaluation.
- ***Risk Control*** includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level.
- ***Risk Communication*** is the exchange or sharing of information about risk and its management between the decision makers and others.
- ***Risk Review*** requires the output/results of the risk management process be reviewed to take into account new knowledge and experience, i.e. not a once only event



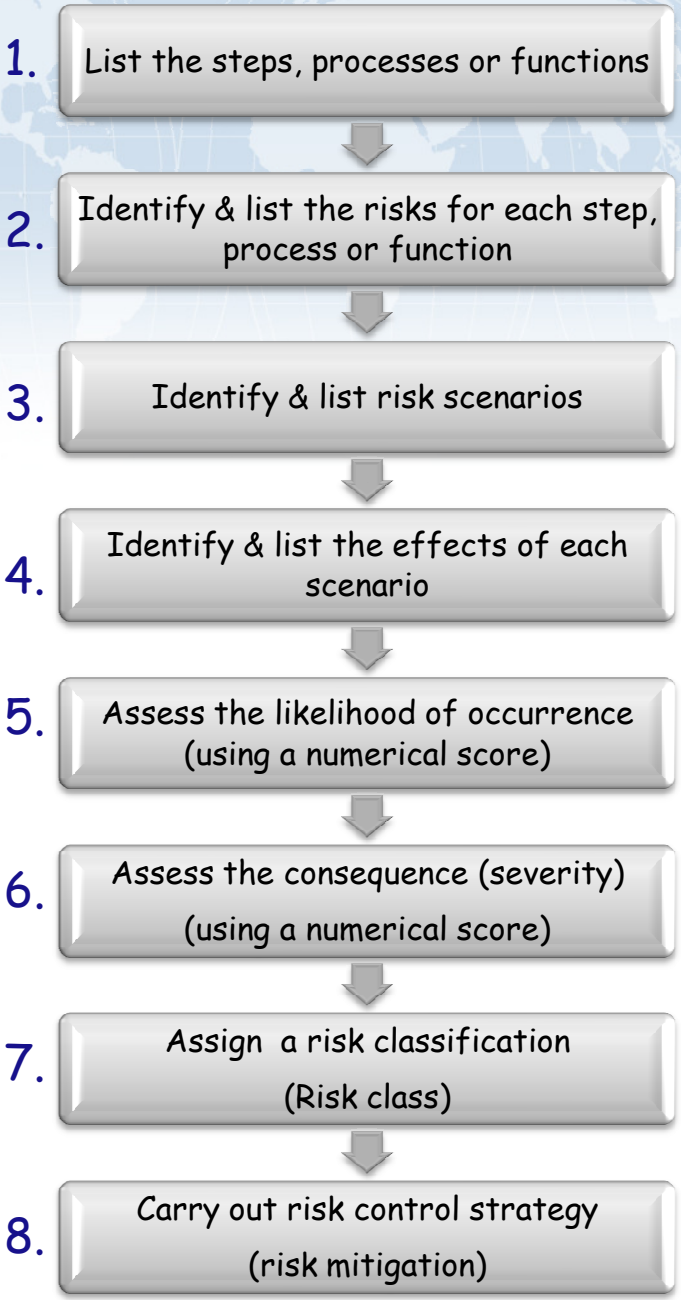
ENGINEERING PHARMACEUTICAL INNOVATION

Undertaking a Risk Assessment

These fundamental questions are usually asked:

1. What might go wrong (identify)?
2. What is the likelihood (probability) that it will go wrong?
3. What are the consequences (severity)?

Undertaking a Risk Assessment



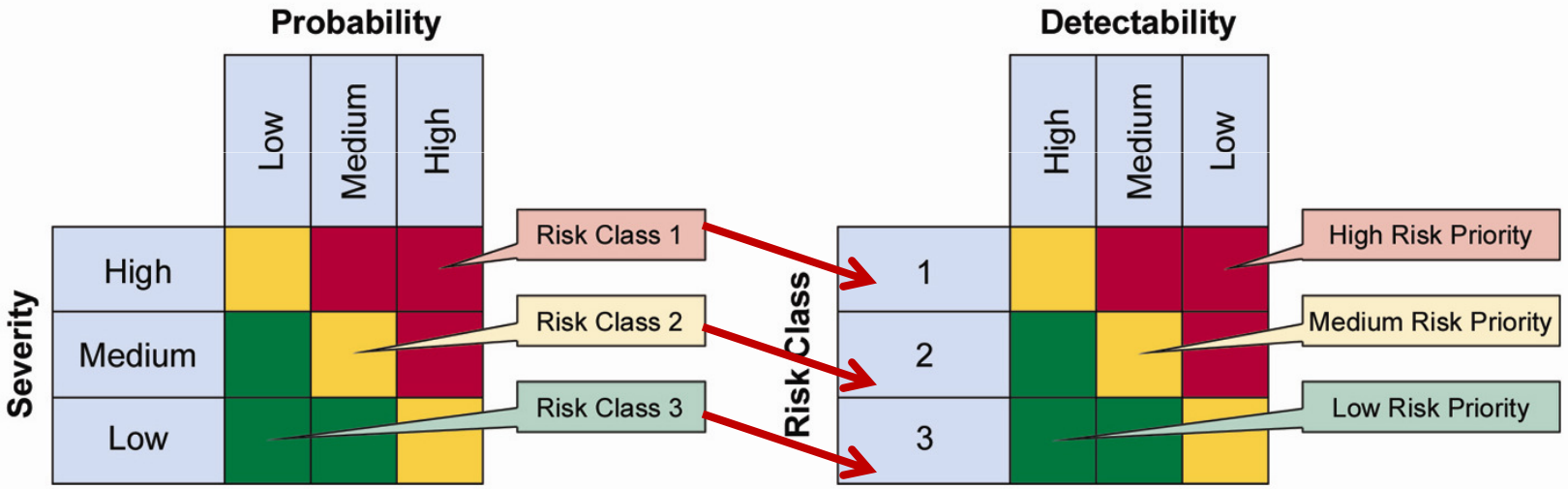
Many different approaches.

One example shown here.

Typical Risk Assessment Method

Assessment of likelihood (probability) of an adverse event occurring.

Determining Risk Priority which is used in risk mitigation.



Severity = Impact on Patient Safety, Product Quality, and Data Integrity (or other harm)
Probability = Likelihood of the fault occuring
Risk Class = Severity × Probability

Detectability = Likelihood that the fault will be noted before harm occurs
Risk Priority = Risk Class × Detectability

Numerical Scores

- It is common to see companies wanting to measure the risk so that they can demonstrate a risk reduction!
- Usually the scores are multiplied (it is recommended to use only 1, 2 and 3).
- SOD risk method*.
- The highest risk number is 3 x 3 x 3 = 27.

* S = severity of risk
O = opportunity or likelihood of occurrence
D = Detection of risk before it occurs

Example of a simple risk assessment form

Risk Assessment Form (Example Only)

Project Title:			Project Number:						
Assessment Scope/Assumptions Made:									
Steps, Tasks, Functions	Risks	Risk Scenarios	Effect of Scenario	Risk Ratings				Risk Priority	Risk Mitigation
				L	S	Risk Class	D		
Risk Assessment carried out by:		Signature		Date:					
Risk Assessment Approved by:		Signature		Date:					

L = Likelihood (or probability) of an adverse event occurring
S = Severity of the event on patient safety, product quality (or other harm)
Risk Class = Severity x Likelihood
D = Detectability (likelihood of fault being noted before harm occurs)
Risk Priority = Risk Class x Detectability
Suggested numerical ratings: 1 = Low risk, 2 = Medium risk, 3 = High risk

Example of a simple risk assessment form

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Assessment Scope/Assumptions Made:									
Steps, Tasks, Functions	Risks	Risk Scenarios	Effect of Scenario	Risk Ratings				Risk Priority	Risk Mitigation
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Risk Priority = Risk Class x Detectability
Suggested numerical ratings: 1 = Low risk, 2 = Medium risk, 3 = High risk

Example of a simple risk assessment

Risk Assessment Form (Example Only)

Project Title: Bungy Jumping | Project Number: 1234

Assessment Scope/Assumptions Made: Assessing Risks of Bungy Jumping

Steps, Tasks, Functions	Risks (from internet)	Risk Scenarios	Effect of Scenario	Risk Ratings				Risk Priority	Risk Mitigation
				L	S	Risk Class	D		
Equipment	Weighing scale not properly calibrated	Incorrect weight of jumper	serious injury	1	3	3	1	3	Investigate the operator *
	Bungy cord frayed/damaged	weak spots in cord	serious injury	1	3	3	1	3	
Operator error	miscalculate required cord length	hit bottom	serious injury or death	1	3	3	1	3	
	cord incorrectly attached to ankle	hit bottom	serious injury or death	1	3	3	1	3	
Jumping	Change mind	anxiety, stress	Do not jump	3	1	3	3	9	Don't Jump
Free fall	body tangles with cord	cord around body	severe bruising	1	2	2	2	4	Investigate the operator *
	cord too long	hit bottom	serious injury or death	1	3	3	1	3	
	cord too weak for weight	hit bottom	serious injury or death	1	3	3	1	3	

p. 1 of 1

Example of a simple risk assessment

Body deceleration	eye injury	eye trauma	retinal haemorrhage	1	2	2	3	6	Don't Jump
	back injury	back trauma	spinal damage	1	2	2	3	6	
	internal injury	internal trauma	uterine prolapse	1	2	2	3	6	
Upward Movement	increase in blood pressure	blood pressure increase	haemorrhage	1	2	2	3	6	
Risk Assessment carried out by:		Signature			Date:				
Risk Assessment Approved by:		Signature			Date:				

L = Likelihood (or probability) of an adverse event occurring
S = Severity of the event on patient safety, product quality (or other harm)
Risk Class = Severity x Likelihood
D = Detectability (likelihood of fault being noted before harm occurs)
Risk Priority = Risk Class x Detectability
Suggested numerical ratings: 1 = Low risk, 2 = Medium risk, 3 = High risk

* Investigate the operator:

Investigate the experience of the bungy jump operator for:

- years of experience.
- any accidents.
- frequency + procedures for checking/maintaining equipment.
- training of staff
- safety precautions in place

Personnel

Principle

- The establishment & maintenance of a satisfactory system of QA and correct manufacture of products relies upon people.
- Must be sufficient qualified personnel to carry out all relevant tasks.
- Individual responsibilities must be clearly understood by individuals concerned, & recorded.
- All personnel should be aware of the principles of GMP that affect them & receive relevant training.

Personnel

General

- Adequate number of qualified people with practical experience.
- An individual's responsibilities should not be so extensive as to present a risk to quality.
- Company organization chart should be available.
- Individual written job description.
- No gaps or unexplained overlaps in responsibilities.
- Adequate authority to carry out responsibilities.

Personnel

Key Personnel

Key personnel (should be full-time positions):

- Head of Production
- Head of Quality Control
- Authorised Person (release of products)
  - May be QA Manager; May be QC Manager.
- Heads of Production and QC or QA should be independent of each other.
- Responsibilities of each must be clearly specified.

Personnel

Training

- Training, in accordance with a written programme for:
  - all personnel whose duties take them into production; or
  - into control laboratories; and
  - for others whose activities could affect the quality of the product.
- Induction and continuing training:
  - on theory and practice of GMP;
  - approved by either the head of Production or QC or QA as appropriate.
  - training records should be kept.
  - training before undertaking any new task.

Personnel

Personal Hygiene

- A written hygiene program
  - Include health, hygiene & clothing.
- Medical examination on recruitment & ongoing.
- Exclude persons with infectious disease or open lesions.
- All persons to wear appropriate protective garments.
- No eating, drinking, chewing, smoking (except in designated areas).
- Avoid direct contact between hands & exposed product.
- Staff instructed to use hand-washing facilities.

Personnel

Possible Inspection Issues

- Limited number of staff.
- Inadequate qualifications &/or experience.
- Unclear or inadequate staff organisation chart
  - eg. QA reports to Production
- Owner interferes in quality decisions.
- Lack of means to develop training materials.
- No training given to contractors, engineers, purchasing staff.
- No SOP covering the wearing of jewellery & makeup.
- Inadequate training records with no training history for individual employees.

Personnel

Remember that:

"The quality of the product ultimately depends upon the quality of the people involved in its control and manufacture".

Sir Derrick Dunlop (Davenport Incident Enquiry)

Premises

Principle

- Premises must be located, designed, constructed, adapted and maintained for the operations:
  - Minimize risks of errors and cross-contamination.
  - Permit effective cleaning.
  - Permit effective maintenance.
  - Minimize build-up of dirt and dust.
  - Eliminate any adverse effects on quality.
  - Situated in environment that presents minimal risk of causing contamination of material or product.

Premises

- Premises should:
  - Be carefully maintained.
  - Be cleaned & disinfected according to SOP.
  - Have lighting, temperature, humidity & ventilation that are appropriate & do not adversely affect products.
  - Be designed & equipped to protect against entry of inspects & animals.

Premises

Example of inadequate ventilation

Premises

Design Principles

Should ensure:

- Material flow
- People flow
- Process flow

Ensure logical flow

Clauses 3.6 & 5.18

Premises

- Production Area:
  - Use dedicated & self contained facilities for highly sensitising materials (eg. penicillins).
  - Use separate facilities for certain highly active drugs (eg. hormones, antibiotics, cytotoxics). But campaign manufacture may be acceptable provided special precautions taken and validations made.

Premises

Production Area

- Layout to enable production to take place in logical order
- Interior surfaces (walls, floors, ceilings) should be smooth & easy to clean/disinfect.
- Pipes, lights, vents, etc should be located to avoid "difficult to clean" recesses.
- Drains to have trapped gullies – no open drains.
- Production areas to be effectively ventilated with air control appropriate for products handled.

Premises

Production Area

- Weighing of raw materials in separate weighing room.
- Where dust is generated, have provisions to avoid cross contamination.
- Packaging operations to be laid out to avoid mix-ups or cross-contamination.
- Should have well lit production areas, particularly where visual on-line controls are carried out.

Premises

Storage Areas

- Sufficient capacity to allow for orderly storage.
- Clean & dry storage, with temperature (& humidity if necessary) monitored within acceptable limits.
- Receiving & dispatch bays protected from weather.
- Clearly designated Quarantine & Reject storage areas.
- Separate sampling area for raw materials, with provision to prevent contamination during sampling.
- Special attention to the safe & secure storage of pre-printed packaging materials.

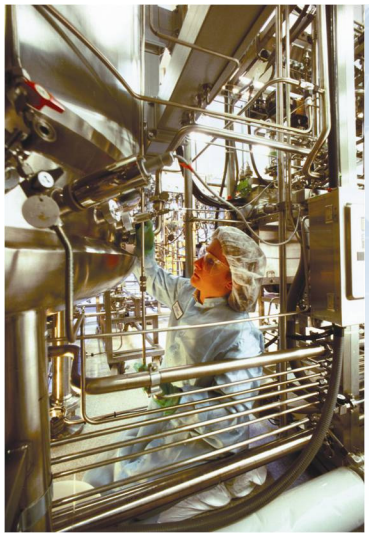
Premises

Possible Inspection Issues

- Pre-printed packaging materials not stored in secure area.
- No airlock at entry to raw material warehouse.
- Doors to airlocks not interlocked.
- Inadequate pressure differentials between different areas.
- Doors not closing properly.
- No air exhaust in equipment wash area.
- No provision for storage of cleaning equipment and materials.

Equipment

- Designed, located & maintained to suit intended purpose.
- Repair & maintenance to present no hazard to product quality.
- Installed in a way to prevent risk of error or of contamination.
- Not present any hazard to the products:
  - Non-reactive
  - Non-additive
  - Not absorptive



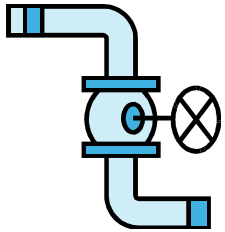
Equipment

- Designed to be easily & thoroughly cleaned.
- Cleaned according to detailed, written SOPs.
- Stored only in cleaned & dry condition.
- Washing & cleaning equipment should not be a source of contamination.

Equipment

- Measuring, weighing, recording & control equipment.
  - Calibrated & checked at defined intervals.
  - Records of such tests maintained.
- Balances & measuring equipment
  - Be available for production & control purposes
  - Be of an appropriate range & precision.

Equipment

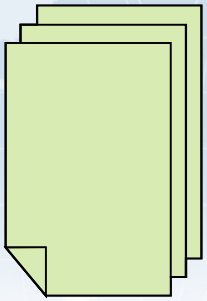


- Fixed pipe-work to be clearly labelled:
  - Indicate contents.
  - Indicate direction flow.
- Pipes for treated water (eg. RO &/or DI water) :
  - Sanitised according to written SOP.
  - This SOP to detail action limits for microbial contamination & measure to be taken.
- Defective equipment:
  - Removed from production & QC areas
  - Clearly labelled as defective.

Equipment

Possible Inspection Issues

- Poor design.
- Lack of safety.
- Poor quality finishes.
- Lack of cleaning.
- Lack of maintenance (eg. rubber gaskets on tank lids perished & shedding rubber particles).
- No usage log or record.
- Use of inappropriate weighing equipment.
- Open-plan location of compressing machines.
- Cleaned equipment not protected from contamination (including punches, sieves, filter bags).



Documentation

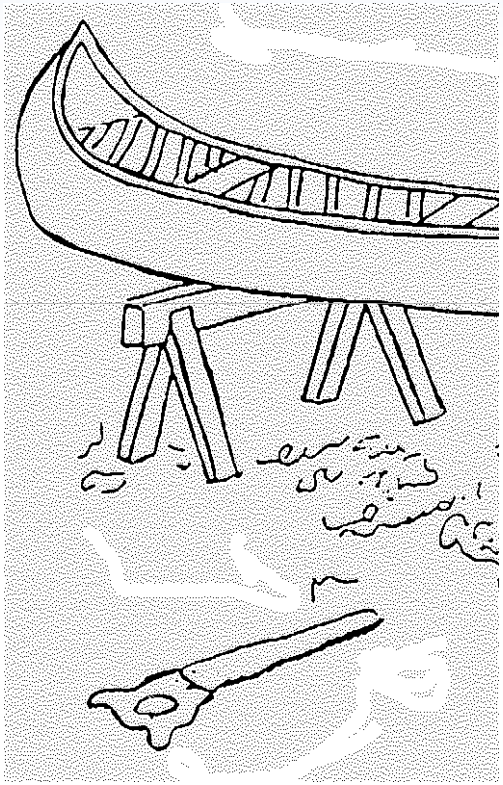
General Principles

- Documentation is an essential part of the Quality Assurance system.
- Clearly written documentation:
  - Prevents errors from spoken communication
  - Permits tracing of batch history
- Specs, formulae, instructions, SOPs & records must:
  - Be free from errors
  - Available in writing
- Legibility of documents is essential.

Documentation

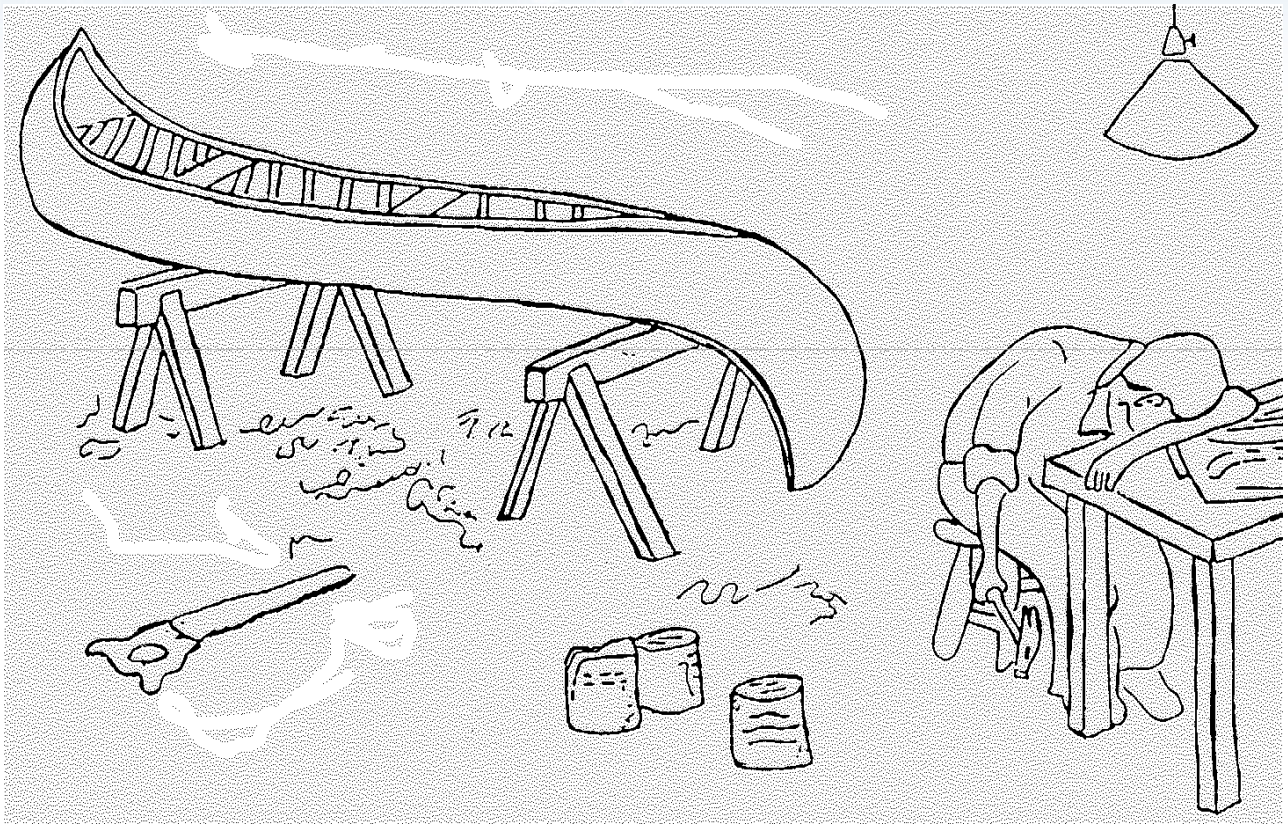
What is being made?

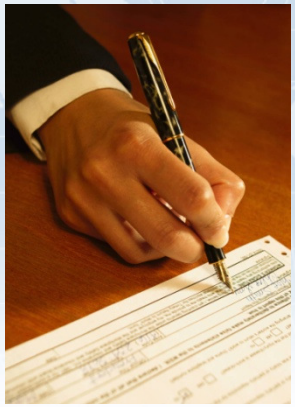
Most of us when attempting a task need some sort of documentation to follow.



Documentation

And if the drawing is wrong!





Documentation

- Documents should:
  - Approved, signed & dated by appropriate authorized person.
  - Laid out in orderly fashion & easy to check.
  - Be clear & legible when reproduced.
  - Regularly reviewed & kept up to date.
  - Incorporate a system that prevents inadvertent use of superseded documents.
  - Not be hand-written, but where data entry is required this should be made in clear, legible, indelible handwriting.

Documentation

- Where data may be recorded by electronic data processing systems (computers):
  - Only authorised persons should enter or modify data in the computer.
  - Should be a record of changes and deletions
  - Access should be restricted with passwords
  - The results of entry of critical data should be independently checked.
  - Batch records electronically stored should be backed-up.
  - Any electronic data should be readily available throughout the period of retention.

Further reading:
PIC/S Recommendation:
"Good Practices for Computerised Systems in Regulated GXP Environments"
PIC/S Document PI 014-3

Documentation

Some well known Clichés related to documentation:

- *"If you do it, document it"*
- *"If you document it, do it"*
- *"If it is not written down, it never happened"*

Documentation

Possible Inspection Issues

- No systematic review of all batch documentation prior to release authorization of a batch of product.
- Start times and end times for key processing steps, eg. mixing, not recorded.
- Limits not specified for reconciliation.
- Batch documentation not held close to the site of manufacture.
- Manufacturing formula does not match formula registered with Health authority.
- Receival numbers for packaging materials not recorded for traceability purposes.

Production

General Principles

- Production operations must follow clearly defined procedures.
- Production operations must comply with the principles of GMP:
  - To obtain product of the requisite quality.
  - To be in accordance with relevant manufacturing and marketing authorisations.

Production

Prevention of cross-contamination:

- Should be avoided by technical or organisational measures, such as:
  - For highly active raw materials:
    - Manufacture in segregated areas.
    - Keep protective clothing inside these areas.
  - Providing air locks & air extraction.
  - Filter incoming air.
  - Use validated cleaning & decontamination procedures.
  - Use "closed systems" of production.
  - Use "cleaning status" labels on equipment & test for residues.
  - Periodically check effectiveness of these measures.

Production

Starting Materials:

- Sampled & tested:
  - All containers to be sampled for ID testing (unless validated procedure established to justify reduced sampling).
  - Discussed in more detail in Annex 8.
  - Sampled containers identified with a "sampled" label.
- Dispensed by designated persons using written SOP.
- Each dispensed material & weight (or volume) to be checked & recorded by 2nd person.
- Dispensed materials to be kept together and conspicuously labelled.

Production

Processing Operations:

- Should carry out:
  - Before processing commences, take steps to ensure work area and equipment are clean & free of materials, products, documents, etc that are not required.
  - In-process and environmental controls.
  - Record & investigate any significant deviations from the expected yield.
  - Critical processes* should be validated.

(* "critical process" not defined)

Further reading:
PIC/S Recommendation:
"Validation Master Plan, IQ, OQ, Process Validation, Cleaning Validation"
PIC/S Document PI 006-3

Production

Possible Inspection Issues

- Raw material sampling:
  - Done in open warehouse
  - Less than 100% containers sampled for ID testing.
- Lack of segregation between different packing lines.
- Line clearance check of packing line only and did not include surrounding area.
- Dispensing operations:
  - No check-weigher's signature.
  - Weigher & check-weigher signed BMR after dispensing all raw materials.
  - Poor segregation between different batches of dispensed raw materials.

Stability Testing

On-going Stability Programme

- Requires monitoring of stability after marketing, against a written protocol.
- Stability program should be extended to the end of the shelf life of the product.
- One batch per year of each product strength & each primary packaging type.
- Maintain a written summary of the data generated.
- Results of stability monitoring to be:
  - made available to the authorised person.
  - Available at the site of manufacture for review by inspectors.
- Summary of all data to be subject to periodic review.

Contract Manufacture & Analysis

General Principles

- Written contract between Contract Giver and Contract Receiver.
- The contract to state how the "authorised person" exercises his full responsibility.
- The arrangements for contract manufacture & analysis should follow the "Marketing Authorisation" for the product concerned.

Recalls

- Distribution records to be readily available to the person responsible for recalls.
- Recalled products to be identified & stored separately in secure area while awaiting their fate.
- Progress of recall to be recorded & final report to be issued showing reconciliation figures (delivered versus recovered).
- The effectiveness of the arrangements for recall to be evaluated regularly (ie. mock recalls)

Further reading:
PIC/S Recommendation:
"Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects"
PIC/S Document PI 010-3

Complaints and Recalls

Possible Inspection Issues

- No response to justified complaints
- Failure to recall
- Failure to correct frequent complaints
- No resources to investigate complaints
- No senior management support
- Senior management interference
- No mock recalls undertaken

PIC/S GMP Requirements for Sterile Medicinal Products

Korea, March 2011

Mr Bob Tribe
Canberra, Australia

ENGINEERING PHARMACEUTICAL INNOVATION

ISPE

PIC/S GMP Guide – Annex 1
(PE 009-9, 1 September 2009)

Manufacturing operations divided into two categories:

- Terminally sterilised products
  - prepared, filled and sterilised
- Aseptically prepared products

PIC/S GMP Guide – Annex 1
(PE 009-9, 1 September 2009)

Note that PIC/S has issued a Guideline document providing an interpretation of the recent changes to Annex 1. That is, new sections added in 2008.

- Was issued on 1 Jan 2010 as document PI 032-2
- Available for download at http://www.picscheme.org/news.php#n7

Reference to PIC/S GMP Guide

Annex 1, Principle

GMP Requirements for Sterile Products

- Additional requirements rather than replacement.
- Special requirements to minimizing risks of contamination (microbial, particulate, pyrogen).
- Dependent on skill, training & attitude of personnel involved.
- QA particularly important.
- Carefully established/validated procedures & methods of preparation must be followed.
- Sole reliance on sterility or other quality aspects must not be placed on any terminal process or final product test.

General Requirements

- Production in clean areas
- Airlocks for entry
  - personnel
  - goods
- Separate areas for:
  - component preparation
  - product preparation
  - Filling

General Requirements

- Clean areas to be classified.
- Should define "in operation" & "at rest" states for each clean room or suite of clean rooms.
- Grade A
  - For high risk operations, eg. aseptic filling.
  - Laminar air flow system (0.36-0.54 m/s for guidance).
- Grade B
  - For aseptic prep/filling - as background environment.
- Grade C & D
  - For less critical stages of manufacture.

Clean Room Classification

- Classify clean rooms in accord with ISO 14644-1.
- For Grade A, min. Sample volume of 1m^3/sample location.
- Portable particle counters with short sample tubing should be used.
- Maximum permitted airborne particle levels:

Grade	Maximum permitted number of particles/m^3 Equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5µm	0.5µm	5µm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	not defined	not defined

Comparing International Cleanroom classifications

Particles / m^3 ≥ 0.5µm	US 209D non-metric	US 209E 1992 metric	PIC/S &EC Annex I	Germany VDI 2083 1990	UK BS 5295 1989	Japan JIS B 9920 1989	ISO 14644-1
1							
3,5				0		2	2
10		M 1					
35	1	M 1.5		1		3	3
100		M 2					
353	10	M 2.5		2		4	4
1.000		M 3					
3.530	100	M 3.5	A, B A= unidirectional B= turbulent	3	E or F	5	5
10.000		M 4					
35.300	1.000	M 4.5		4	G or H	6	6
100.000		M 5					
353.000	10.000	M 5.5	C	5	J	7	7
1.000.000		M 6					
3.530.000	100.000	M 6.5	D	6	K	8	8
10.000.000		M 7					

Clean Room Monitoring

- Use risk analysis to set up monitoring program.
- Continuous particulate monitoring for Grade A.
- Similar for Grade B, but frequency can be less.
- For remote sampling systems, length of tubing and radii of bends need care (particle losses).
- Grades C & D monitoring – use risk management to determine frequency.
- Aseptic operations to be monitored frequently for viable particulates using eg. settle plates, volumetric air and surface sampling.

Cleanroom monitoring program

Recommended limits for microbial contamination

Grade	Air sample cfu/m^3	Settle plates (diam. 90mm) cfu/4 hours	Contact plates (diam 55mm) cfu/plate	Glove print 5 fingers cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Isolator Technology

- Helps decrease risk of micro contamination of aseptically prepared products (human interventions minimized).
- Transfer of material in & out = greatest source of contamination.
- Should be located in at least a Grade D environment.
- Use only after appropriate validation.
- Should be routinely monitored, especially leak testing of isolator & glove/sleeve system.

Further reading:
PIC/S Recommendation:
"Isolators Used for Aseptic Processing & Sterility Testing"
PIC/S Document PI 014-3

Blow/Fill/Seal Technology

- B/F/S equipment for aseptic production fitted with Grade A air shower:
  - Install in at least a Grade C environment.
- B/F/S equipment for terminally sterilised products:
  - Install in at least a Grade D environment.
- Particular attention should be given to:
  - Equipment design & qualification
  - Validation and reproducibility of "cleaning-in-place" (CIP) and "sterilisation-in-place" (SIP).
  - Operator training & clothing
  - Interventions in the critical filling zone.

Clean Room Environments

Grade	Operations for **terminally sterilised products**	Operations for **aseptically prepared products**
A	Filling of products, when unusually at risk*.	• Aseptic preparation & filling (Grade B background). • Transfer of partially closed freeze dried vials (Grade B background).
C	• Preparation of solutions, when unusually at risk*. • Filling of products.	Preparation of solutions to be sterile filtered.
D	Preparation of solutions & components for subsequent filling.	Handling of components after washing.

* eg. Those that support microbial growth, or lengthy time between preparation & sterilisation.

Personnel (Clothing required)

Grade D:

- Hair and, where relevant, beard should be covered.
- A general protective suit and appropriate shoes or overshoes should be worn.
- Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

Personnel (Clothing required)

Grade C:

- Hair and, where relevant, beard and moustache should be covered.
- A single or two-piece trouser suit, gathered at the wrists and with high neck
- appropriate shoes or overshoes should be worn.
- They should shed virtually no fibres or particulate matter.

Personnel (Clothing required)

Grade A/B:

- Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit.
- A face mask should be worn to prevent the shedding of droplets. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn.
- Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves.
- The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

Personnel Dress in Grade A/B

Annex 1, clause 43

Headgear
(tucked into the neck of the suit)

Face mask

Gloves
(garment sleeves into the gloves)

Footwear
(trouser-legs should be tucked inside the footwear)

Premises

- Clean areas:
  - smooth, impervious, unbroken surfaces.
  - permit cleaning (& repeated application of disinfectants/cleaning agents).
  - no un-cleanable recesses, ledges, cupboards, equipment.
  - no sliding doors (difficult to clean cavity).
  - ceilings (sealed; access to lights from above).
  - pipes and ducts (outside area or boxed in).
  - sinks and drains (prohibited in Grade A & B areas; if in Grade C or D areas, use air breaks & traps or water seals to prevent backflow).

Premises

- Changing rooms:
  - design as airlocks (ideally, separate airlocks for people & materials).
  - flushed effectively with filtered air.
  - separate for entry and exit desirable.
  - hand washing facilities (at 1st stage of the changing room).
  - interlocking system (both doors not be opened at same time).
  - visual and/or audible warning system (when doors at either end of airlock are opened at the same time).

Premises

- Air supply:
  - +ve pressure air flow relative to surrounding areas (flush room).
  - Pressure differential between adjacent rooms: 10 – 15 Pascals* (guidance values).
  - Protect zone of greatest risk (filling point).
  - Warning system to indicate failure of air supply.
  - Indicators of pressure differential (& recorded).

* 0.05" W.G. = 12.7 Pa

Equipment

- Conveyer belts
  - Not to pass through a partition between a Grade A or B area unless belt sterilised (eg a sterilising tunnel).
- Maintenance and repairs
  - Where possible, able to do from outside clean area.
  - Where done inside clean area, proper cleaning, disinfection or sterilization of equipment before processing recommences.
- Validation & Maintenance
  - Should be subject to planned validation and maintenance.
  - Their return to use should be approved.

Water Treatment System

- What GMP Inspectors likely to look for:
  - Is there a plan diagram? (flow, sampling points, filters, storage, etc)
  - What is daily production capability?
  - Is the water stored & distributed in a manner that prevents microbial growth?
  - Are there water quality specifications?
  - What are controls for microorganisms, endotoxins, chemical, temperature, pH, conductivity, etc?
  - What is the procedure for taking samples for these tests?
  - How is the system maintained, cleaned, disinfected?
  - Does the system produce water of reliable quality? Is there trending data available?

Processing

- Validation of Aseptic Processing
  - Should include process simulation using nutrient media (media fill).
  - Should imitate routine aseptic processes.
  - Should include interventions & worst case situations.
  - Perform as initial validation with 3 consecutive satisfactory simulation tests per shift. Repeat twice per year per shift and process, or after significant modifications to HVAC, equipment, process, etc.
  - Intermittent contamination may be indicative of low level contamination.
  - Gross contamination; review all batches made since last successful media fill.

Processing

- Guidance on media fill simulations:
  - Target should be zero, but:
  - < 5000 units: no +ve contaminants allowed .
  - 5000 to 10,000 units: 1 +ve, investigate & consider repeat media fill.
    2 +ve's, investigate & revalidation.
  - > 10,000 units: 1 +ve, investigate.
    2 +ve's, investigate & revalidation.

Further reading:
PIC/S Recommendation:
"Validation of Aseptic Processes"
PIC/S Document PI 007-5

Processing

- Bio-burden:
  - Monitor before sterilization, against working limits.
  - Determine bioburden for each batch of aseptically prepared & terminally sterilised product (but "at suitable intervals" for products sterilised by overkill method).
- Filtration of solutions:
  - All solutions to be passed through microbial-retaining filter, sited immediately before filling.
- Components/containers/equipment used in aseptic work:
  - Sterilise & pass through double ended steriliser sealed in wall.
- Gases used in manufacturing process:
  - Pass through microbial-retaining filters.
- Validate:
  - the efficiency of any new procedure or when significant change made to process or equipment.

Sterilisation - General

- Validate all sterilisation processes. Heat sterilisation to be method of choice.
- Suitability of sterilisation method to be demonstrated.
- Validated loading patterns to be established.
- Biological indicators to be properly controlled:
  - Properly stored.
  - Quality checked with +ve controls.
- Clear differentiation between sterilised products and products awaiting sterilisation.
- Sterilisation records to be available for each sterilisation run.

Aseptic Filtration

- Use only where steam sterilisation is not possible.
- Use 0.22 micron (or less) filter.
  - A 2nd sterilising filter is advisable.
  - Final filter to be as close as possible to the filling point.
  - Integrity of filter to be verified before use and immediately after use.
  - Integrity of air vent filters & critical gas filters – confirm after use.
- Time for aseptic filtration of bulk solutions to be determined during validation.
- Same filter not to be used for more than 1 day.
- The filter used should not affect the product by:
  - Removal of ingredients.
  - Release of substances into the product.

Finishing of Sterile Products

- Partially stoppered freeze drying vials
  - Maintain under Grade A until stopper inserted.
- Containers to be closed by validated methods.
- Vial capping to be done under Grade A.
- Crimping of vial caps – do immediately after stopper inserted.
- Crimping equipment to be located in separate work station equipped with air extraction.

Quality Control

- Sterility test to be regarded as the last in a series of controls by which sterility is assured.
- Sterility test to be validated for the product(s) concerned.
- Where parametric release is authorised, special attention needed for validation & monitoring of the entire manufacturing process.

Further reading:
PIC/S Recommendation:
"Guidance on Parametric Release"
PIC/S Document PI 005-3

Quality Control

- Sterility test samples to be representative of whole batch.
  - For aseptically prepared products:
    samples from start & end of run and after any significant intervention.
  - For terminally sterilised products:
    some samples should be taken from the potentially coolest part of the load.

Further reading:
PIC/S Recommendation:
"Recommendation on Sterility Testing"
PIC/S Document PI 012-3

Sterile Production

Possible Inspection Issues (with examples)

- Poor design of the building (same airlock for people & materials)
- Poor design of equipment (sterilisers without correct instrumentation)
- Inadequate ventilation system (insufficient pressure differentials between rooms)
- Inadequately controlled services (superheated steam; unfiltered compressed gas)
- Flow of materials (not a logical flow)
- Poorly maintained facilities (performance of filters not monitored)
- Removal of air from autoclave not demonstrated (inadequate validation data)
- Inadequate qualification/validation (no VMP)

Sterile Production

Possible Inspection Issues (with examples)

- Particulate levels/micro-organisms (monitoring too infrequent)
- Badly planned monitoring (settle plates exposed for too long)
- Differential pressures (not monitored)
- Air changes (no specification)
- Temperature/humidity (not controlled; too high for operator comfort)
- Bad practices (interlocks not operational on airlocks)
- Old facilities not complying with current requirements (company using old GMP requirements)

Comparison of PIC/S Annex 1 & FDA Guidance on Aseptic Processing (Sept'04)

PIC/S Annex 1 (Sept'09)	FDA Aseptic Guidance (Sept'04)
Aseptic processing & terminal sterilisation	Aseptic processing only
Isolator technology discussed	Isolator technology not discussed
Grade D area specified	No Grade D equivalent
0.5µm and 5µm particles/m^3 specified for clean air classification	Only 0.5µm particles/m^3 specified for clean air classification
Recovery time (15-20 mins) specified	Air change rates (20/hr for Class 100,000) specified
No discussion of HEPA filters (except for use in hot air steriliser)	HEPA filters discussed

PIC/S Inspection Approach

(With tips and suggestions on how to handle logistics)

Korea, March 2011

Mr Bob Tribe
Canberra, Australia

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

Overview

- What happens (before, during & after the inspection).
- Tips and suggestions for these stages.
- Documents & reports used by inspectors.
- GMP deficiency classification process.
- Common GMP deficiencies reported by MHRA, EMEA, FDA.
- The most common GMP deficiencies reported by TGA, Australia.

Before the Inspection

- The need for the inspection is determined:
  - New site (usually scheduled to suit manufacturer)
  - Re-inspection (risk based scheduling)
- Inspection frequency based on risk factors
  - Results of previous inspection
  - Type of products manufactured
  - Any recalls, complaints, adverse reactions since last inspection
  - Any testing failures since last inspection
  - Significant changes within company, eg. Key personnel, buildings, equipment, products, intention to cease business.
- A system of computerised scheduling usually used

TGA's Risk Approach to Scheduling

Risk Category	A1 rating	A2 rating	A3 rating	Unacceptable rating
	Frequency of re-audit (months)			Internal Review Panel decides on what action to take.
High	24	18	12	
Medium	30	20	12	
Low	36	24	12	

Risk Category (examples)		
	High:	manufacturer of sterile medicines
	Medium:	manufacturer of OTC medicines
	Low:	manufacturer of vitamins

Company Rating		
A1	Good compliance	(<10 "other" deficiencies)
A2	Satisfactory compliance	(1-5 "major" & <11 "other")
A3	Basic compliance	(>5 "major", but no "critical")
Unacceptable	Unacceptable	(1 or more "critical")

MHRA (UK) Risk-based Inspection Process

- MHRA launched Risk-based inspection process on 1 April'09.
- Participating sites are those UK sites that hold a Manufacturing Authorization & 3rd country sites named on a UK Marketing Authorization.
- Sites required to complete a **Compliance Report** in advance of the inspection. This report must identify risks. Examples of Compliance Reports given on MHRA web site
- The inspector will identify a risk rating for the site; this will in turn equate to a future inspection frequency.
- Risk ratings identify the degree of surveillance required within the licensing and inspection program.

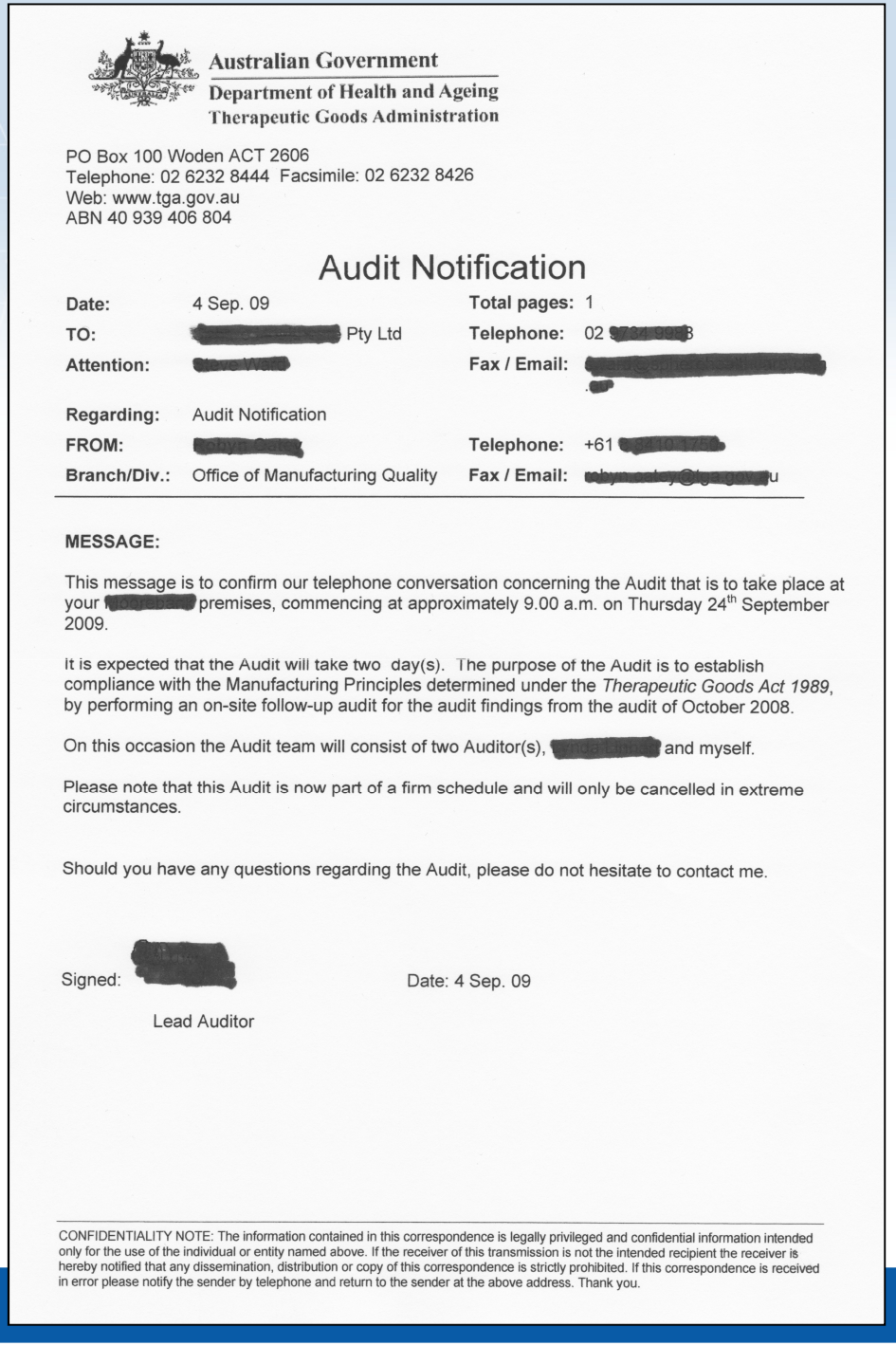
Before the Inspection

- Lead inspector is assigned
- Inspection team selected, which could include:
  - Qualified inspectors
  - Technical specialists (eg. Microbiologist)
  - Drug assessors
  - Trainee inspectors
- Inspection duration determined, based on:
  - Previous inspector's recommendation
  - Level of compliance at last inspection
  - Risk factors (previously discussed)

Before the Inspection

- Sponsor & manufacturer notified:
  - Date, number of days, names of inspectors.
  - Usually by fax, but email may also be used.
  - Usually 1 week's notice for local manufacturers
  - Usually 1 to 2 month's notice for overseas manufacturers
- Unannounced inspections:
  - Where history of poor GMP compliance exists
  - Where true extent of GMP compliance cannot be assessed otherwise.
  - Common for local inspections; unusual for overseas inspections.

Example of TGA's notification fax



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

PO Box 100 Woden ACT 2606
Telephone: 02 6232 8444 Facsimile: 02 6232 8426
Web: www.tga.gov.au
ABN 40 939 406 804

Audit Notification

Date:	4 Sep. 09	**Total pages:**	1
TO:	[redacted] Pty Ltd	**Telephone:**	02 [redacted]
Attention:	[redacted]	**Fax / Email:**	[redacted]
Regarding:	Audit Notification		
FROM:	[redacted]	**Telephone:**	+61 [redacted]
Branch/Div.:	Office of Manufacturing Quality	**Fax / Email:**	[redacted]

MESSAGE:

This message is to confirm our telephone conversation concerning the Audit that is to take place at your [redacted] premises, commencing at approximately 9.00 a.m. on Thursday 24th September 2009.

It is expected that the Audit will take two day(s). The purpose of the Audit is to establish compliance with the Manufacturing Principles determined under the *Therapeutic Goods Act 1989*, by performing an on-site follow-up audit for the audit findings from the audit of October 2008.

On this occasion the Audit team will consist of two Auditor(s), [redacted] and myself.

Please note that this Audit is now part of a firm schedule and will only be cancelled in extreme circumstances.

Should you have any questions regarding the Audit, please do not hesitate to contact me.

Signed: [redacted] Date: 4 Sep. 09

Lead Auditor

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Before the Inspection

- For overseas inspections, manufacturer is usually contacted by email to discuss or request:
  - Hotel accommodation.
  - Guidance on travel to hotel & facility.
  - Arrangements for translation during the inspection.
  - Request for documentation such as Site Master File.

Just Before the Inspection

- Inspection team reviews documentation on file:
  - Site Master File.
  - Product marketing authorisations.
  - Complaints, recalls, product test results.
  - Last GMP inspection report.
  - Copies of these made and brought to the inspection.
- Lead inspector prepares inspection plan:
  - Usually sent to manufacturer just before the inspection.
- Travel to reach facility:
  - For overseas inspections, 3 or 4 companies in the one country inspected during the same trip.

Typical Inspection Plan – 1st page

Proposed Agenda for GMP Inspection

Company: ABC Pharmaceuticals Pty Ltd
1 Main Street, Pleasantville, NSW, Australia

Dates: 17-20 January 2011

Purpose: TGA GMP inspection

Scope: All operations associated with the manufacture, packaging, QC testing and release of non-sterile medicinal products.

Inspection Team: Mr Bill Smith, Lead Inspector
Dr Mark Jones, Inspector

Standard Used: PIC/S GMP Guide for Medicinal Products, PE 009-9, 1 Sept'09

Proposed Inspection Plan:

Date/times	Areas to be inspected
17/1/11	
08.30 – 09.30	Opening Meeting o Introductions (& attendance record) o Timetable o Company overview o Product range & licence conditions o Questions arising from company's SMF
09.30 – 12.30	Quality Management System review o Personnel; Org Chart; Job Descriptions o List of SOPs & SOP index o SOP preparation, review, approval, distribution, retrieval o Batch numbering system o Annual product review & reports o Deviations; Change Control; OOS & registers o Self inspections, plans & reports o Complaints handling system and register o Product recall system & register o Reprocessing, reworking policy & register o Supplier evaluation/approval system & list of approved suppliers o Finished product release procedure
13.30 – 14.30	Review of site plans & HVAC system o Site layout, floor plans, material & personnel flow o HVAC layout, area classification, pressure differentials o Brief orientation tour of site

Typical Inspection Plan – 2nd page

14.30-17.00	Starting Materials & Warehouse o Housekeeping & Pest control o Receipt, handling, status labelling & storage o Sampling of starting materials o Storage areas – quarantine, release, reject o Approval for use o Temperature & humidity mapping & monitoring o Finished goods warehouse & distribution records
17.00	Summary of observations for the day
18/1/11	
08.30 – 12.30	Production & facilities o Building and facilities; surfaces & finishes o Housekeeping, gowning procedures & personal hygiene o Dispensing of raw materials o In-process controls o Equipment; suitability, cleanliness & storage o Storage of bulk/intermediates – validated holding times o Packaging operations o Control of labels & pre-printed packaging materials o Line clearance checks o Batch documentation & Reconciliation
13.30-17.00	Engineering & Services o Preventative maintenance & calibration o Pest control o Waste disposal Review of the HVAC System o HVAC schematic drawing & specifications o Qualification, requalification, monitoring the system o Inspection of HVAC system & dust extraction Review of the Water Treatment System(s) o PW system drawings, specifications & capabilities o Qualification, requalification, monitoring the system o Sampling & trend analysis o Inspection of system Review of the Compressed Air System o Compressed air schematic drawing & specifications o Qualification, requalification, monitoring the system o Inspection of system
17.00	Summary of observations for the day
19/1/11	
08.30 – 12.30	QC Laboratory o Analyst training, competencies & assessment o Sample receipt, storage & allocation o Wet chemistry laboratory o Instrument laboratory – qualification, calibration, maintenance

Typical Inspection Plan – 3rd page

	o Laboratory materials – reference & working standards, reagents o Method validation o Specifications and test methods o Analysts work books/records, test results & trending o Microbial testing – room, equipment, media prep o Environmental & water monitoring o Retention samples o Stability testing program o OOS o Contract testing
13.30-17.00	Validation o VMP o Equipment qualification/requalification (DQ,IQ,OQ & PQ) o Preventative maintenance schedules & records o Calibration schedules & records o Process validation & revalidation for products o Cleaning validation & reports o Computer systems validation
17.00	Summary of observations for the day
20/1/11	
08.30 – 12.30	Staff training & assessment o Job descriptions o Training program o Training records & traceability of training history o Assessment of effectiveness of training Review of documents o Review of BMRs, BPRs, testing records of selected batches o Contract manufacturing & GMP agreements o Marketing authorizations
13.30 – 1500	Review of any documents outstanding from previous days
15.00-16.30	Closed meeting of inspectors only
16.30	Closing meeting with company representatives (& attendance record)

Prepared by: Bill Smith, Lead Inspector

Date: 12/1/11

Travel & Hotel Arrangements

- Business class air travel for overseas inspections:
  - Economy air travel for local inspections.
- Hotels may be booked by inspectors.
  - But common for TGA to request manufacturer to book hotel (local knowledge).
  - However, inspectors will pay their hotel bill.
- Ground transport (eg. trains) may be booked by inspectors:
  - But common for TGA to request manufacturer to book.
  - However inspectors will usually pay for own train tickets.

Charges

- TGA inspections fully cost recovered.
- Australian sponsor is invoiced the cost of inspection
  - Inspection fee (A$1060/hour = A$34,000 for a 4 day inspection, ie. approx US$27,000.
  - Apportioned air fare cost (total air fare shared by all sponsors involved in that trip).
- Costs of hotels, ground transport, meals:
  - Are part of the inspection fee.
- Invoice sent to Australian sponsor after the inspection:
  - That is, after reconciliation of hours taken to inspect.

Tips - Before the Inspection

- Ensure SMF is up-to-date and ready:
  - Usually the 1st document requested by inspectors.
- When notified of inspection date, offer to:
  - Book hotel accommodation.
  - Arrange ground transportation (train to hotel; van to facility).
  - Arrange to meet at airport or central station to guide to hotel.
  - Do not book very expensive hotels.
  - Inspectors are civil servants & have a limit on hotel costs.
- Do not book hotel a long distance from facility:
  - May frustrate inspectors if time is wasted travelling to site.

Tips - Before the Inspection

- Inspection team in transit to facility:
  - Escort should phone ahead to enable senior staff to be at front entrance to greet inspection team.
- Display a sign or computer screen greeting the inspectors by name.
- Have a meeting room arranged with:
  - Country flags.
  - Flowers.
  - Tea & coffee facilities.
- Have a pre-prepared presentation on the company:
  - But keep it brief & do not cover sales/marketing.
- Have several scribes designated:
  - Inspection team may split up.

The Inspection

- Arrival and greeting.
- Opening meeting:
  - Meeting attendance record circulated.
  - Introductions.
  - Scope, objective, inspection plan discussed.
  - Discussion of resources and facilities needed.
- Inspection:
  - Usually starts with review of key documents.
  - Inspection team may split for part of the inspection.
- Summary session at end of each day may be offered.
- May take product samples, copies of records, etc.

Typical Meeting Attendance Record

Meeting Attendance Sheet

Company: ABC Pharmaceuticals Pty Ltd
Address: 16 Main Street, Bondi, NSW 2345
Topic: GMP inspection

Name: (please print)	**Title / Organisation:**	**Opening:** Date:1.11.06 Time: **Initials:**	**Closing:** Date:3.11.06 Time: **Initials:**

Logistics

- Meals:
  - Coffee and lunch: usually accepted on-site.
  - Evening dinner: inspectors not allowed to accept, but some inspectors may accept
- Gifts:
  - Inexpensive gifts: usually accepted to avoid offending company.
  - Expensive gifts: inspectors not allowed to accept & will be refused or returned.
  - All gifts offered are required to be declared by the inspectors.
- Entertainment:
  - Inspectors not allowed to accept (but some do).
- Sightseeing
  - May or may not be accepted during the inspector's weekend off.

Code of Ethics for Inspectors

- As part of the Inspectorate's Quality System, there are rules in place to:
  - Ensure impartiality and integrity.
  - Avoid real or potential conflict of interest (commercial/financial).
  - Avoid undue & improper influence (bribes, gifts, threats).
  - Distinguish between the inspection process & the issue of a license to manufacture medicines.
  - Distinguish between the inspection process & providing an advisory service.
- Inspectors can be subject to disciplinary action if these rules are breached.

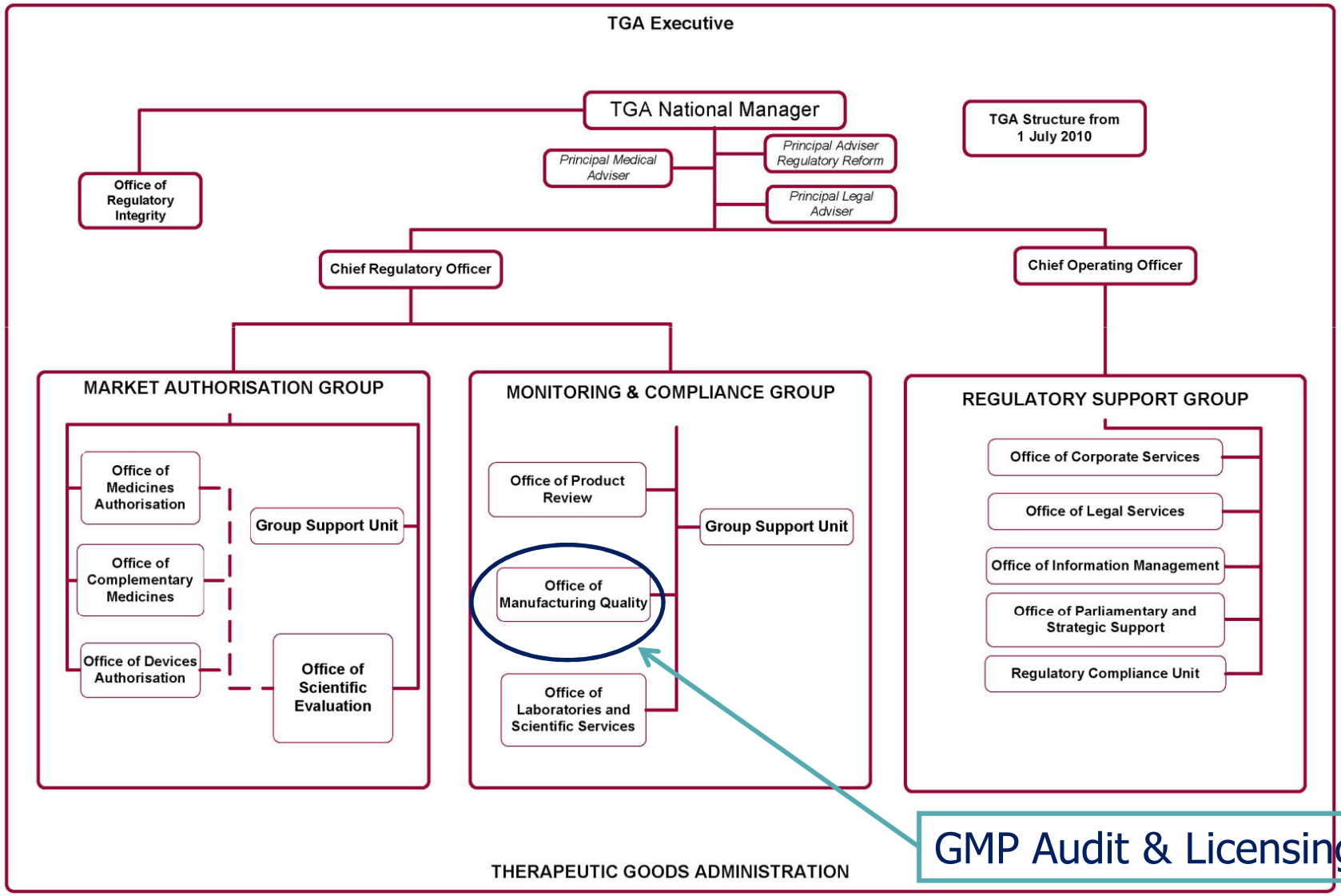
The Closing Meeting

- Audit team has meeting on their own (on site):
  - May take 2 or more hours.
  - Prepare list of deficiencies & classify.
  - Discuss overall summary of findings.
- Closing meeting with company:
  - Company may select whoever they like to attend.
  - Meeting attendance sheet completed.
  - Verbal summary of deficiencies given (no report left on site).
  - Discussion is encouraged.
  - Timetable of future actions discussed:
    - Timing of written list of deficiencies from TGA
    - Timing of company's response to this list of deficiencies

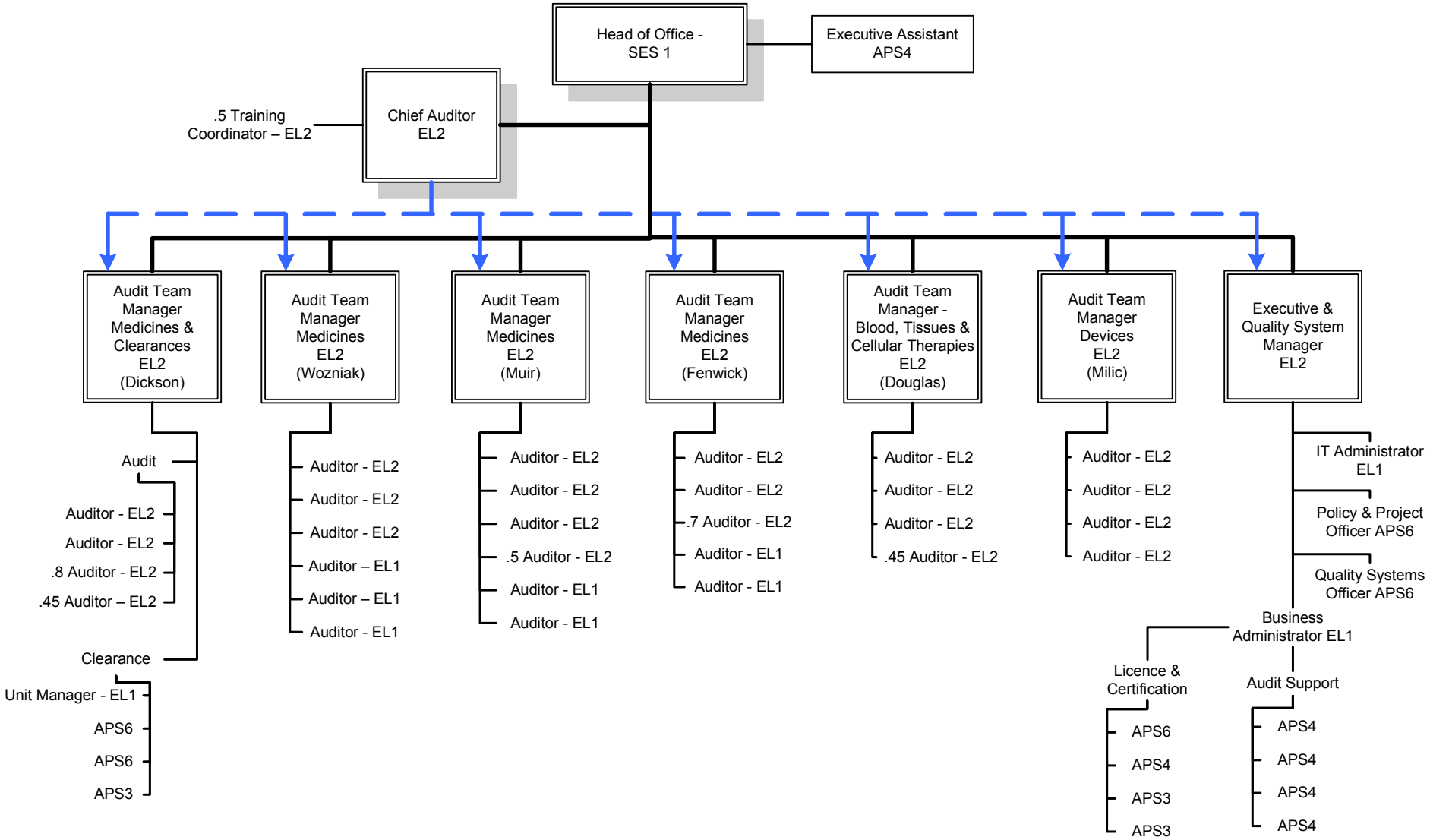
After the Inspection

- Audit Close-out record (deficiency report) prepared.
- Deficiencies checked by Audit Manager
  - To help ensure consistency within TGA.
- "Inspection Close-out Record" sent to company within 3 weeks of inspection
  - Company requested to respond with corrective actions.
  - Objective evidence is requested (eg. photos; revised SOPs, invoice that shows purchase of new equipment).

New Structure of TGA – 1 July 2010



TGA's Office of Manufacturing Quality



Office locations = Canberra, Sydney, Melbourne & Adelaide
Total No. Auditors = 34 (all "qualified" for specific types of audits)
Clerical Staff = 18
Tech. Specialist Pool = from TGA's Testing Laboratories

Example of Inspection Close-out Record (p.1)
(as received from TGA)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Manufacturing Quality
Inspection Close Out Record

Manufacturer: [redacted] Pty Ltd	**Manufacturer address:** [redacted]
Inspector(s): [redacted]	**Audit date:** 27-30 June 2009

Manufacturer to complete columns 1, 2, 3, 4 and 5. (Please note, objective evidence is only required for critical and major deficiencies)

Please note requested extension to licence cannot be granted until all relevant deficiencies have been satisfactorily addressed. This may include on-site verification of some corrective actions.

1	2	3	4	5	6	7
Deficiency number	✓ if objective evidence required	Response number / Date	Description of deficiency, corrective actions and, if applicable, reference to supportive objective evidence	Completion, or proposed completion, date dd/mm/yy	Inspector('s) Comment(s)	Response accepted Y/N
MAJOR DEFICIENCIES						
1	✓		Rework/reprocessing of batches of products was not adequately controlled, as there was no documented procedure describing the company's approach to rework/reprocessing.			
2	✓		The investigation or process deviations, non-conformances and customer complaints were not adequately documented to demonstrate that appropriate corrective and preventive actions had been implemented. *(This was also an issue at the last TGA inspection).* For example, for manufacture of Glucosamine Sulfate with Chondroitin Tablets Bx F1568, The deviation was approved by QC and not QA.			

Example of Inspection Close-out Record (p.1)
(after 2 responses to TGA from company)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Manufacturing Quality
Inspection Close Out Record

Manufacturer: [redacted] Pty Ltd	**Manufacturer address:** [redacted]
Inspector(s): [redacted]	**Audit date:** 27-30 June 2009

Manufacturer to complete columns 1, 2, 3, 4 and 5. (Please note, objective evidence is only required for critical and major deficiencies)

Please note requested extension to licence cannot be granted until all relevant deficiencies have been satisfactorily addressed. This may include on-site verification of some corrective actions.

1	2	3	4	5	6	7
Deficiency number	✓ if objective evidence required	Response number / Date	Description of deficiency, corrective actions and, if applicable, reference to supportive objective evidence	Completion, or proposed completion, date dd/mm/yy	Inspector('s) Comment(s)	Response accepted Y/N
MAJOR DEFICIENCIES						
1	✓		Rework/reprocessing of batches of products was not adequately controlled, as there was no documented procedure describing the company's approach to rework/reprocessing.			
		Resp: 1 Date: 28/7/09	Corrective Action taken: Rework Procedure is to be written. This SOP is to include a Rework Evaluation Form, which will be completed and approved, before the rework is carried out.	28/8/09	Please submit objective evidence.	N
		Resp: 2 Date: 28/8/09	Corrective Action taken: SOP PA129.01 has been written and approved. This SOP is now in operation Evidence provided: SOP PA129.01 and the Rework Evaluation Form are attached (Appendix 1).	28/9/09	SOP PA129.01 has been referred internally within the TGA for further evaluation and discussion as the current content does not meet Code Requirements or the principles of GMP.	N

Completed by company

Example of Inspection Close-out Record (p.2)
(after 2 responses to TGA from company)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Manufacturing Quality
Inspection Close Out Record

2	✓		The investigation or process deviations, non-conformances and customer complaints were not adequately documented to demonstrate that appropriate corrective and preventive actions had been implemented. *(This was also an issue at the last TGA inspection)*. For example, for manufacture of [redacted] with [redacted] Tablets [redacted], The deviation was approved by QC and not QA.			
		Resp: 1 Date: 28/7/09	Corrective Action taken: QA Manager Delegation of Authority Matrix completed and is to be included into an SOP.	28/8/09	Please submit objective evidence.	N
		Resp: 2 Date: 28/8/09	Corrective Action taken: Draft SOP attached. Evidence provided: Copy of authorised SOP PA114-03 "Delegation of Authority" dated March 2009 attached (Appendix 2).		**Action taken is acceptable. Effectiveness of corrective actions to be verified at next on-site audit.**	Y
3	✓		The company's validation programme was deficient in that there was insufficient detail in the VMP describing validation requirements including when changes were made to qualified or validated systems.			
		Resp: 1 Date: 28/7/09	Corrective Action taken: VMP to be rewritten	28/8/09	Please submit objective evidence.	N
		Resp: 2 Date: 28/8/09	Corrective Action taken: No progress	28/9/09	Please submit objective evidence.	N

Completed by company

Unacceptable GMP Compliance

- One or more "critical" deficiencies usually attracts an "Unacceptable" rating.
- Audit Manager & Audit Governance Committee involved in confirming "Unacceptable" status.
- For new manufacturers:
  - Local company: not licensed by TGA.
  - Overseas company: not approved by TGA to supply to Australia.
- For existing manufacturers:
  - Local company: licence amended, suspended or revoked.
  - Overseas company: approval status revoked.
- Company has option to appeal the decision.

Myth: Inspectors are tougher on Australian companies than they are on overseas companies

Medicines audits March 2004 – May 2008

Location	Critical Deficiencies	Major Deficiencies	Other Deficiencies	Total Deficiencies
Overseas Average	0.07	3.92	8.12	12.11
Local Average	0.01	3.63	8.31	11.95
Grand Average	0.03	3.74	8.24	12.01

Number of Deficiencies per inspection

PIC/S Classification of GMP deficiencies

Critical Deficiency

A deficiency that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

(A critical deficiency is a serious situation that will result in regulatory action being considered and a definite connection between the deficiency and a harmful product must be able to be reasonably made. If this connection cannot be reasonably made, the deficiency should be recorded as "major").

Examples of Critical GMP Deficiencies

Examples of Critical Deficiencies:

- No or grossly inadequate air filtration to minimise airborne contaminants (non-sterile production).
- Lack of sterilisation validation (sterile production).

PIC/S Classification of GMP deficiencies

Major Deficiency

A non-critical deficiency that:

- *has produced or may produce a product which does not comply with its marketing authorisation; and/or*
- *indicates a major deviation from the Code of GMP; and/or*
- *indicates a major deviation from the terms of the manufacturing licence or GMP approval (overseas manufacturers); and/or*
- *indicates a failure to carry out satisfactory procedures for release of batches; and/or*
- *indicates a failure of the person responsible for QA/QC to fulfil his/her duties; and/or*
- *consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.*

Examples of Major GMP Deficiencies

Examples of Major Deficiencies:

- No Product Quality Review undertaken.
- Stored equipment (used for the manufacture of non-sterile medicines) was not protected from contamination.

PIC/S Classification of GMP deficiencies

"Other" Deficiency (or Minor Deficiency)

- *A deficiency that cannot be classified as either critical or major, but indicates a departure from good manufacturing practice.*
- *A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as major or critical.*
- *One-off minor lapses or less significant issues are usually not formally reported, but are brought to the attention of the manufacturer.*

Examples of "Other" GMP Deficiencies

Examples of "Other" Deficiencies:

- Person making alteration to batch document did not initial the change.
- Equipment not calibrated by the due date

Common Inspection Deficiencies

MHRA, UK (2004/05)

Inspection finding	%
Quality management	8.2
Batch release and duties of QP	6.7
Quality system documentation	6.7
Design and maintenance of premises	5.2
Environmental monitoring	5.2
Process validation	5.2
Cleaning validation	4.5

Common Inspection Deficiencies

EMEA (inspections by EU regulatory authorities on behalf of the EMEA for 2006)

Inspection finding	%
Quality system documentation	10.9
Manufacturing documentation	10.2
Design and maintenance of premises	6.5
Specifications and testing documentation	5.2
Status labeling	4.7
Contamination, microbiological	4.7

Common Inspection Deficiencies

FDA (GMP deficiencies for foreign manufacturers for FY 2004)

Inspection finding	%
Failure / OOS investigation	11
Laboratory controls	9
Equipment / cleaning validation	8
Inadequate SOPs	7
Water systems	5
Production / process controls	5
Environmental controls	5

Common Inspection Deficiencies

TGA (common GMP deficiencies for local & overseas manufacturers)

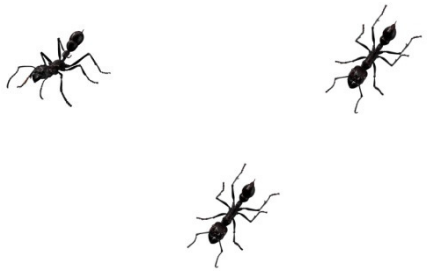
Inspection finding	%
Change control	*
Supplier approval	*
Equipment / facilities	*
Sampling of starting materials	*
Water systems	*
Computer systems	*
Laboratory controls	*

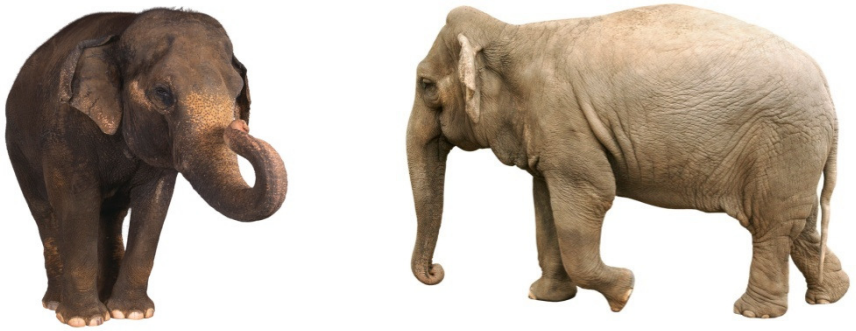
* Do not publish

Common Inspection Findings
(TGA, Australia)

Change Control Deficiencies

"Counting the ants and
missing the elephants"





Common Inspection Findings
(TGA, Australia)

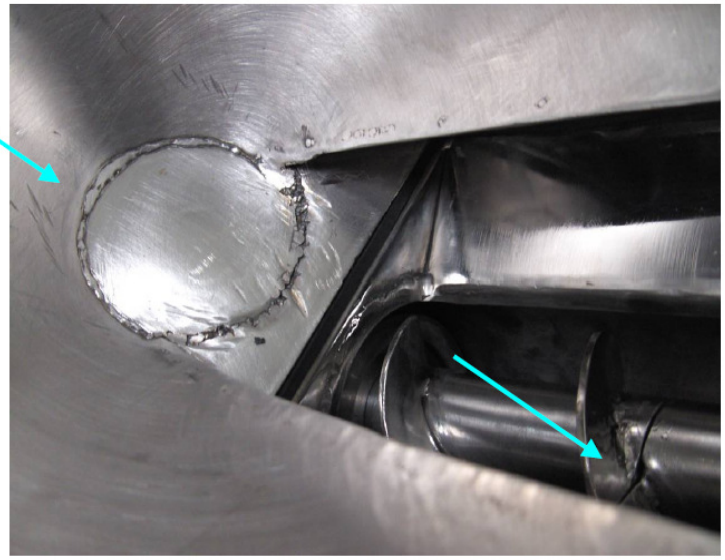
- Change Control
  - Change control systems did not include all items relevant to the quality of products (Annex 15, clause 44).
  - The change control process was limited to document changes and did not include changes to equipment, process, facility & systems.
  - Some change control systems include small document changes but did not include large plant alterations.

Common Inspection Findings
(TGA, Australia)

- Supplier approval:
  - Using suppliers before they are approved.
  - Approving suppliers only and not considering the manufacturer of the starting materials.
  - Approving suppliers using uncontrolled samples.

Common Inspection Findings
(TGA, Australia)

- Equipment and facilities:
  - Cleaning validation not done.
  - Inappropriate location of equipment for cleaning and maintenance.
  - Inappropriate materials of construction.
  - Surfaces not crevice free and smooth.



Common Inspection Findings
(TGA, Australia)

- Equipment
  - Inappropriate material used in construction, eg. surfaces and welds on equipment not smooth or free from cracks.
  - No evidence of the quality of welds of stainless steel pipe-work for purified water system (eg. weld certificates, sample welds).
  - Equipment parts (eg. de-dusting hoods from FBDs) were not cleaned using validated procedures.
  - Washing machines & cleaning equipment (themselves a potential source of contamination) were not subject to cleaning validation (if not dedicated).
  - Equipment holding times before cleaning – not part of cleaning validation.

Common Inspection Findings
(TGA, Australia)

- Equipment
  - Where testing was part of the cleaning validation, valid analytical methods were not used.
  - Cleaning procedures did not include sufficient details to ensure the cleaning method could be consistently applied.
  - The records of cleaning were not always kept.
  - Cleaning SOP did not include the requirement that equipment needed to be, at least, visually clean (powder residues found on outside of two drums which were tagged as "clean").

Common Inspection Findings
(TGA, Australia)

- Water systems:
  - Inappropriate materials of construction.

Common Inspection Findings
(TGA, Australia)

- Water Systems:
  - Inappropriate materials used in water treatment systems, eg. Nylex (plastic) garden hose.
  - No validated flushing procedure after chemical sanitization (ie. to show sanitizing agent has been effectively removed).
  - The volumes flushed when taking QC samples were more than Production staff was required to flush (ie. QC sampling did not simulate how Production staff took water for use in manufacturing/cleaning).
  - No time limit by which samples of purified water must be tested.

Common Inspection Findings
(TGA, Australia)

- HVAC:
  - Room pressure differentials not designed to prevent cross-contamination.
  - No design documents defining the expected pressure differentials for manufacturing & packaging areas.
  - Ventilation systems not adequately controlled.
  - Inadequate control of maintenance (e.g. filters not monitored for leakage and blockage).
  - The SOP for operating AHUs and cleaning AHU filters did not indicate the sequence for switching on and off the AHU units (to prevent reversal of pressure gradient & direction).

Common Inspection Findings
(TGA, Australia)

- HVAC:
  - The "at rest" qualification of the HVAC system was undertaken with production machines switched off.
  - Installed filters were not as per specification.
  - The type of filters required in the HVAC system were not defined.
  - The ventilation system inadequately controlled (ie. the pressure differentials between manufacturing area & filling room defined as 10 – 15 Pa. But measurements carried out over last few months showed only 5 Pa).

Common Inspection Findings
(TGA, Australia)

- Laboratories:
  - No QC staff competency matrix available for the allocation of samples for QC testing.
  - Failure to adequately train personnel.
  - Failure to ensure that analysts are competent on new test methods (eg. by testing a know reference standard or a sample tested by an experienced analyst).
  - Exposing starting materials to inappropriate environmental conditions during sampling.
  - Inappropriate handling of utensils used for sampling.

Common Inspection Findings
(TGA, Australia)

- Contract Laboratories:
  - No GMP agreement with contract testing laboratory.
  - Inadequate GMP agreements
    - Failure to ensure that the agreement clearly defines which company is responsible for method validation.
    - Failure to define what method should be used by the contract laboratory.
    - Failure to ensure that the method used by the contract laboratory is validated.
  - Failure of the contract laboratory to check whether the sample being tested is for GMP purposes.

Common Inspection Findings
(TGA, Australia)

- Sampling:
  - Exposure of starting materials & primary packaging materials to inappropriate environments during sampling.
  - Inappropriate blending of starting material samples for ID testing.
  - Failure to set limits on the number of samples that can be blended for tests other than ID.

Common Inspection Findings
(TGA, Australia)

- Sampling:
  - Sampling utensils not treated as product contact equipment.
    - Failure to use purified water as final washing rinse.
    - Washing sampling utensils in inappropriate environment, ie. in a multi-purpose laboratory sink.
  - Cleaned utensils not covered when carried outside a controlled environment.
  - The cleaning of dispensing utensils had not been validated (because QA & validation personnel believed that dedicated utensils were used).

Common Inspection Findings
(TGA, Australia)

- Computer Systems – Security:
  - Systems that were used for release for supply had not been defined as critical.
  - Failure to ensure that computer access to release product was restricted to authorised personnel.
  - Computer system failed to remove access
    - When staff on leave
    - When staff transfer Departments
    - When staff go on maternity or long service leave
  - Computers left unattended while logged in, with no compulsory "time-outs", password-protected timesavers, etc.

Common Inspection Findings
(TGA, Australia)

- Computer Systems – Source Code:
  - Failure to define what version of critical systems had been validated, ie. no record of the system version in validation documents.
  - Failure to control who has access to change the production source code.
  - Failure to control external contractors who log directly into company systems.

Common Inspection Findings
(TGA, Australia)

- Liquids, Creams & Ointments:
  - Transfer hoses not controlled after cleaning.
    - Not labelled as clean.
    - Not protected from contamination.
    - Water residues left in hoses upon storage.
  - Cleaning validation of transfer hoses were either not adequately addressed or were ineffective.
  - Transfer hoses used in manufacturing were not included in cleaning validation.

After the Inspection

- Communication continues until inspection closed out.
- Company advised of audit close-out.
- Final inspection report prepared and sent to company.
- Audit Manager involved in close-out process & reviewing final inspection report (for consistency).
- Manufacturer may a request GMP certificate.
  - Small cost involved.
- Inspection cycle recommences (risk based).

PIC/S Inspection Report Format

- Described in "PIC/S Inspection report Format", PI 013-3, 25 September 2007.
- This covers:
  - Summary of inspection activities.
  - Inspection observations (+ve observations).
  - Deficiencies (-ve observations).
  - Assessment of SMF.
  - Summary of GMP compliance status.
- Identical to the format used by EU Inspectorates.

Typical Final Inspection Report (1st page)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

GMP Audit Report

Audited site(s):	[redacted] Ophthalmic Laboratories Pty Ltd (Trading as Pharmalab) 332 Burns Bay Road Lane Cove NSW 2066	
Activities carried out by company	Manufacture of active ingredient Manufacture of finished medicinal product Manufacture of intermediate or bulk Packaging Laboratory testing Release for supply Other ([redacted] Schedule 5A Exemption products)	[ ] [X] [ ] [ ] [ ] [ ] [X]
Audit date(s):	[redacted] 18 – 20 August, 2003	
Auditor(s):	[redacted] (Lead Auditor) [redacted] (Trainee Lead Auditor) [redacted] (Chief Microbiologist) [redacted] (Trainee Microbiology Specialist)	
References:	Manufacturing Licence number: [redacted] File reference numbers: [redacted]	
Manufacturing Standard:	Australian Code of GMP for Medicinal Products	

Typical Final Inspection Report (2nd page)

Introduction

The company manufactures a wide range of injectable products, which are terminally sterilized by moist heat at the facility. They also manufacture many products under the [redacted]

Tablets are not manufactured on-site, however, tablets are sourced from [redacted] manufacturers, which are released by [redacted]

The company is based in the light industrial sector at [redacted] The three story building that accommodates the company is shared with a [redacted] manufacturer and a [redacted] company.

Date of previous audit: 5/6/02

Names of auditors involved in previous audit: [redacted]

Major changes since the previous audit: The company has continued with the commissioning of the new facility and qualification of equipment at [redacted] There have been some changes to the range of [redacted] (These products are not patient specific) There have also been changes to manufacturing personnel and an increase in resources in the QA area.

Brief report of the audit activities undertaken

Scope of Audit

The manufacturing activities at the facility were audited in accordance with the Australian Code of GMP for Medicinal Products (2002). The audit was a general GMP audit of the new facility for renewal of their license to manufacture sterile medicinal products

Audited areas

All areas of the facility

Personnel met during the audit

Refer to attendance sheet attached.

[redacted]

Audit Team's findings and observations relevant to the audit and deficiencies

Quality Management The company had an effective quality management system in place and it was pleasing to note that the company had increased resources in quality areas since the last audit. However the market authorisation checks for products manufactured on site and externally needed improvement. (deficiency 1.1, 1.2)

Typical Final Inspection Report

(3rd page)

Personnel

A number of staff left the company at the time of the relocation from the old facility.
The training records for two production staff, [redacted] and [redacted] were examined. Training included 8 modules based on [redacted] program and on-the-job training as outlined in SOP [redacted] *General Staff Training*.
There were no records of continuing training or periodic reassessment of competency of operators (see Deficiency #13).
The quality control nominee for the licence, [redacted], and the production nominee, [redacted] were well qualified and experienced for their respective roles.

Premises and Equipment

The premises were clean and the layout was satisfactory albeit a bit cramped and corridors were being used as storage areas, which led to inadequate segregation of materials. (deficiency 4.1).
The starting material warehouse at the base of the building was barely adequate with a number of issues identified at audit in this area. (deficiencies 2.1-2.5)

The sterile manufacturing area comprised a vial preparation area, a dispensary, small and large blending rooms, 3 vial filling rooms (class C), an Atherton autoclave and wash bay. There was also a holding room where unlabelled sterilized finished goods were held in plastic bins. A batch of [redacted] was erroneously labelled as quarantined on [redacted], which was a date in the future (see Deficiency #4.3).

Entry to the production area was via a pressurised, zoned change area and air shower. The pressure between areas was monitored continuously and the area maintained under class C conditions. The areas were monitored monthly for non-viable particulates according to SOP [redacted] and for viable particulates (SOP [redacted]). An external provider checked the area annually.

The production areas were sanitised with chlorhexidine gluconate (1% w/v), 70% isopropyl alcohol sachets ([redacted], or a quaternary ammonium compound. These disinfectants were not monitored for contamination (see Deficiency #4.6).

Clean room operators changed into clean coveralls and over-boots, beard and hair covers, and sterile gloves on entry to the production suite. (The Gowning SOP [redacted] erroneously indicated that the coveralls were sterile). Operators disinfected their hands with Hexfoam sterile spray. There was no mirror in the first part of the change area to check hair was tucked under paper hairnets.

Materials were introduced to the production areas via pass through cabinets.

Typical Final Inspection Report (last page)

Some anomalies were identified and will require correction.

Miscellaneous

Samples taken: nil

Distribution of Report: company, TGA

Attachments

Meeting attendance sheet
Site Plan

List of Deficiencies

Please refer to the Deficiency Report provided to the manufacturer at the end of the audit.

Close out of Deficiencies

The company responded to the deficiency report on [redacted] and [redacted]. Deficiencies have been closed out with either objective evidence or a corrective action plan with and an agreed time frame for completion of corrective actions. Progress reports are due on [redacted] and then every six months until corrective actions are completed.

Summary and conclusions

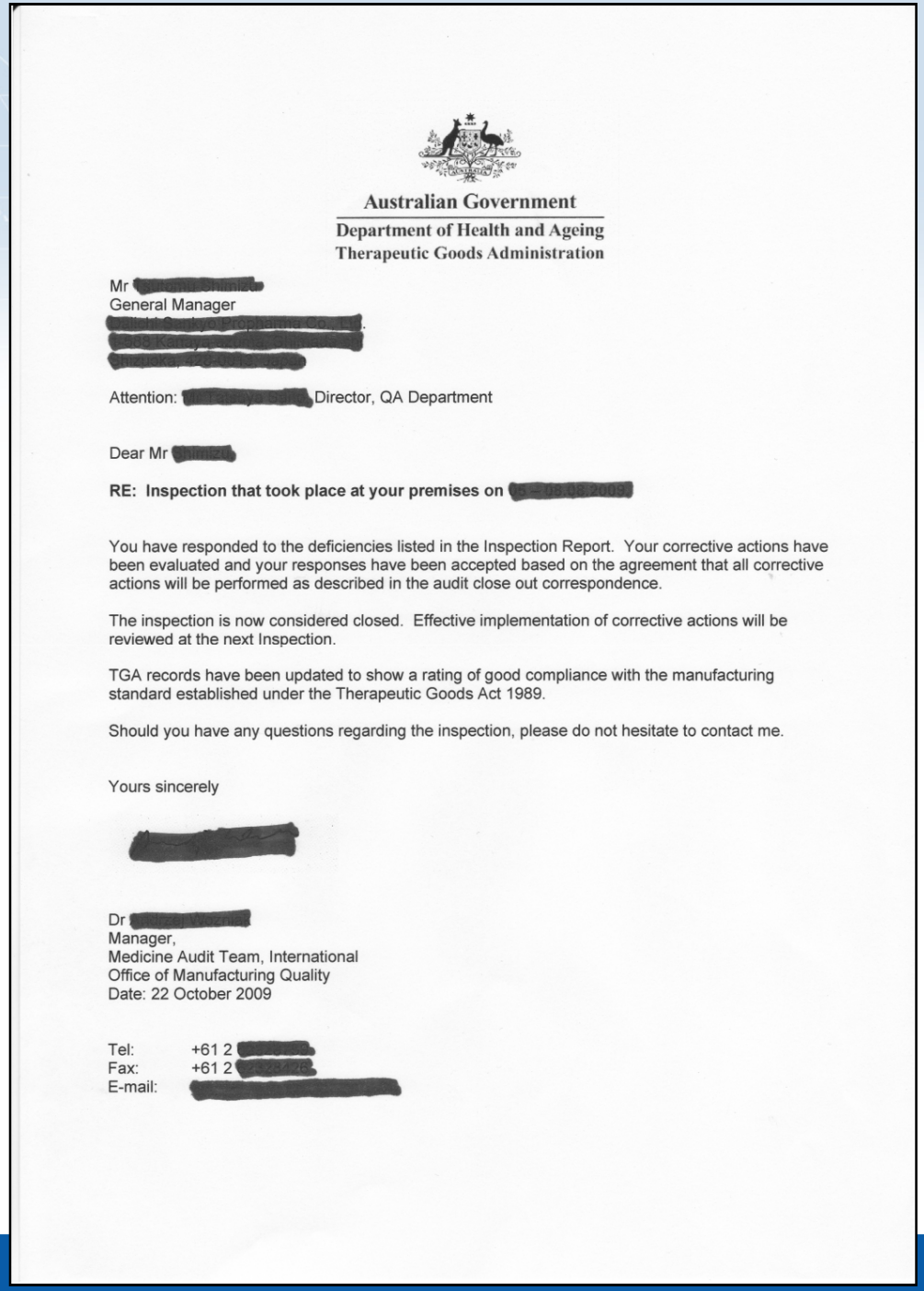
[redacted] is considered to be operating at an acceptable level of compliance with the Australian Code of GMP for Medicinal Products for the manufacture of sterile products.

Lead Auditor's Name: [redacted]

Signatures: [redacted]

Date: [redacted]

Example of TGA Acceptance Letter



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Mr [redacted]
General Manager
[redacted]

Attention: [redacted] Director, QA Department

Dear Mr [redacted]

RE: Inspection that took place at your premises on [redacted]

You have responded to the deficiencies listed in the Inspection Report. Your corrective actions have been evaluated and your responses have been accepted based on the agreement that all corrective actions will be performed as described in the audit close out correspondence.

The inspection is now considered closed. Effective implementation of corrective actions will be reviewed at the next Inspection.

TGA records have been updated to show a rating of good compliance with the manufacturing standard established under the Therapeutic Goods Act 1989.

Should you have any questions regarding the inspection, please do not hesitate to contact me.

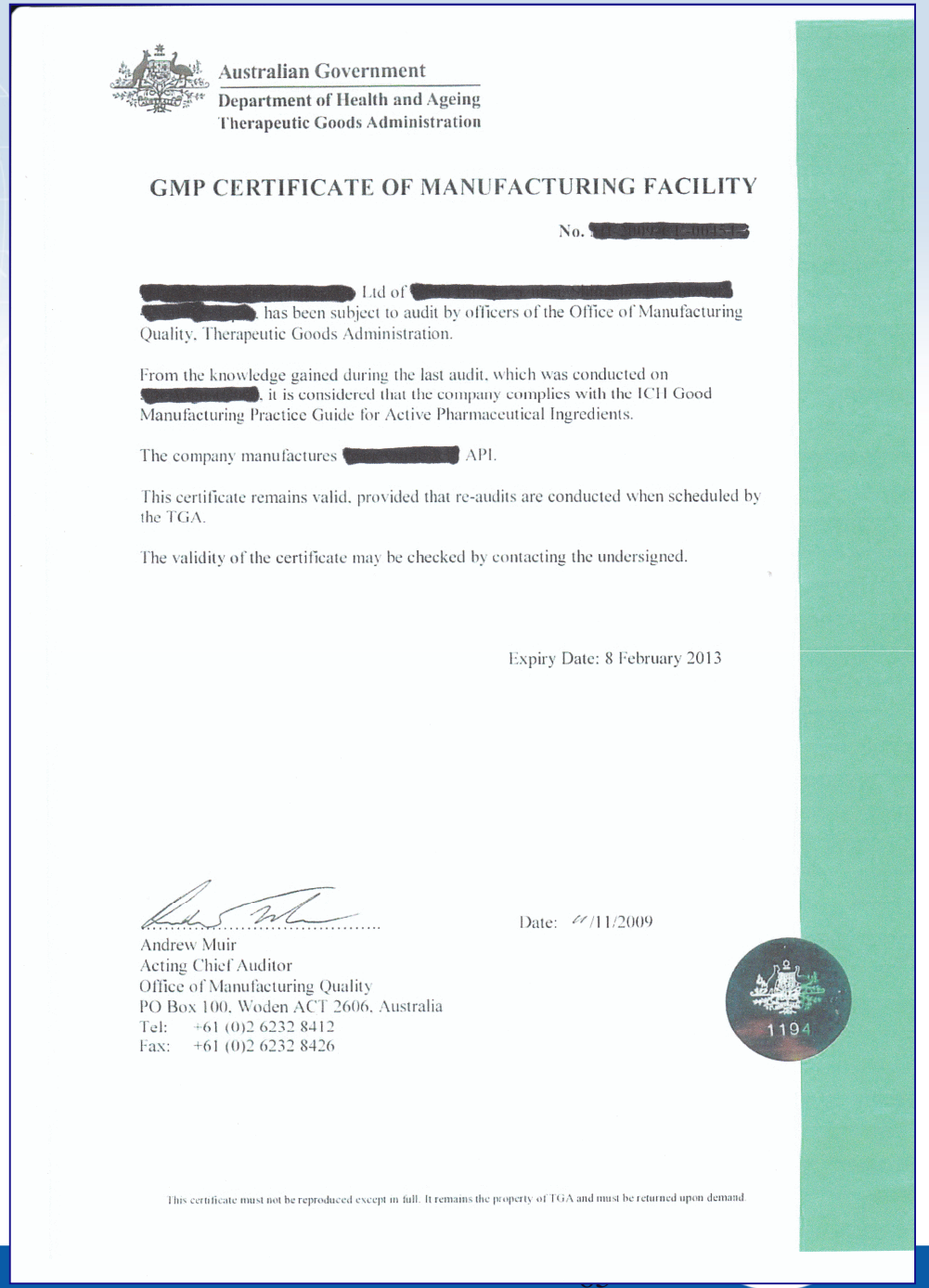
Yours sincerely

[redacted]

Dr [redacted]
Manager,
Medicine Audit Team, International
Office of Manufacturing Quality
Date: 22 October 2009

Tel: +61 2 [redacted]
Fax: +61 2 [redacted]
E-mail: [redacted]

Example of TGA GMP Certificate



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

GMP CERTIFICATE OF MANUFACTURING FACILITY

No. [redacted]

[redacted] Ltd of [redacted] has been subject to audit by officers of the Office of Manufacturing Quality, Therapeutic Goods Administration.

From the knowledge gained during the last audit, which was conducted on [redacted], it is considered that the company complies with the ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients.

The company manufactures [redacted] API.

This certificate remains valid, provided that re-audits are conducted when scheduled by the TGA.

The validity of the certificate may be checked by contacting the undersigned.

Expiry Date: 8 February 2013

Date: 11/11/2009

Andrew Muir
Acting Chief Auditor
Office of Manufacturing Quality
PO Box 100, Woden ACT 2606, Australia
Tel: +61 (0)2 6232 8412
Fax: +61 (0)2 6232 8426

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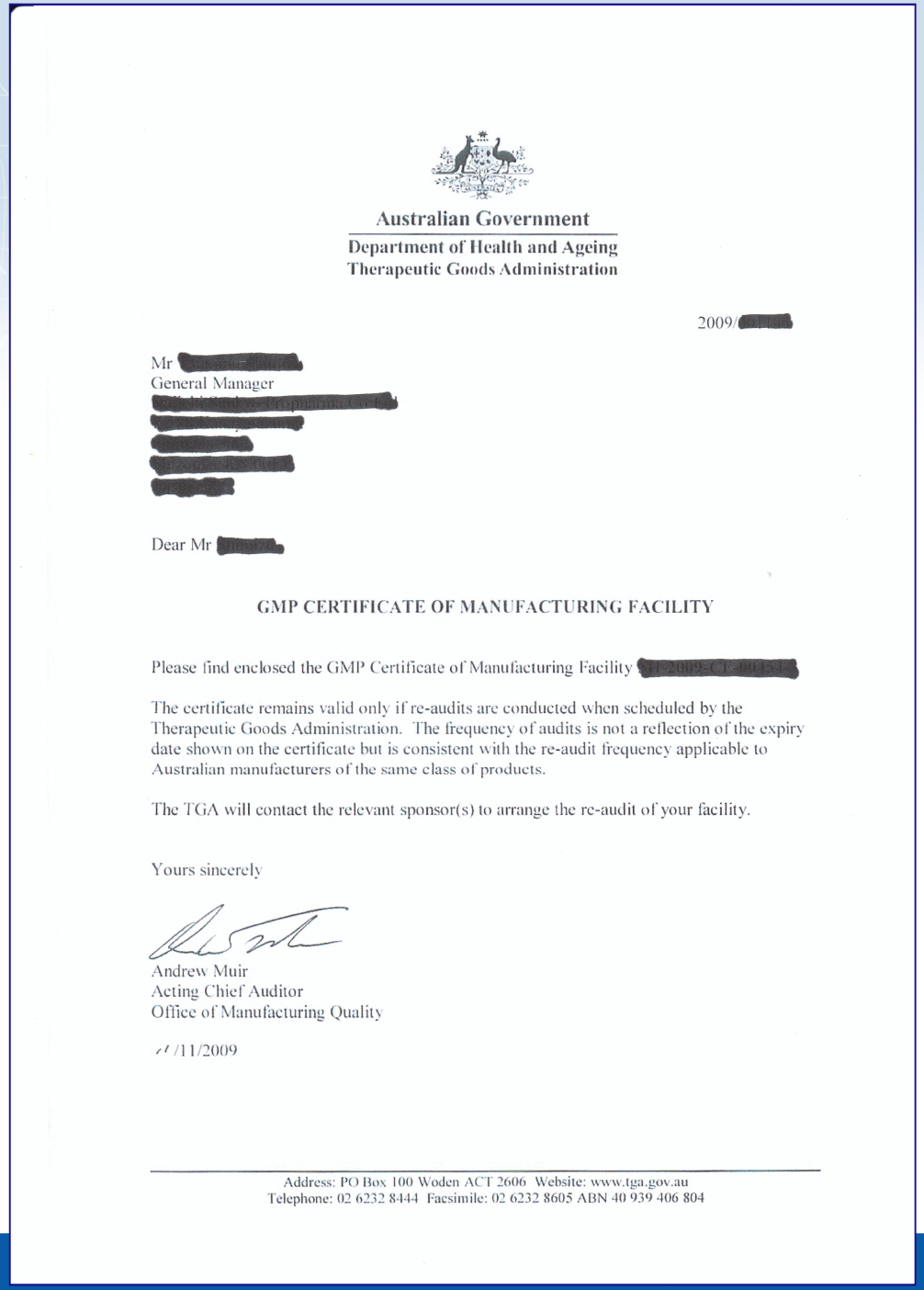
This certificate must not be reproduced except in full. It remains the property of TGA and must be returned upon demand.

Example of TGA GMP Certificate covering letter



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

2009/[redacted]

Mr [redacted]
General Manager
[redacted]

Dear Mr [redacted]

GMP CERTIFICATE OF MANUFACTURING FACILITY

Please find enclosed the GMP Certificate of Manufacturing Facility [redacted]

The certificate remains valid only if re-audits are conducted when scheduled by the Therapeutic Goods Administration. The frequency of audits is not a reflection of the expiry date shown on the certificate but is consistent with the re-audit frequency applicable to Australian manufacturers of the same class of products.

The TGA will contact the relevant sponsor(s) to arrange the re-audit of your facility.

Yours sincerely

Andrew Muir
Acting Chief Auditor
Office of Manufacturing Quality

/ /11/2009

Address: PO Box 100 Woden ACT 2606 Website: www.tga.gov.au
Telephone: 02 6232 8444 Facsimile: 02 6232 8605 ABN 40 939 406 804

Preparing for Regulatory GMP Inspections

Korea, March 2011

Mr Bob Tribe
Canberra, Australia

ENGINEERING PHARMACEUTICAL INNOVATION

Preparing for Regulatory GMP Inspections

Overview

- Secrets of Success
- Actions Before the inspection
- The Opening Meeting
- Actions During the inspection
- The Closing Meeting
- After the inspection
- Responding to the inspection report

Secrets for Success

- Be well prepared.
- First impressions are important.
- Careful selection of people who front the inspectors, ie. technical ability, confidence, presentation, etc.
- You should convince the inspector(s) that:
  - everything is under control.
  - that you know what you are doing.
- Different perspective (seek independent advice)

Secrets for Success

- Have a documented procedure to define:
  - How to manage an inspection (from opening meeting to closing meeting).
  - inspection behaviour by staff (honesty, co-operation).
  - The procedure for an "unannounced" inspection.
  - Roles and responsibilities (security, reception, escort, scribe, subject experts, runners, etc.).
  - Company policy on:
    - entering controlled areas.
    - Taking photos / video evidence.
    - Taking copies of electronic data.
    - taking samples of raw materials / products.

Before the Inspection

- Establish when the inspection is likely:
  - If an initial inspection: ask regulatory authority.
  - If a re-inspection: anticipate when.
- Determine the scope of inspection:
  - Ask for an inspection plan.
- Do some research:
  - Previous inspection reports (own files; other companies).
  - Intelligence on the inspectors (network to find out from others; areas of expertise & focus; request their CVs).
  - Google the inspector(s).
  - Web site information (GMP Guides & Guidelines; Q & As, inspection procedures, policies, complaint's procedure, appeal rights, etc).

Before the Inspection

- Prepare or update Site Master File (SMF) and forward to regulatory authority.
  - As this is usually 1st document to be reviewed by the inspector, set good first impression by:
    - Following requirements of PIC/S PE 008-3 (SMF Guidelines).
    - Treat SMF as a controlled document (doc. #, pagination, etc).
    - Have SMF independently checked for grammar & spelling.
- Review documentation:
  - Know the location of relevant documentation for easy retrieval.
  - Ensure only "controlled copies" are in use.
  - Review current documented procedures against actual methods used.

Before the Inspection

- Define likely "tour" routes through the facility.
  - Select a host for each location.
  - Prepare mock questions for each location.
  - Do a mock inspection to prepare people in each location.
- Undertake comprehensive internal inspection against the relevant GMP requirements:
  - For initial inspections: use of a GMP consultant can be useful.
  - Use PIC/S Aide Memoires where possible.
  - Identify weaknesses & deficiencies and correct them.
  - Focus on the "most common GMP deficiencies" reported by regulatory authorities (eg. available on EMEA, MHRA & FDA web sites).

Grade Internal Inspection Findings

Non-conformities can be graded;
below is an example:

Grade	Comment
Critical	The observation is a non-compliance with regulations or is likely to result in a product that will cause serious harmful effect to the user.
Major	The observation may result in a non-compliance or a product failure that could have a minor effect on the user.
Minor	The observation is a deviation from a procedure that is unlikely to affect the final product.
Observation	The observation is a suggested improvement to the system or procedure.

Before the inspection

- For newly introduced or revised SOPs/documents:
  - Provide training to relevant personnel on these SOPs/documents
  - Ensure that there is documentary evidence of this training.
- If GMP consultants are used at any stage:
  - Obtain CV of each consultant used.
  - Have evidence that the education, training and experience of consultants used was formally assessed.
  - Maintain record of name, address, qualifications & type of service provided by each consultant.
  - Particularly important for API manufacturers (clause 3.3 of Q7A GMP Guide).

Before the Inspection

- Brief & train staff on how to conduct themselves, eg:
  - Be polite & helpful, but do not provide or say more than is required.
  - Do not try and second guess the next request.
  - Do not be obstructive or argumentative.
  - Be aware of "the silent treatment" & avoid the temptation to say something.
- Brief & train staff on the different inspection techniques usually used by regulatory inspectors:
  - Helps staff anticipate the next step in the inspection process.
  - Therefore, staff can be more proactive and get prepared for the inspector's arrival at the next stage.

Different Inspection Techniques

- Trace forward:
  - Most common approach.
  - Start with a raw material & follow production flow.
- Trace backwards:
  - Review history of a specific batch of product.
    eg. final product ➡ processes ➡ raw materials.
  - Usually used to investigate cause of product defect leading to complaints and/or recall.
- Random:
  - Start from points that appear significant.
    eg. PQR ➡ Complaint ➡ CAPA ➡ Change Control ➡ Training.

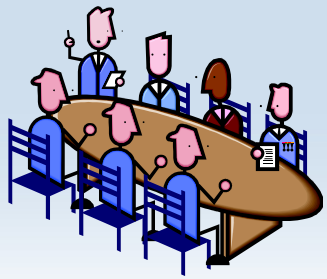
Before the Inspection

- Anticipate and keep abreast of changes to GMP requirements by visiting relevant regulatory web sites.
- Commence early implementation of any new GMP requirements, even during the transition period (when there is usually no legal obligation to comply with the new requirement).
- GMP inspectors will be impressed to see that you have commenced early implementation of expected changes to the relevant GMP requirements.

Before the Inspection

- Decide about translation arrangements:
  - Select several staff members with good English, or
  - Use a professional translation service (at least two translators, preferably with technical background).
- Simultaneous translation works best:
  - Can be expensive, but company staff benefit by being free to devote their attention to the inspectors.
  - Request translators with some technical knowledge.
  - The use microphones & ear pieces.
  - Brief translators on the day before the inspection.
- Make the necessary arrangements.

Opening Meeting



- On arrival, could check identification of the inspectors.
- On arrival, ensure they register in visitor's book & are given name badges.
- Reconfirm scope of inspection.
- Request inspection plan (in order to have key staff available).
- Have available a room where inspection team can be located.
- Have your own "war room".
- If not offered, request summary session at the end of each day.

The "War" Room
(or Operations Room)

- Supports the people fronting the inspectors.
- Needs senior people in charge to support staff.
- Coordinates:
  - Keeping track of the inspectors' location.
  - Keeping the schedule on time.
  - Temporary holding area for documents likely to be requested.
  - Reviewing documentation before submission.
  - Lining up the experts.
  - Follow-up on questions that cannot be answered immediately.
- Passes on information to Senior Management on progress, areas of attention & any significant deficiencies noted.

Opening Meeting

- Advise inspector(s):
  - Company health, hygiene & safety rules.
  - Company policy on photographs, video & sound recording.
  - An escort will be provided at all times while at the company.
  - If a question cannot be answered by the escort, the responsible person in the company will be found to provide the answer.
  - Normal operating hours are (eg. 8am to 5pm).
  - Set the times for breaks, at lunch, coffee, end of day.
  - Offer lunch on site.
- Keep company's opening summary succinct.

Opening Meeting

Two short presentations by company are suggested:

- Presentation giving brief background on company, eg.
  - brief history, product range, site & factory layout, staff structure, etc.
- Presentation giving company safety rules, including:
  - Safety rules & warning signs; no smoking; closed shoes to be worn (no high heels); rules regarding jewellery, watches, etc.
  - visitors (including inspectors) will be escorted at all times.
  - personnel protective garments to be used as instructed.
  - photos not allowed except with permission.
  - In case of emergency (fire, earthquake, etc)
    - What alarms will sound
    - Evacuation procedure & assembly area(s)

During the Inspection

- Mark photocopies given to inspectors as "uncontrolled copy" &/or "commercial-in-confidence" (as necessary).
- Keep copies of everything given to inspectors (or at least a list of documents given):
  - Make sure current version is given.
- Attempt to correct deficiencies immediately:
  - Provide evidence while inspectors still on site.
  - This may impress the inspection team.
  - Request that such corrective actions be acknowledged in the final inspection report.

During the Inspection

- When asked for a document, provide what has been requested and no more.
- Prepare internal summary of the inspection each day:
  - Key players meet to discuss if any action is necessary.
- Do not volunteer information.
- Do not guess the answer; tell them you will find the responsible person.
- Ensure consultants take a low profile.
- Allow inspectors to question any staff member (ie. do not steer inspector away)

During the Inspection

- If the inspector is looking around without asking questions, do not ask if you can help.
- Do not try and hide information.
- Do not argue or display anger, even if you are frustrated.
- Never cause deliberate delay.
- Always deliver something you have promised.
- Anticipate that inspectors will examine rubbish/scrap in rubbish bins.
  - Advise staff not to be alarmed about this.

The Closing Meeting

- Scribe should attend to compare deficiencies presented with what he/she recorded.
- Question deficiencies that you do not understand; seek clarification.
- If a deficiency is clearly wrong, suggest the inspector re-visit the area or document.
- Discuss any deficiencies that are clearly outside the scope of the Code of GMP.

The Closing Meeting

- Be cooperative & commit to providing a written response with objective evidence of corrective actions within an agreed time frame.
- Do not be argumentative.
- Indicate who will be the company's contact for:
  - Receiving the inspection report.
  - Answering any queries inspectors may have after leaving the site.

The Closing Meeting

- If the inspectors:
  - Are taking an intimidating approach.
  - Are likely to request the recall of a product.
  - Are likely to report critical deficiencies.
  - Are likely to threaten changes to the manufacturing licence.
- Consider inviting the company's legal representative to the closing meeting.

After the inspection

- One person should coordinate corrective actions and written response to regulatory authority.
- Use internal CAPA system to correct and close out each deficiency.
- Conduct post-inspection review of areas of weakness, & take corrective action (particularly through staff training):
  - Weaknesses identified by regulatory authority.
  - Weaknesses identified by escort & not detected by regulatory authority.

Responding to the GMP Inspection Report

- Made easy with the TGA approach (Inspection Close-out Record). Other Inspectorates may adopt.
- Use similar approach internally, through CAPA.
- Provide "objective evidence" with the response wherever possible, eg. photos, invoices, amended SOPs.
- Respond by the deadline date set by the regulator.
- Request an extension of time if necessary.
- Provide timetable of corrective actions if some actions will take longer to implement than the deadline date.
- If necessary, use an external consultant to assist and to review the response.

Secrets for Success

- Be well prepared.
- First impressions are important.
- Careful selection of people who front the inspectors, ie. technical ability, confidence, presentation, etc.
- You should convince the inspector(s) that:
  - everything is under control.
  - that you know what you are doing.
- Different perspective (seek independent advice)

Common Challenging Areas Prior to Being Assessed for PIC/S Membership – Tips from a Former PIC/S Chairman

Mr. Bob Tribe

PIC/S 40th Anniversary Symposium
31 May 2011
Geneva

Overview

- The Challenge & the Reward
- Common areas of weakness
- Tips on addressing these weaknesses
- Hosting the PIC/S Delegation
- Summary

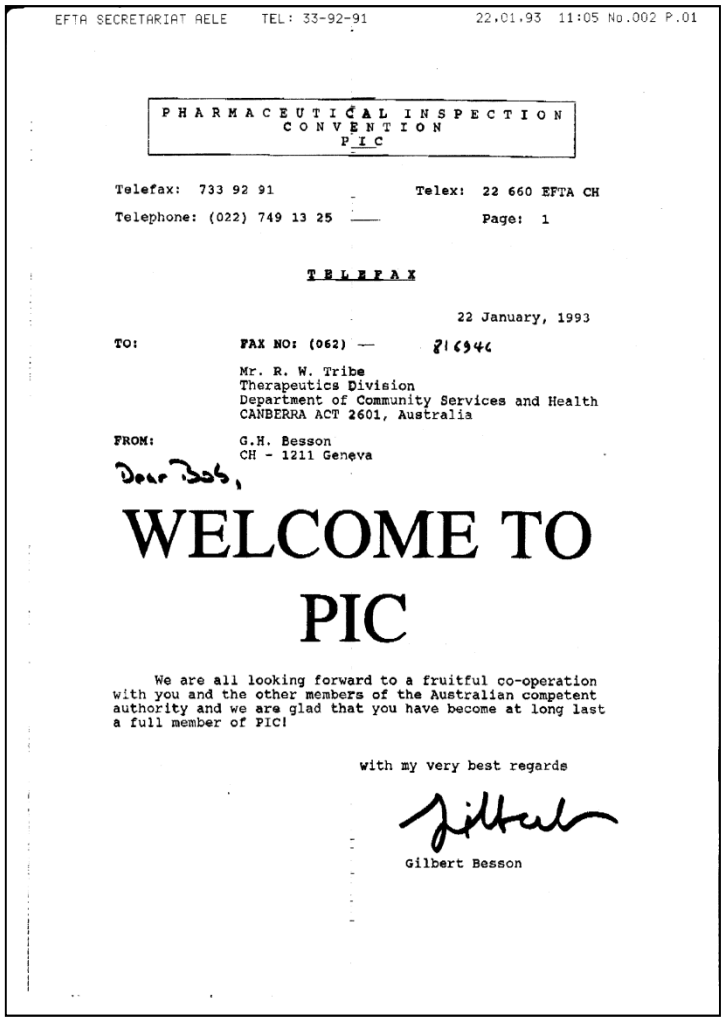
My Previous Involvement in PIC/S Membership Assessments

- As a GMP Regulator:
  - Assessment of TGA by PIC in 1993.
- As a PIC/S Rapporteur:
  - Lead PIC/S assessments of Singapore, Malaysia & Chinese Taipei in 1999, 2001 & 2002 respectively.
- As a Consultant:
  - Since 2004, consultant to 10 regulatory authorities seeking PIC/S membership.
  - Four of these have since obtained PIC/S membership.

The Challenge

To receive formal notification from PIC/S that your Agency has become a member of PIC/S.

The Reward



EFTA SECRETARIAT AELE TEL: 33-92-91 22.01.93 11:05 No.002 P.01

PHARMACEUTICAL INSPECTION CONVENTION
PIC

Telefax: 733 92 91 Telex: 22 660 EFTA CH
Telephone: (022) 749 13 25 Page: 1

TELEFAX

22 January, 1993

TO: FAX NO: (062) — 216946

Mr. R. W. Tribe
Therapeutics Division
Department of Community Services and Health
CANBERRA ACT 2601, Australia

FROM: G.H. Besson
CH - 1211 Geneva

Dear Bob,

WELCOME TO PIC

We are all looking forward to a fruitful co-operation with you and the other members of the Australian competent authority and we are glad that you have become at long last a full member of PIC!

with my very best regards

Gilbert Besson

- This is TGA's notification of its membership of PIC in 1991.
- Historic & important document for Australia.
- TGA applied in: 1987
- Member of PIC in: 1991
- Reason for 5 year timeframe:
  - New National legislation needed to be introduced for the control of medicines.
- Resulted in huge improvement in regulatory controls for medicines in Australia.

Obtain Support Before Applying

- From Agency:
  - Need to sell the benefits of PIC/S membership.
  - Obtain agreement to establish a “PIC/S budget” to fund:
    - Travel to PIC/S events (eg. PIC/S Committee meetings)
    - Training of inspectors (eg. Seminars, Exert Circles, Joint Visits)
    - Consultant(s)
    - Ongoing PIC/S commitments (eg. membership fee, training)
  - Obtain additional resources (if necessary)
- From Industry:
  - Need to sell the benefits of PIC/S membership.
  - Educational Seminars to improve industry standards.
  - Advise of likely extra scrutiny of industry.
  - Advise non-compliant manufacturers not tolerated.
- PIC/S membership difficult without this support.

Timing of Application

- Do not be too hasty with lodging application:
  - The 6 year clock runs faster than you realise.
- Before lodging application:
  - Carefully assess weaknesses using the “PIC/S Audit Checklist”.
  - Preferably, use independent, experienced person(s) to undertake this assessment.
  - Develop a timetable of actions & targets.
  - Commence taking corrective actions.
  - Train & coach inspectors in the PIC/S approach.
  - Develop a team spirit & commitment.
  - Be patient.
- Several past applicants have either exceeded the 6 year time limit or come very close to exceeded it.

Lodging the Application

- Ensure information provided in application is accurate.
- Nominate only one person for all contact with PIC/S & establish a friendly working relationship with the PIC/S Rapporteur.
- Ensure that a single Quality System covers both central and regional offices.
- Ensure that the Quality System is consistent with current version of PIC/S Quality System Requirements (PIC/S document PI 002-3).
- Quality System need not be certified (to ISO 17020 or ISO 9001:2008), but this is an advantage during the application stage (as it provides a discipline).

Quality Management System

- An essential prerequisite to PIC/S membership.
- Undertake GAP analysis against the PIC/S Quality System requirements.
- Common areas of weakness:
  - No Quality Manager.
  - No Code of Ethics.
  - No written procedure covering “conflict of interest”, “undue influence”, “confidentiality”, etc.
  - No Management Reviews undertaken.
  - Quality Manual too brief or having poor English & grammar.
  - No internal audits of systems & procedures.
  - No SOP for the handling of complaints about:
    - GMP inspections
    - GMP inspectors

Quality Risk Management

- Make use of Quality Risk Management for:
  - Scheduling GMP inspections.
  - Classifying GMP deficiencies.
  - Assessing product defects.
  - Crisis management.
- Provide training to relevant staff in:
  - Risk management tools and techniques.
  - Classification of GMP deficiencies (using the PIC/S deficiency classification system).
- Common areas of weakness:
  - Risk management approach not used for inspection scheduling.
  - GMP deficiency classification not equivalent to PIC/S.

GMP Standard

- Undertake GAP analysis against existing GMP standard:
  - Preferable to involve industry.
  - Determine if equivalent to PIC/S GMP Guide & Annexes.
- If necessary:
  - Amend existing GMP standard, or
  - Adopt PIC/S GMP Guide & Annexes into legislation.
- Ensure the GMP standard is a legal requirement.
- Common areas of weakness:
  - GMP standard not legally binding.
  - GMP standard not equivalent to PIC/S GMP Guide & Annexes.
  - Significant gap between the GMP Guide for Medicines and the GMP Guide for traditional medicines.

Legislation

- Ensure the GMP standard is a legal requirement.
- Ensure manufacturer authorisation enables licences to be modified, suspended or revoked.
- Common areas of weakness:
  - Lack of uniform National licensing system for manufacturers of medicinal products; rely on product licences alone.
  - Once licences are issued, no legal power to suspend or revoke.
  - Government manufacturing sites not inspected and licensed to same standard expected of commercial sites.
  - Lack of legal authority to enter premises to carry out GMP inspections, seize documents, take samples, etc.

Legislation

- Common areas of weakness (continued):
  - The PIC/S GMP Guide had not been translated accurately.
  - No right of appeal against adverse decisions relating to inspections and licensing.
  - No legal powers to inspect & licence manufacturers of:
    - Medicinal gases
    - Clinical trial product manufacturers
    - “Export only” medicines
    - Contract manufacturers of medicines
    - Traditional medicines

Manufacturer Authorisations

Common areas of weakness:

- Wording on manufacturer licences does not specify:
  - Categories of products authorised to manufacture.
  - Name of person authorised to release products.
- Unacceptable or partially compliant manufacturers issued with manufacturing licences.
- Licensing system for traditional medicines different to the licensing system used for modern medicines.

GMP Inspectors

Common areas of weakness:

- Inspectors not sufficiently experienced to carry out inspections to the same depth as PIC/S member authorities.
- Not enough training provided in basic GMP & inspection techniques.
- Regional inspectors often have less experience than central inspections.
- Inspectors not formally qualified to inspect specific categories of manufacturing.
- Individual files showing “training history” for each inspector not available.
- Lack of industry experience within the Inspectorate.
- Technical specialists not used for GMP inspections of complex/high risk manufacturing operations or QC testing.

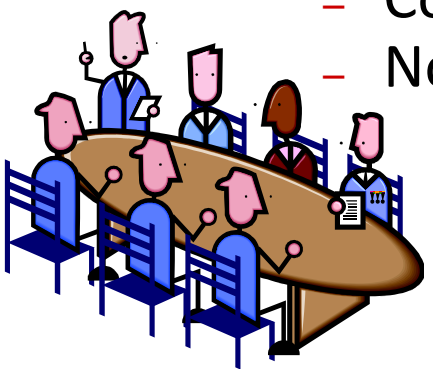
GMP Inspections

Common areas of weakness:

- Length (& depth) of inspections not consistent with PIC/S inspections.
- Lack of consistency of inspections, especially between central inspectors & regional inspectors.
- Use of large inspection teams (inefficient & wasteful).
- Inadequate inspection planning process.
- Reliance on check-lists during inspections (narrows focus).
- Large backlog of inspections (lack of resources).
- PIC/S inspection report format not used.
- GMP deficiencies not classified according to risk.
- Unfamiliarity with specific PIC/S GMP requirements
  (eg. Annex 8 requirements for the sampling of starting materials).

Hosting the PIC/S Delegation

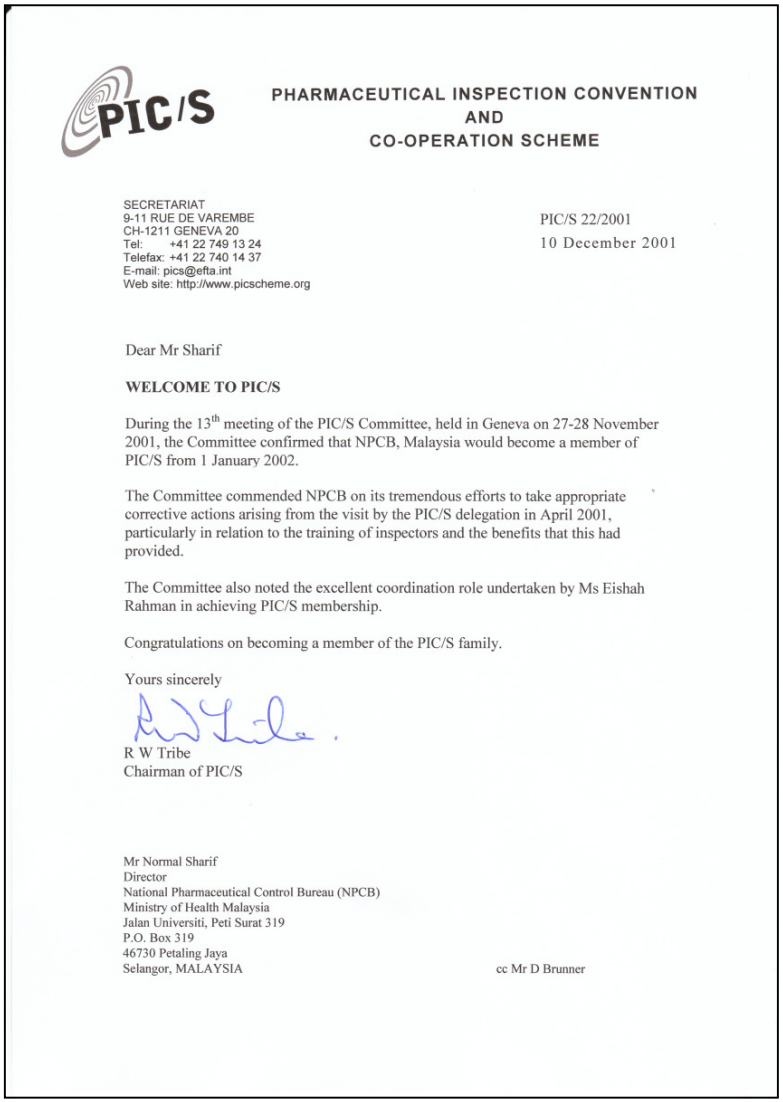
- Understand the program and logistics for the visit so that a successful program can be organised.
- Be aware that the Delegation will:
  - Most likely want to assess the Agency's testing laboratories (ie. warn the labs to prepare).
  - Most likely want to observe the inspection planning process for the observed inspections.
  - Assess the Inspectorate; not the industry (ie. advise the industry of this fact).
- Be careful when selecting manufacturers for the observed inspections:
  - Companies selected should be on the inspection schedule.
  - No special preparation or coaching of the companies.



Summary

- Obtain support from Agency and industry.
- Take care with the timing of the application.
- Assess systems & procedures against the “PIC/S Audit Checklist”.
- Use independent, experienced person(s) to assess & advise/coach.
- Be aware, lot of hard work ahead.
- Look forward to the rewards:
  - The prestige of being a member of PIC/S.
  - Improved control of medicine manufacturers.
  - Internationally harmonised GMP inspections.
  - Better public health protection.

The Ultimate Reward



PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
AND
CO-OPERATION SCHEME

SECRETARIAT
9-11 RUE DE VAREMBE
CH-1211 GENEVA 20
Tel: +41 22 749 13 24
Telefax: +41 22 740 14 37
E-mail: pics@efta.int
Web site: http://www.picscheme.org

PIC/S 22/2001
10 December 2001

Dear Mr Sharif

WELCOME TO PIC/S

During the 13th meeting of the PIC/S Committee, held in Geneva on 27-28 November 2001, the Committee confirmed that NPCB, Malaysia would become a member of PIC/S from 1 January 2002.

The Committee commended NPCB on its tremendous efforts to take appropriate corrective actions arising from the visit by the PIC/S delegation in April 2001, particularly in relation to the training of inspectors and the benefits that this had provided.

The Committee also noted the excellent coordination role undertaken by Ms Eishah Rahman in achieving PIC/S membership.

Congratulations on becoming a member of the PIC/S family.

Yours sincerely

R W Tribe
Chairman of PIC/S

Mr Normal Sharif
Director
National Pharmaceutical Control Bureau (NPCB)
Ministry of Health Malaysia
Jalan Universiti, Peti Surat 319
P.O. Box 319
46730 Petaling Jaya
Selangor, MALAYSIA

cc Mr D Brunner

Receiving your welcome letter from PIC/S

And Finally .....

Thank You.
Any Questions?

bob.tribe@tpg.com.au

Training Opportunities for GMP Inspectors

Mr. Bob Tribe

Overview

- PIC/S Training opportunities
- Other Training opportunities

Background on PIC/S Training

- PIC/S Sub-committee on Training:
  - Meets 6 monthly
  - Chaired by 1st Deputy Chairman of PIC/S
  - Coordinates all training activities for PIC/S
- Document entitled “PIC/S Pluriannual Training Schedule (2009-2012)” :
  - Available on PIC/S web site as document PS/INF 18/2008
  - Describes existing and future training tools within PIC/S.
  - Describes objectives & priorities for the next 4 years.
- Availability of PIC/S training:
  - Inspectors from PIC/S member authorities & applicant authorities may attend.

PIC/S Training for GMP Inspectors

- Annual Training Seminars
- Basic Seminar for New Inspectors
- Expert Circles
- Joint Visits Programme (JVP)
- Coached inspections
- PIC/S-Industry Workshops

Annual Training Seminars

- Specific topic each year; each Seminar lasting 3 days.
- Usually held in conjunction with the bi-annual meeting of the PIC/S Committee.
- Newer members of PIC/S usually host these Seminars:
  - South Africa's MCC will host 2011 Seminar on "Good Inspection Practices". Ukraine will host 2012 Seminar.
- Combination of plenary lectures and practical, hands-on workshops.
- The workshop sessions often result in generation of PIC/S aide memoires.
- Additional Seminars sometimes run during the year:
  - eg. training Seminar on APIs (basic & advanced) being planned.
- Training Seminars open to inspectors from PIC/S member authorities and applicant authorities.
- Inspectors wishing to attend are charged a Registration fee (for Seminar & meals) and accommodation costs.

Recent PIC/S Training Seminars

Biotechnology	France, 2000
Inspection of Utilities	Czech Rep, 2001
Interface between GCP and GMP	Canada, 2002
Inspection of QC laboratories	Slovak Rep, 2003
Inspection of APIs	Spain, 2004
Packaging/Labelling/Prevention of Mix-ups	Romania, 2005
Risk Management	Germany, 2006
Inspection of Solid Dosage Forms	Singapore, 2007
Inspection of GDP	Poland, 2008
Sterile Aseptic Manufacturing	Sweden, 2009 *
Inspection of Traditional/Herbal Medicines	Malaysia, 2011

* 120 participants from 44 different countries

(Booklets/CDs of Seminar proceedings available for purchase)

Basic Seminar for New Inspectors

- A four day Seminar covering basic GMP principles.
- Designed for new inspectors with limited inspection experience.
- Limited to about 25 inspectors
- Last one was held in Dublin, Ireland in January 2011.
  - Organised by the Irish Board of Medicines (IMB).
- Open to inspectors from PIC/S member authorities and applicant authorities.
- Participants pay registration fee & accommodation costs.

Expert Circles

- Set up to facilitate discussions & to exchange information on specific areas of interest.
- Aim is to develop guidance documents & sometimes to provide training to inspectors in specialist fields.
- Limited to about 30 inspectors.
- Usually meet annually.
- Open to inspectors from PIC/S member authorities and applicant authorities whenever training is conducted.
- Participants pay registration fee & accommodation costs.

Current Expert Circle Groups

- Human Blood and Tissues
- Computerized systems
- APIs
- Quality Risk Management
- Radiopharmaceuticals within Hospitals

Joint Visits Programme (JVP)

- Currently 27 groups operating, with each group comprising 3 inspectors from 3 different countries.
- 1 inspection conducted per year per country.
- Each group can focus on a specific type of inspection, eg. aseptic processing, APIs, GCP, etc.
- Open to inspectors from PIC/S member authorities and applicant authorities (each inspector pays own costs).
- Benefits:
  - for training purposes
  - for uniform GMP interpretation
  - for uniform inspection procedures
  - for mutual confidence
  - Mechanism to report on any differences to PIC/S Committee.

Coached Inspections

- New initiative by PIC/S.
- Expected to commence in near future.
- Extensive list of inexperienced inspectors have applied.
- Presently looking for experienced trainers to volunteer.
- Only small groups of inspectors to be coached.
- Open to inspectors from PIC/S member authorities and applicant authorities.

PIC/S-Industry Workshops

- Joint PIC/S, ISPE, PDA Workshops on specific subjects, held on an ad-hoc basis.
- Nov. 2007: Joint Workshop on “Quality Risk Management” was held in Singapore (immediately following the PIC/S Seminar on “Inspection of Solid Dosage Forms”).
- Nov. 2008: Joint Workshop on “Manufacture of Sterile Medicinal Products EU/PIC/S revised GMP Annex 1” (held immediately after the PIC/S Seminar on “Sterile Aseptic Manufacturing”).
- 2012: Another Joint Workshop possible.

Other Training (with PIC/S member)

- Some PIC/S members run training courses in their country for GMP inspectors from non-PIC/S countries (eg. TGA).
- Some PIC/S members will agree to individual inspectors from non-PIC/S countries observing typical GMP inspections in their country (eg TGA).
- Accompany PIC/S or WHO inspectors when inspecting in Korea.

Other Training (Non-PIC/S)

- Industry Conferences & Seminars:
  - ISPE, PDA, DIA, etc (check their web sites).
- On-line Webinars:
  - Available from ISPE, PDA & private consultants.
- Coached inspections:
  - By former PIC/S inspectors.
  - Very cost effective as large groups can be trained.
- Accompany PIC/S or WHO inspectors when inspecting in Korea.
- ISPE initiative to develop a training curriculum for ASEAN inspectors.

PIC/S Inspection Approach & Inspection Techniques

Korea, March 2010

Mr Bob Tribe
Canberra, Australia

ENGINEERING PHARMACEUTICAL INNOVATION

Overview

- What happens (before, during & after the inspection).
- Documents & reports used by inspectors.
- GMP deficiency classification process.
- Common GMP deficiencies reported by MHRA, EMEA, FDA.
- The most common GMP deficiencies reported by TGA, Australia.
- GMP Inspection techniques.

Before the Inspection

- The need for the inspection is determined:
  - New site (usually scheduled to suit manufacturer)
  - Re-inspection (risk based scheduling)
- Inspection frequency based on risk factors
  - Results of previous inspection
  - Type of products manufactured
  - Any recalls, complaints, adverse reactions since last inspection
  - Any testing failures since last inspection
  - Significant changes within company, eg. Key personnel, buildings, equipment, products, intention to cease business.
- A system of computerised scheduling usually used

TGA's Risk Approach to Scheduling

Risk Category	A1 rating	A2 rating	A3 rating	Unacceptable rating
	Frequency of re-audit (months)			Internal Review Panel decides on what action to take.
High	24	18	12	
Medium	30	20	12	
Low	36	24	12	

Risk Category (examples)		
	High:	manufacturer of sterile medicines
	Medium:	manufacturer of OTC medicines
	Low:	manufacturer of vitamins

Company Rating		
A1	Good compliance	(<10 "other" deficiencies)
A2	Satisfactory compliance	(1-5 "major" & <11 "other" deficiencies)
A3	Basic compliance	(>5 "major" deficiencies)
Unacceptable	Unacceptable	(1 or more "critical" deficiencies)

MHRA (UK) Risk-based Inspection Process

- MHRA launched Risk-based inspection process on 1 April'09.
- Participating sites are those UK sites that hold a Manufacturing Authorization & 3rd country sites named on a UK Marketing Authorization.
- Sites required to complete a **Compliance Report** in advance of the inspection. This report must identify risks. Examples of Compliance Reports given on MHRA web site
- The inspector will identify a risk rating for the site; this will in turn equate to a future inspection frequency.
- Risk ratings identify the degree of surveillance required within the licensing and inspection program.

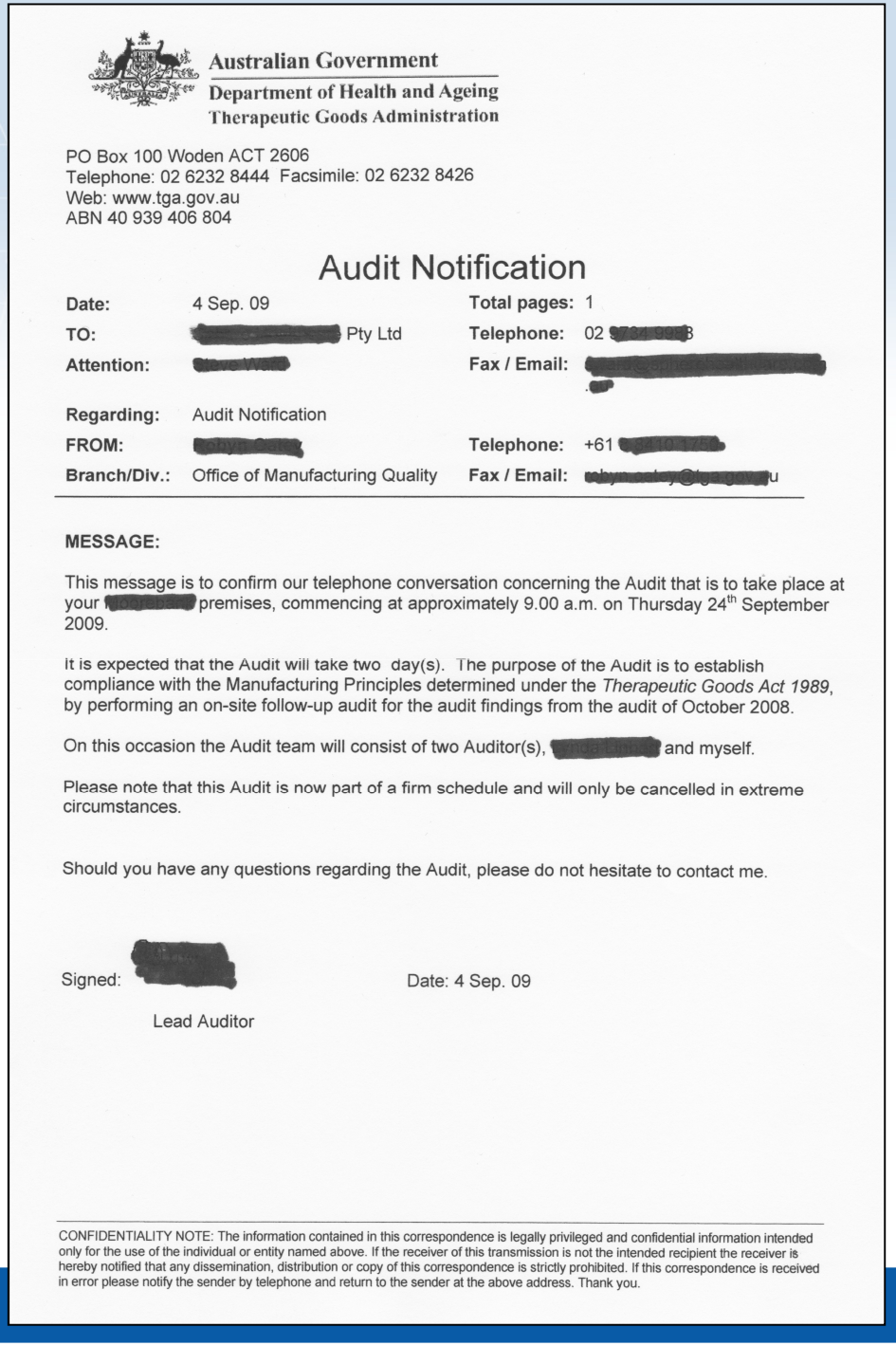
Before the Inspection

- Lead inspector is assigned
- Inspection team selected, which could include:
  - Qualified inspectors
  - Technical specialists (eg. Microbiologist)
  - Drug assessors
  - Trainee inspectors
- Inspection duration determined, based on:
  - Previous inspector's recommendation
  - Level of compliance at last inspection
  - Risk factors (previously discussed)

Before the Inspection

- Sponsor & manufacturer notified:
  - Date, number of days, names of inspectors.
  - Usually by fax, but email may also be used.
  - Usually 1 week's notice for local manufacturers
  - Usually 1 to 2 month's notice for overseas manufacturers
- Unannounced inspections:
  - Where history of poor GMP compliance exists
  - Where true extent of GMP compliance cannot be assessed otherwise.
  - Common for local inspections; unusual for overseas inspections.

Example of TGA's notification fax



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

PO Box 100 Woden ACT 2606
Telephone: 02 6232 8444 Facsimile: 02 6232 8426
Web: www.tga.gov.au
ABN 40 939 406 804

Audit Notification

Date:	4 Sep. 09	**Total pages:**	1
TO:	[redacted] Pty Ltd	**Telephone:**	02 [redacted]
Attention:	[redacted]	**Fax / Email:**	[redacted]
Regarding:	Audit Notification		
FROM:	[redacted]	**Telephone:**	+61 [redacted]
Branch/Div.:	Office of Manufacturing Quality	**Fax / Email:**	[redacted]

MESSAGE:

This message is to confirm our telephone conversation concerning the Audit that is to take place at your [redacted] premises, commencing at approximately 9.00 a.m. on Thursday 24th September 2009.

It is expected that the Audit will take two day(s). The purpose of the Audit is to establish compliance with the Manufacturing Principles determined under the *Therapeutic Goods Act 1989*, by performing an on-site follow-up audit for the audit findings from the audit of October 2008.

On this occasion the Audit team will consist of two Auditor(s), [redacted] and myself.

Please note that this Audit is now part of a firm schedule and will only be cancelled in extreme circumstances.

Should you have any questions regarding the Audit, please do not hesitate to contact me.

Signed: [redacted] Date: 4 Sep. 09

Lead Auditor

CONFIDENTIALITY NOTE: The information contained in this correspondence is legally privileged and confidential information intended only for the use of the individual or entity named above. If the receiver of this transmission is not the intended recipient the receiver is hereby notified that any dissemination, distribution or copy of this correspondence is strictly prohibited. If this correspondence is received in error please notify the sender by telephone and return to the sender at the above address. Thank you.

Before the Inspection

- For overseas inspections, manufacturer is usually contacted by email to discuss or request:
  - Hotel accommodation.
  - Guidance on travel to hotel & facility.
  - Arrangements for translation during the inspection.
  - Request for documentation such as Site Master File.

Just Before the Inspection

- Inspection team reviews documentation on file:
  - Site Master File.
  - Product marketing authorisations.
  - Complaints, recalls, product test results.
  - Last GMP inspection report.
  - Copies of these made and brought to the inspection.
- Lead inspector prepares inspection plan:
  - Usually sent to manufacturer just before the inspection.
- Travel to reach facility:
  - For overseas inspections, 3 or 4 companies in the one country inspected during the same trip.

Typical Inspection Plan – 1st page

Proposed Agenda for GMP Inspection

Company: ABC Pharmaceuticals Pty Ltd
1 Main Street, Pleasantville, NSW, Australia

Dates: 17-20 January 2011

Purpose: TGA GMP inspection

Scope: All operations associated with the manufacture, packaging, QC testing and release of non-sterile medicinal products.

Inspection Team: Mr Bill Smith, Lead Inspector
Dr Mark Jones, Inspector

Standard Used: PIC/S GMP Guide for Medicinal Products, PE 009-9, 1 Sept'09

Proposed Inspection Plan:

Date/times	Areas to be inspected
17/1/11	
08.30 – 09.30	Opening Meeting o Introductions (& attendance record) o Timetable o Company overview o Product range & licence conditions o Questions arising from company's SMF
09.30 – 12.30	Quality Management System review o Personnel; Org Chart; Job Descriptions o List of SOPs & SOP index o SOP preparation, review, approval, distribution, retrieval o Batch numbering system o Annual product review & reports o Deviations; Change Control; OOS & registers o Self inspections, plans & reports o Complaints handling system and register o Product recall system & register o Reprocessing, reworking policy & register o Supplier evaluation/approval system & list of approved suppliers o Finished product release procedure
13.30 – 14.30	Review of site plans & HVAC system o Site layout, floor plans, material & personnel flow o HVAC layout, area classification, pressure differentials o Brief orientation tour of site

Typical Inspection Plan – 2nd page

14.30-17.00	Starting Materials & Warehouse o Housekeeping & Pest control o Receipt, handling, status labelling & storage o Sampling of starting materials o Storage areas – quarantine, release, reject o Approval for use o Temperature & humidity mapping & monitoring o Finished goods warehouse & distribution records
17.00	Summary of observations for the day
18/1/11	
08.30 – 12.30	Production & facilities o Building and facilities; surfaces & finishes o Housekeeping, gowning procedures & personal hygiene o Dispensing of raw materials o In-process controls o Equipment; suitability, cleanliness & storage o Storage of bulk/intermediates – validated holding times o Packaging operations o Control of labels & pre-printed packaging materials o Line clearance checks o Batch documentation & Reconciliation
13.30-17.00	Engineering & Services o Preventative maintenance & calibration o Pest control o Waste disposal Review of the HVAC System o HVAC schematic drawing & specifications o Qualification, requalification, monitoring the system o Inspection of HVAC system & dust extraction Review of the Water Treatment System(s) o PW system drawings, specifications & capabilities o Qualification, requalification, monitoring the system o Sampling & trend analysis o Inspection of system Review of the Compressed Air System o Compressed air schematic drawing & specifications o Qualification, requalification, monitoring the system o Inspection of system
17.00	Summary of observations for the day
19/1/11	
08.30 – 12.30	QC Laboratory o Analyst training, competencies & assessment o Sample receipt, storage & allocation o Wet chemistry laboratory o Instrument laboratory – qualification, calibration, maintenance

Typical Inspection Plan – 3rd page

	o Laboratory materials – reference & working standards, reagents o Method validation o Specifications and test methods o Analysts work books/records, test results & trending o Microbial testing – room, equipment, media prep o Environmental & water monitoring o Retention samples o Stability testing program o OOS o Contract testing
13.30-17.00	Validation o VMP o Equipment qualification/requalification (DQ,IQ,OQ & PQ) o Preventative maintenance schedules & records o Calibration schedules & records o Process validation & revalidation for products o Cleaning validation & reports o Computer systems validation
17.00	Summary of observations for the day
20/1/11	
08.30 – 12.30	Staff training & assessment o Job descriptions o Training program o Training records & traceability of training history o Assessment of effectiveness of training Review of documents o Review of BMRs, BPRs, testing records of selected batches o Contract manufacturing & GMP agreements o Marketing authorizations
13.30 – 1500	Review of any documents outstanding from previous days
15.00-16.30	Closed meeting of inspectors only
16.30	Closing meeting with company representatives (& attendance record)

Prepared by: Bill Smith, Lead Inspector

Date: 12/1/11

Travel & Hotel Arrangements

- Business class air travel for overseas inspections:
  - Economy air travel for local inspections.
- Hotels may be booked by inspectors.
  - But common for TGA to request manufacturer to book hotel (local knowledge).
  - However, inspectors will pay their hotel bill.
- Ground transport (eg. trains) may be booked by inspectors:
  - But common for TGA to request manufacturer to book.
  - However inspectors will usually pay for own train tickets.

Charges

- TGA inspections fully cost recovered.
- Australian sponsor is invoiced the cost of inspection
  - Inspection fee (A$1060/hour = A$34,000 for a 4 day inspection, ie. approx US$27,000.
  - Apportioned air fare cost (total air fare shared by all sponsors involved in that trip).
- Costs of hotels, ground transport, meals:
  - Are part of the inspection fee.
- Invoice sent to Australian sponsor after the inspection:
  - That is, after reconciliation of hours taken to inspect.

The Inspection

- Arrival and greeting.
- Opening meeting:
  - Meeting attendance record circulated.
  - Introductions.
  - Scope, objective, inspection plan discussed.
  - Discussion of resources and facilities needed.
- Inspection:
  - Usually starts with review of key documents.
  - Inspection team may split for part of the inspection.
- Summary session at end of each day may be offered.
- May take product samples, copies of records, etc.

Typical Meeting Attendance Record

Meeting Attendance Sheet

Company: ABC Pharmaceuticals Pty Ltd
Address: 16 Main Street, Bondi, NSW 2345
Topic: GMP inspection

Name: (please print)	**Title / Organisation:**	**Opening:** Date:1.11.06 Time: **Initials:**	**Closing:** Date:3.11.06 Time: **Initials:**

Logistics

- Meals:
  - Coffee and lunch: usually accepted on-site.
  - Evening dinner: inspectors not allowed to accept, but some inspectors may accept
- Gifts:
  - Inexpensive gifts: usually accepted to avoid offending company.
  - Expensive gifts: inspectors not allowed to accept & will be refused or returned.
  - All gifts offered are required to be declared by the inspectors.
- Entertainment:
  - Inspectors not allowed to accept (but some do).
- Sightseeing
  - May or may not be accepted during the inspector's weekend off.

Code of Ethics for Inspectors

- As part of the Inspectorate's Quality System, there are rules in place to:
  - Ensure impartiality and integrity.
  - Avoid real or potential conflict of interest (commercial/financial).
  - Avoid undue & improper influence (bribes, gifts, threats).
  - Distinguish between the inspection process & the issue of a license to manufacture medicines.
  - Distinguish between the inspection process & providing an advisory service.
- Inspectors can be subject to disciplinary action if these rules are breached.

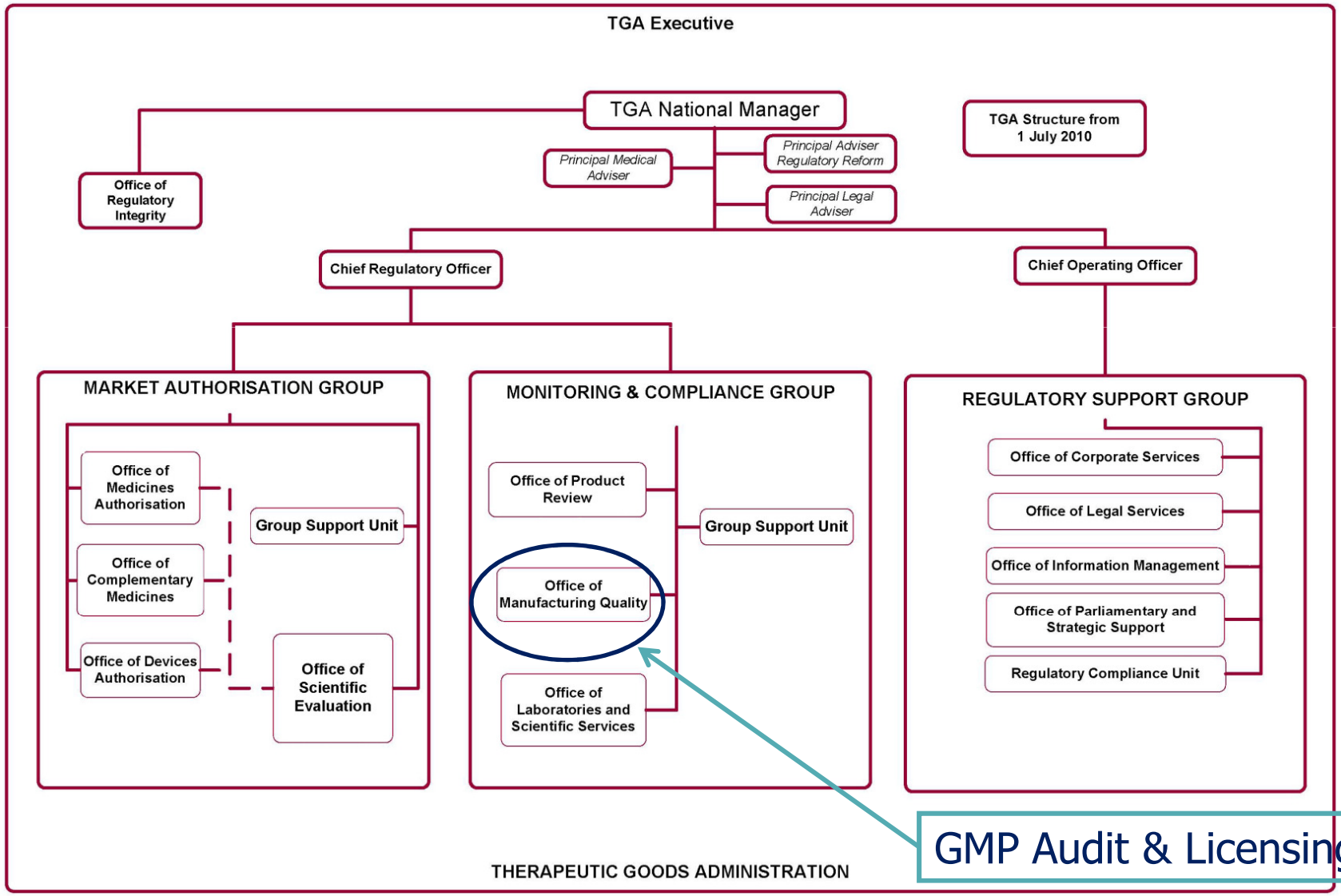
The Closing Meeting

- Inspection team has meeting on their own (on site):
  - May take 2 or more hours.
  - Prepare list of deficiencies & classify.
  - Discuss overall summary of findings.
- Closing meeting with company:
  - Company may select whoever they like to attend.
  - Meeting attendance sheet completed.
  - Verbal summary of deficiencies given (no report left on site).
  - Discussion is encouraged.
  - Timetable of future actions discussed:
    - Timing of written list of deficiencies from TGA
    - Timing of company's response to this list of deficiencies

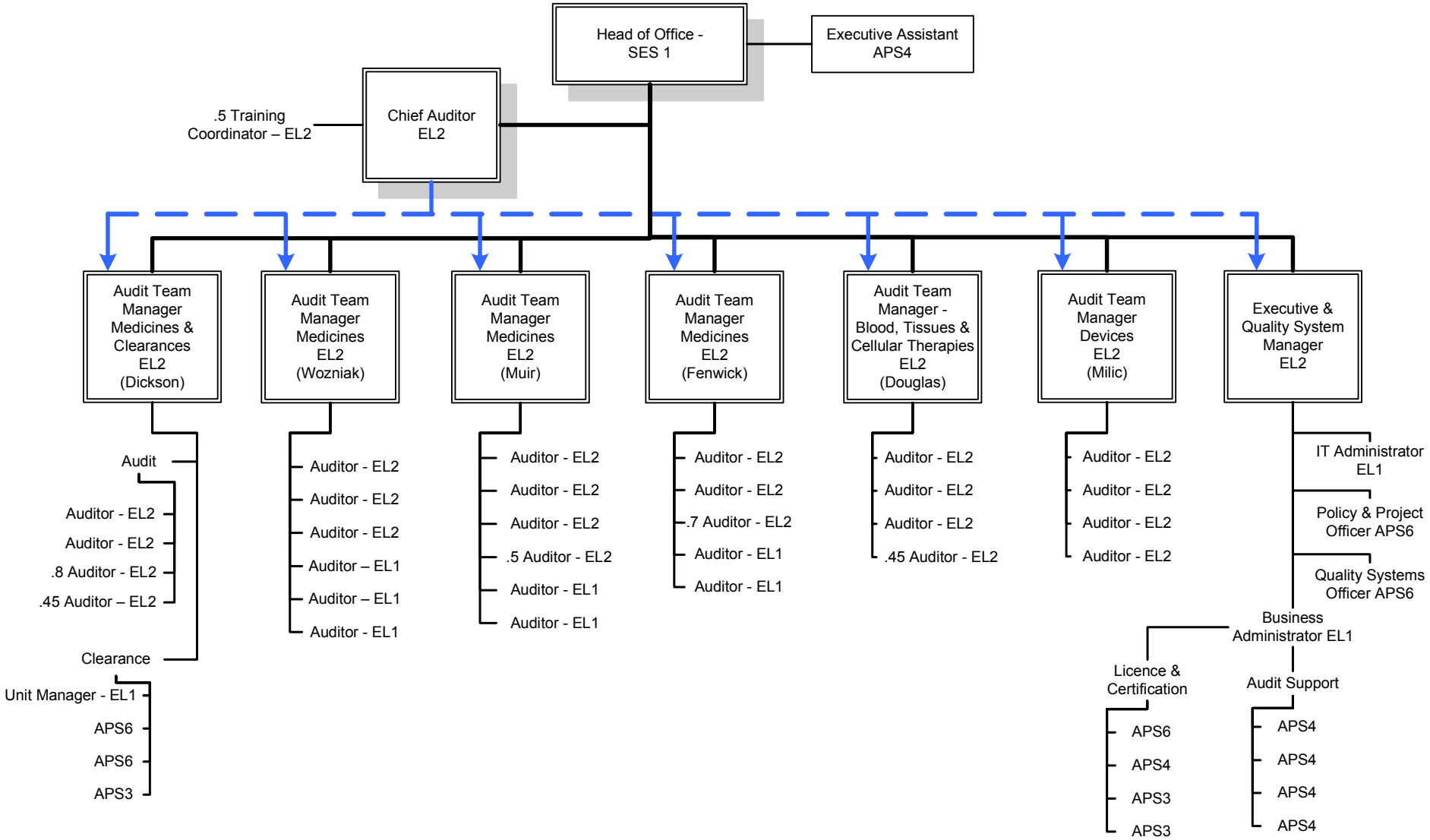
After the Inspection

- Inspection Close-out record (deficiency report) prepared.
- Deficiencies checked by Inspection Manager
  - To help ensure consistency within TGA.
- "Inspection Close-out Record" sent to company within 3 weeks of inspection
  - Company requested to respond with corrective actions.
  - Objective evidence is requested (eg. photos; revised SOPs, invoice that shows purchase of new equipment).

New Structure of TGA – 1 July 2010



TGA's Office of Manufacturing Quality



Office locations = Canberra, Sydney, Melbourne & Adelaide
Total No. Auditors = 34 (all "qualified" for specific types of audits)
Clerical Staff = 18
Tech. Specialist Pool = from TGA's Testing Laboratories

Example of Inspection Close-out Record (p.1)
(as received from TGA)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Manufacturing Quality
Inspection Close Out Record

Manufacturer: [redacted] Pty Ltd	**Manufacturer address:** [redacted]
Inspector(s): [redacted]	**Audit date:** 27-30 June 2009

Manufacturer to complete columns 1, 2, 3, 4 and 5. (Please note, objective evidence is only required for critical and major deficiencies)

Please note requested extension to licence cannot be granted until all relevant deficiencies have been satisfactorily addressed. This may include on-site verification of some corrective actions.

1	2	3	4	5	6	7
Deficiency number	✓ if objective evidence required	Response number / Date	Description of deficiency, corrective actions and, if applicable, reference to supportive objective evidence	Completion, or proposed completion, date dd/mm/yy	Inspector('s) Comment(s)	Response accepted Y/N
MAJOR DEFICIENCIES						
1	✓		Rework/reprocessing of batches of products was not adequately controlled, as there was no documented procedure describing the company's approach to rework/reprocessing.			
2	✓		The investigation or process deviations, non-conformances and customer complaints were not adequately documented to demonstrate that appropriate corrective and preventive actions had been implemented. *(This was also an issue at the last TGA inspection).* For example, for manufacture of Glucosamine Sulfate with Chondroitin Tablets Bx F1568, The deviation was approved by QC and not QA.			

Example of Inspection Close-out Record (p.1)
(after 2 responses to TGA from company)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Manufacturing Quality
Inspection Close Out Record

Manufacturer: [redacted] Pty Ltd	**Manufacturer address:** [redacted]
Inspector(s): [redacted]	**Audit date:** 27-30 June 2009

Manufacturer to complete columns 1, 2, 3, 4 and 5. (Please note, objective evidence is only required for critical and major deficiencies)

Please note requested extension to licence cannot be granted until all relevant deficiencies have been satisfactorily addressed. This may include on-site verification of some corrective actions.

1	2	3	4	5	6	7
Deficiency number	✓ if objective evidence required	Response number / Date	Description of deficiency, corrective actions and, if applicable, reference to supportive objective evidence	Completion, or proposed completion, date dd/mm/yy	Inspector('s) Comment(s)	Response accepted Y/N
MAJOR DEFICIENCIES						
1	✓		Rework/reprocessing of batches of products was not adequately controlled, as there was no documented procedure describing the company's approach to rework/reprocessing.			
		Resp: 1 Date: 28/7/09	Corrective Action taken: Rework Procedure is to be written. This SOP is to include a Rework Evaluation Form, which will be completed and approved, before the rework is carried out.	28/8/09	Please submit objective evidence.	N
		Resp: 2 Date: 28/8/09	Corrective Action taken: SOP PA129.01 has been written and approved. This SOP is now in operation Evidence provided: SOP PA129.01 and the Rework Evaluation Form are attached (Appendix 1).	28/9/09	SOP PA129.01 has been referred internally within the TGA for further evaluation and discussion as the current content does not meet Code Requirements or the principles of GMP.	N

Completed by company

Example of Inspection Close-out Record (p.2)
(after 2 responses to TGA from company)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Manufacturing Quality
Inspection Close Out Record

2	✓		The investigation or process deviations, non-conformances and customer complaints were not adequately documented to demonstrate that appropriate corrective and preventive actions had been implemented. *(This was also an issue at the last TGA inspection)*. For example, for manufacture of [redacted] with [redacted] Tablets [redacted], The deviation was approved by QC and not QA.			
		Resp: 1 Date: 28/7/09	Corrective Action taken: QA Manager Delegation of Authority Matrix completed and is to be included into an SOP.	28/8/09	Please submit objective evidence.	N
		Resp: 2 Date: 28/8/09	Corrective Action taken: Draft SOP attached. Evidence provided: Copy of authorised SOP PA114-03 "Delegation of Authority" dated March 2009 attached (Appendix 2).		**Action taken is acceptable. Effectiveness of corrective actions to be verified at next on-site audit.**	Y
3	✓		The company's validation programme was deficient in that there was insufficient detail in the VMP describing validation requirements including when changes were made to qualified or validated systems.			
		Resp: 1 Date: 28/7/09	Corrective Action taken: VMP to be rewritten	28/8/09	Please submit objective evidence.	N
		Resp: 2 Date: 28/8/09	Corrective Action taken: No progress	28/9/09	Please submit objective evidence.	N

Completed by company

Unacceptable GMP Compliance

- One or more "critical" deficiencies usually attracts an "Unacceptable" rating.
- Inspection Manager & Inspection Governance Committee involved in confirming "Unacceptable" status.
- For new manufacturers:
  - Local company: not licensed by TGA.
  - Overseas company: not approved by TGA to supply to Australia.
- For existing manufacturers:
  - Local company: licence amended, suspended or revoked.
  - Overseas company: approval status revoked.
- Company has option to appeal the decision.

Myth: Inspectors are tougher on Australian companies than they are on overseas companies

Medicines audits March 2004 – May 2008

Location	Critical Deficiencies	Major Deficiencies	Other Deficiencies	Total Deficiencies
Overseas Average	0.07	3.92	8.12	12.11
Local Average	0.01	3.63	8.31	11.95
Grand Average	0.03	3.74	8.24	12.01

Number of Deficiencies per inspection

PIC/S Classification of GMP deficiencies

Critical Deficiency

A deficiency that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

(A critical deficiency is a serious situation that will result in regulatory action being considered and a definite connection between the deficiency and a harmful product must be able to be reasonably made. If this connection cannot be reasonably made, the deficiency should be recorded as "major").

Examples of Critical GMP Deficiencies

Examples of Critical Deficiencies:

- No or grossly inadequate air filtration to minimise airborne contaminants (non-sterile production).
- Lack of sterilisation validation (sterile production).

PIC/S Classification of GMP deficiencies

Major Deficiency

A non-critical deficiency that:

- *has produced or may produce a product which does not comply with its marketing authorisation; and/or*
- *indicates a major deviation from the Code of GMP; and/or*
- *indicates a major deviation from the terms of the manufacturing licence or GMP approval (overseas manufacturers); and/or*
- *indicates a failure to carry out satisfactory procedures for release of batches; and/or*
- *indicates a failure of the person responsible for QA/QC to fulfil his/her duties; and/or*
- *consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.*

Examples of Major GMP Deficiencies

Examples of Major Deficiencies:

- No Product Quality Review undertaken.
- Stored equipment (used for the manufacture of non-sterile medicines) was not protected from contamination.

PIC/S Classification of GMP deficiencies

"Other" Deficiency (or Minor Deficiency)

- *A deficiency that cannot be classified as either critical or major, but indicates a departure from good manufacturing practice.*
- *A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as major or critical.*
- *One-off minor lapses or less significant issues are usually not formally reported, but are brought to the attention of the manufacturer.*

Examples of "Other" GMP Deficiencies

Examples of "Other" Deficiencies:

- Person making alteration to batch document did not initial the change.
- Equipment not calibrated by the due date

Common Inspection Deficiencies

MHRA, UK (2004/05)

Inspection finding	%
Quality management	8.2
Batch release and duties of QP	6.7
Quality system documentation	6.7
Design and maintenance of premises	5.2
Environmental monitoring	5.2
Process validation	5.2
Cleaning validation	4.5

Common Inspection Deficiencies

EMEA (inspections by EU regulatory authorities on behalf of the EMEA for 2006)

Inspection finding	%
Quality system documentation	10.9
Manufacturing documentation	10.2
Design and maintenance of premises	6.5
Specifications and testing documentation	5.2
Status labeling	4.7
Contamination, microbiological	4.7

Common Inspection Deficiencies

FDA (GMP deficiencies for foreign manufacturers for FY 2004)

Inspection finding	%
Failure / OOS investigation	11
Laboratory controls	9
Equipment / cleaning validation	8
Inadequate SOPs	7
Water systems	5
Production / process controls	5
Environmental controls	5

Common Inspection Deficiencies

TGA (Common GMP deficiencies for local & overseas manufacturers)

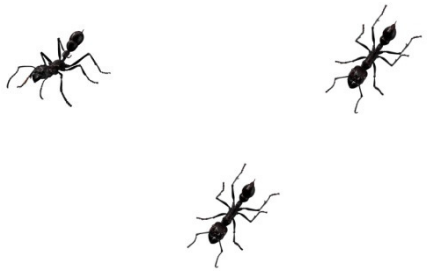
Inspection finding	%
Change control	*
Supplier approval	*
Equipment / facilities	*
Sampling of starting materials	*
Water systems	*
Computer systems	*
Laboratory controls	*

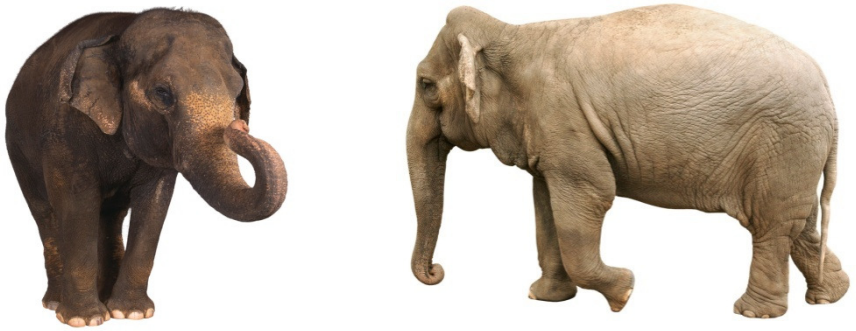
* Do not publish

Common Inspection Findings
(TGA, Australia)

Change Control Deficiencies

"Counting the ants and
missing the elephants"





Common Inspection Findings
(TGA, Australia)

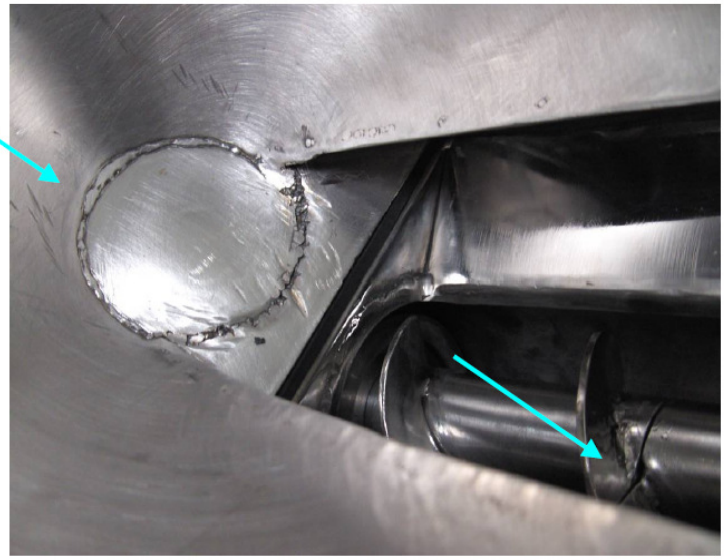
- Change Control
  - Change control systems did not include all items relevant to the quality of products (Annex 15, clause 44).
  - The change control process was limited to document changes and did not include changes to equipment, process, facility & systems.
  - Some change control systems include small document changes but did not include large plant alterations.

Common Inspection Findings
(TGA, Australia)

- Supplier approval:
  - Using suppliers before they are approved.
  - Approving suppliers only and not considering the manufacturer of the starting materials.
  - Approving suppliers using uncontrolled samples.

Common Inspection Findings
(TGA, Australia)

- Equipment and facilities:
  - Cleaning validation not done.
  - Inappropriate location of equipment for cleaning and maintenance.
  - Inappropriate materials of construction.
  - Surfaces not crevice free and smooth.



Common Inspection Findings
(TGA, Australia)

- Equipment
  - Inappropriate material used in construction, eg. surfaces and welds on equipment not smooth or free from cracks.
  - No evidence of the quality of welds of stainless steel pipe-work for purified water system (eg. weld certificates, sample welds).
  - Equipment parts (eg. de-dusting hoods from FBDs) were not cleaned using validated procedures.
  - Washing machines & cleaning equipment (themselves a potential source of contamination) were not subject to cleaning validation (if not dedicated).
  - Equipment holding times before cleaning – not part of cleaning validation.

Common Inspection Findings
(TGA, Australia)

- Equipment
  - Where testing was part of the cleaning validation, valid analytical methods were not used.
  - Cleaning procedures did not include sufficient details to ensure the cleaning method could be consistently applied.
  - The records of cleaning were not always kept.
  - Cleaning SOP did not include the requirement that equipment needed to be, at least, visually clean (powder residues found on outside of two drums which were tagged as "clean").

Common Inspection Findings
(TGA, Australia)

- Water systems:
  - Inappropriate materials of construction.

Common Inspection Findings
(TGA, Australia)

- Water Systems:
  - Inappropriate materials used in water treatment systems, eg. Nylex (plastic) garden hose.
  - No validated flushing procedure after chemical sanitization (ie. to show sanitizing agent has been effectively removed).
  - The volumes flushed when taking QC samples were more than Production staff was required to flush (ie. QC sampling did not simulate how Production staff took water for use in manufacturing/cleaning).
  - No time limit by which samples of purified water must be tested.

Common Inspection Findings
(TGA, Australia)

- HVAC:
  - Room pressure differentials not designed to prevent cross-contamination.
  - No design documents defining the expected pressure differentials for manufacturing & packaging areas.
  - Ventilation systems not adequately controlled.
  - Inadequate control of maintenance (e.g. filters not monitored for leakage and blockage).
  - The SOP for operating AHUs and cleaning AHU filters did not indicate the sequence for switching on and off the AHU units (to prevent reversal of pressure gradient & direction).

Common Inspection Findings
(TGA, Australia)

- HVAC:
  - The "at rest" qualification of the HVAC system was undertaken with production machines switched off.
  - Installed filters were not as per specification.
  - The type of filters required in the HVAC system were not defined.
  - The ventilation system inadequately controlled (ie. the pressure differentials between manufacturing area & filling room defined as 10 – 15 Pa. But measurements carried out over last few months showed only 5 Pa).

Common Inspection Findings
(TGA, Australia)

- Laboratories:
  - No QC staff competency matrix available for the allocation of samples for QC testing.
  - Failure to adequately train personnel.
  - Failure to ensure that analysts are competent on new test methods (eg. by testing a know reference standard or a sample tested by an experienced analyst).
  - Exposing starting materials to inappropriate environmental conditions during sampling.
  - Inappropriate handling of utensils used for sampling.

Common Inspection Findings
(TGA, Australia)

- Contract Laboratories:
  - No GMP agreement with contract testing laboratory.
  - Inadequate GMP agreements
    - Failure to ensure that the agreement clearly defines which company is responsible for method validation.
    - Failure to define what method should be used by the contract laboratory.
    - Failure to ensure that the method used by the contract laboratory is validated.
  - Failure of the contract laboratory to check whether the sample being tested is for GMP purposes.

Common Inspection Findings
(TGA, Australia)

- Sampling:
  - Exposure of starting materials & primary packaging materials to inappropriate environments during sampling.
  - Inappropriate blending of starting material samples for ID testing.
  - Failure to set limits on the number of samples that can be blended for tests other than ID.

Common Inspection Findings
(TGA, Australia)

- Sampling:
  - Sampling utensils not treated as product contact equipment.
    - Failure to use purified water as final washing rinse.
    - Washing sampling utensils in inappropriate environment, ie. in a multi-purpose laboratory sink.
  - Cleaned utensils not covered when carried outside a controlled environment.
  - The cleaning of dispensing utensils had not been validated (because QA & validation personnel believed that dedicated utensils were used).

Common Inspection Findings
(TGA, Australia)

- Computer Systems – Security:
  - Systems that were used for release for supply had not been defined as critical.
  - Failure to ensure that computer access to release product was restricted to authorised personnel.
  - Computer system failed to remove access
    - When staff on leave
    - When staff transfer Departments
    - When staff go on maternity or long service leave
  - Computers left unattended while logged in, with no compulsory "time-outs", password-protected timesavers, etc.

Common Inspection Findings
(TGA, Australia)

- Computer Systems – Source Code:
  - Failure to define what version of critical systems had been validated, ie. no record of the system version in validation documents.
  - Failure to control who has access to change the production source code.
  - Failure to control external contractors who log directly into company systems.

Common Inspection Findings
(TGA, Australia)

- Liquids, Creams & Ointments:
  - Transfer hoses not controlled after cleaning.
    - Not labelled as clean.
    - Not protected from contamination.
    - Water residues left in hoses upon storage.
  - Cleaning validation of transfer hoses were either not adequately addressed or were ineffective.
  - Transfer hoses used in manufacturing were not included in cleaning validation.

After the Inspection

- Communication continues until inspection closed out.
- Company advised of inspection close-out.
- Final inspection report prepared and sent to company.
- Inspection Manager involved in close-out process & reviewing final inspection report (for consistency).
- Manufacturer may a request GMP certificate.
  - Small cost involved.
- Inspection cycle recommences (risk based).

PIC/S Inspection Report Format

- Described in "PIC/S Inspection Report Format", PI 013-3, 25 September 2007.
- This covers:
  - Summary of inspection activities.
  - Inspection observations (+ve observations).
  - Deficiencies (-ve observations).
  - Assessment of SMF.
  - Summary of GMP compliance status.
- Identical to the format used by EU Inspectorates.

Typical Final Inspection Report (1st page)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

GMP Audit Report

Audited site(s):	[redacted] Ophthalmic Laboratories Pty Ltd (Trading as Pharmalab) 332 Burns Bay Road Lane Cove NSW 2066	
Activities carried out by company	Manufacture of active ingredient Manufacture of finished medicinal product Manufacture of intermediate or bulk Packaging Laboratory testing Release for supply Other ([redacted] Schedule 5A Exemption products)	[ ] [X] [ ] [ ] [ ] [ ] [X]
Audit date(s):	[redacted] 18 – 20 August, 2003	
Auditor(s):	[redacted] (Lead Auditor) [redacted] (Trainee Lead Auditor) [redacted] (Chief Microbiologist) [redacted] (Trainee Microbiology Specialist)	
References:	Manufacturing Licence number: [redacted] File reference numbers: [redacted]	
Manufacturing Standard:	Australian Code of GMP for Medicinal Products	

Typical Final Inspection Report (2nd page)

Introduction

The company manufactures a wide range of injectable products, which are terminally sterilized by moist heat at the facility. They also manufacture many products under the [redacted]

Tablets are not manufactured on-site, however, tablets are sourced from [redacted] manufacturers, which are released by [redacted]

The company is based in the light industrial sector at [redacted] The three story building that accommodates the company is shared with a [redacted] manufacturer and a [redacted] company.

Date of previous audit: 5/6/02

Names of auditors involved in previous audit: [redacted]

Major changes since the previous audit: The company has continued with the commissioning of the new facility and qualification of equipment at [redacted] There have been some changes to the range of [redacted] (These products are not patient specific) There have also been changes to manufacturing personnel and an increase in resources in the QA area.

Brief report of the audit activities undertaken

Scope of Audit

The manufacturing activities at the facility were audited in accordance with the Australian Code of GMP for Medicinal Products (2002). The audit was a general GMP audit of the new facility for renewal of their license to manufacture sterile medicinal products

Audited areas

All areas of the facility

Personnel met during the audit

Refer to attendance sheet attached.

[redacted]

Audit Team's findings and observations relevant to the audit and deficiencies

Quality Management The company had an effective quality management system in place and it was pleasing to note that the company had increased resources in quality areas since the last audit. However the market authorisation checks for products manufactured on site and externally needed improvement. (deficiency 1.1, 1.2)

Typical Final Inspection Report

(3rd page)

Personnel

A number of staff left the company at the time of the relocation from the old facility.
The training records for two production staff, [redacted] and [redacted] were examined. Training included 8 modules based on [redacted] program and on-the-job training as outlined in SOP [redacted] *General Staff Training*.
There were no records of continuing training or periodic reassessment of competency of operators (see Deficiency #13).
The quality control nominee for the licence, [redacted], and the production nominee, [redacted] were well qualified and experienced for their respective roles.

Premises and Equipment

The premises were clean and the layout was satisfactory albeit a bit cramped and corridors were being used as storage areas, which led to inadequate segregation of materials. (deficiency 4.1).
The starting material warehouse at the base of the building was barely adequate with a number of issues identified at audit in this area. (deficiencies 2.1-2.5)

The sterile manufacturing area comprised a vial preparation area, a dispensary, small and large blending rooms, 3 vial filling rooms (class C), an Atherton autoclave and wash bay. There was also a holding room where unlabelled sterilized finished goods were held in plastic bins. A batch of [redacted] was erroneously labelled as quarantined on [redacted], which was a date in the future (see Deficiency #4.3).

Entry to the production area was via a pressurised, zoned change area and air shower. The pressure between areas was monitored continuously and the area maintained under class C conditions. The areas were monitored monthly for non-viable particulates according to SOP [redacted] and for viable particulates (SOP [redacted]). An external provider checked the area annually.

The production areas were sanitised with chlorhexidine gluconate (1% w/v), 70% isopropyl alcohol sachets ([redacted], or a quaternary ammonium compound. These disinfectants were not monitored for contamination (see Deficiency #4.6).

Clean room operators changed into clean coveralls and over-boots, beard and hair covers, and sterile gloves on entry to the production suite. (The Gowning SOP [redacted] erroneously indicated that the coveralls were sterile). Operators disinfected their hands with Hexfoam sterile spray. There was no mirror in the first part of the change area to check hair was tucked under paper hairnets.

Materials were introduced to the production areas via pass through cabinets.

Typical Final Inspection Report (last page)

Some anomalies were identified and will require correction.

Miscellaneous

Samples taken: nil

Distribution of Report: company, TGA

Attachments

Meeting attendance sheet
Site Plan

List of Deficiencies

Please refer to the Deficiency Report provided to the manufacturer at the end of the audit.

Close out of Deficiencies

The company responded to the deficiency report on [redacted] and [redacted]. Deficiencies have been closed out with either objective evidence or a corrective action plan with and an agreed time frame for completion of corrective actions. Progress reports are due on [redacted] and then every six months until corrective actions are completed.

Summary and conclusions

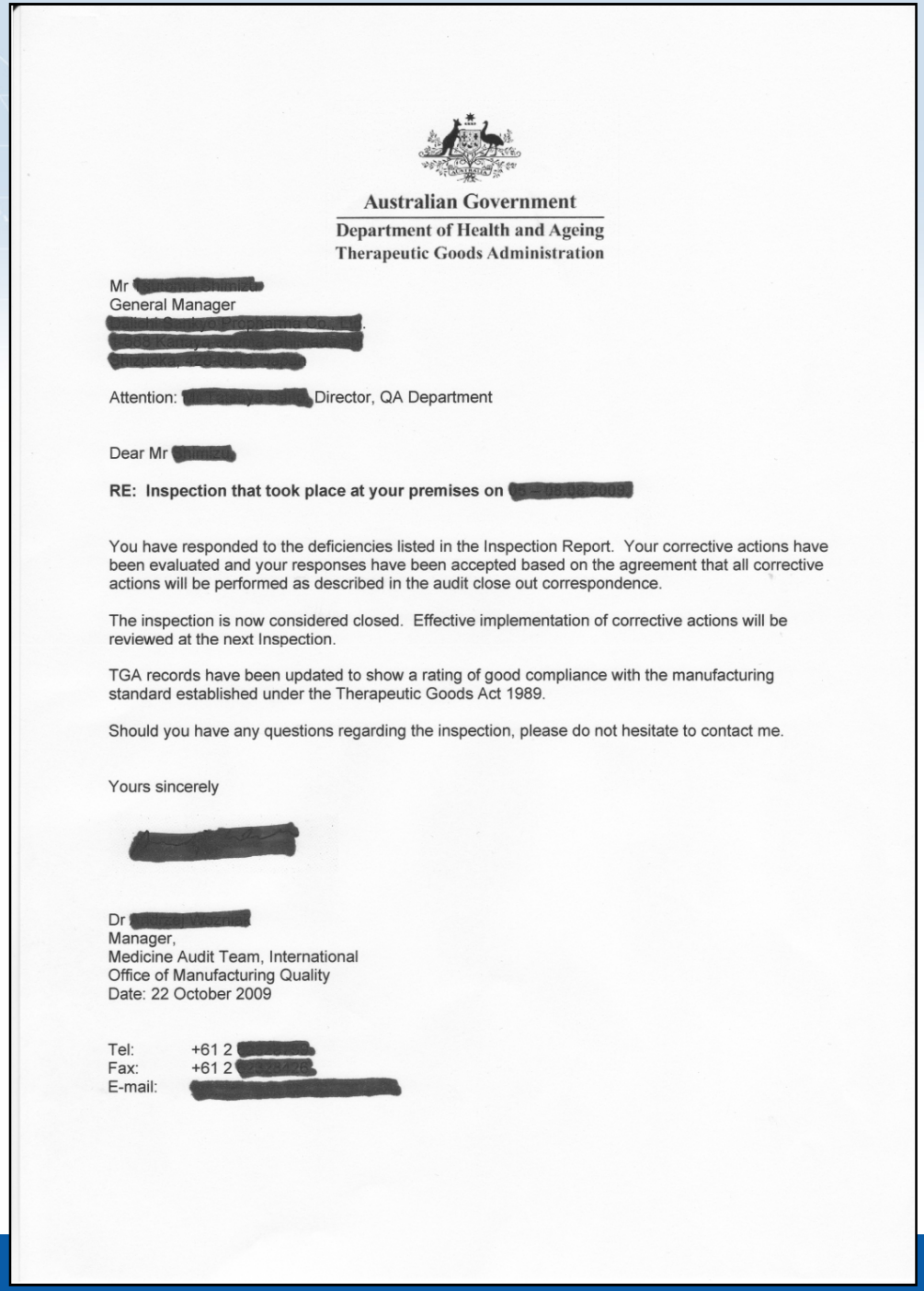
[redacted] is considered to be operating at an acceptable level of compliance with the Australian Code of GMP for Medicinal Products for the manufacture of sterile products.

Lead Auditor's Name: [redacted]

Signatures: [redacted]

Date: [redacted]

Example of TGA Acceptance Letter



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Mr [redacted]
General Manager
[redacted]

Attention: [redacted] Director, QA Department

Dear Mr [redacted]

RE: Inspection that took place at your premises on [redacted]

You have responded to the deficiencies listed in the Inspection Report. Your corrective actions have been evaluated and your responses have been accepted based on the agreement that all corrective actions will be performed as described in the audit close out correspondence.

The inspection is now considered closed. Effective implementation of corrective actions will be reviewed at the next Inspection.

TGA records have been updated to show a rating of good compliance with the manufacturing standard established under the Therapeutic Goods Act 1989.

Should you have any questions regarding the inspection, please do not hesitate to contact me.

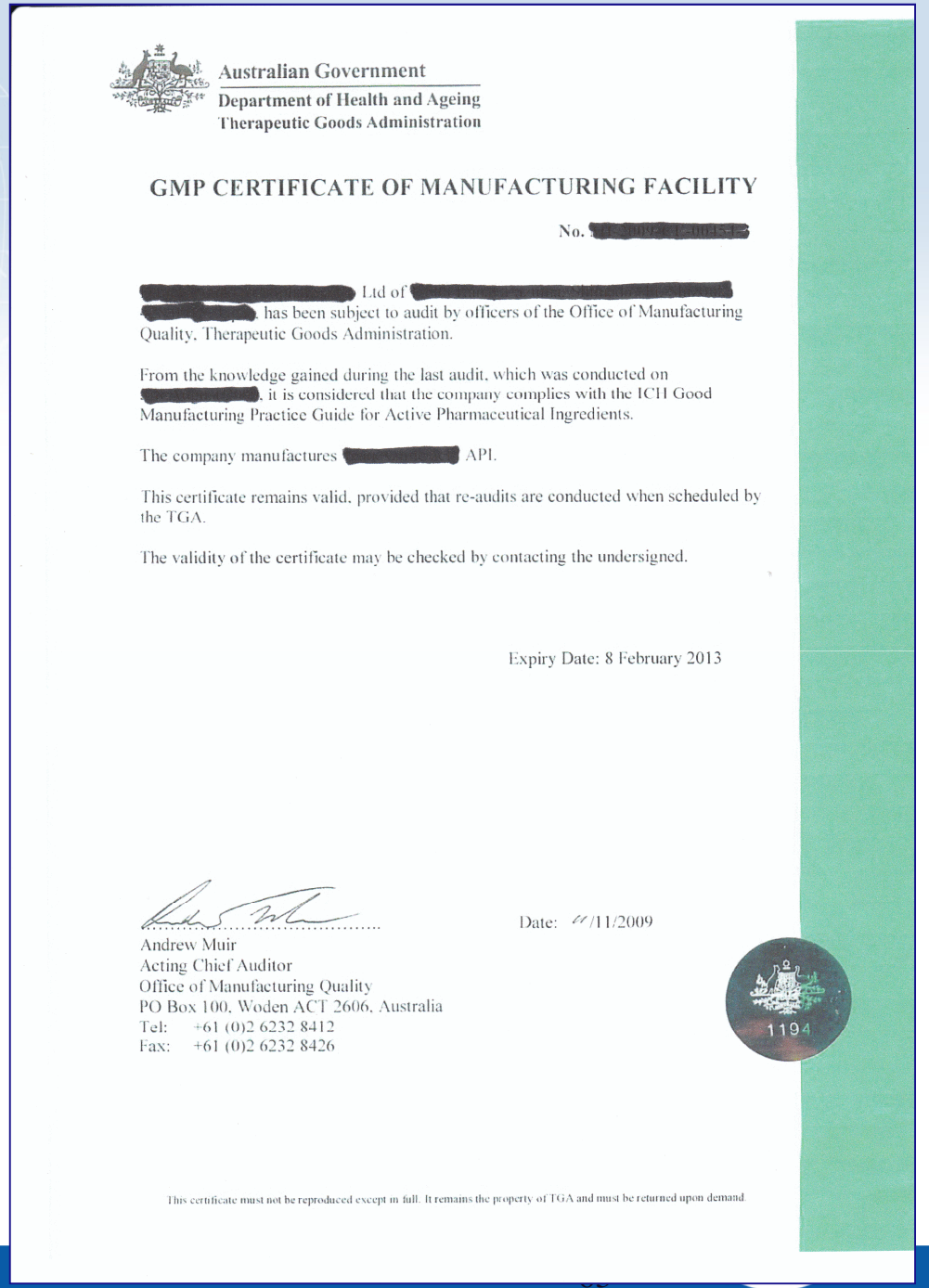
Yours sincerely

[redacted]

Dr [redacted]
Manager,
Medicine Audit Team, International
Office of Manufacturing Quality
Date: 22 October 2009

Tel: +61 2 [redacted]
Fax: +61 2 [redacted]
E-mail: [redacted]

Example of TGA GMP Certificate



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

GMP CERTIFICATE OF MANUFACTURING FACILITY

No. [redacted]

[redacted] Ltd of [redacted] has been subject to audit by officers of the Office of Manufacturing Quality, Therapeutic Goods Administration.

From the knowledge gained during the last audit, which was conducted on [redacted], it is considered that the company complies with the ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients.

The company manufactures [redacted] API.

This certificate remains valid, provided that re-audits are conducted when scheduled by the TGA.

The validity of the certificate may be checked by contacting the undersigned.

Expiry Date: 8 February 2013

Date: 11/11/2009

Andrew Muir
Acting Chief Auditor
Office of Manufacturing Quality
PO Box 100, Woden ACT 2606, Australia
Tel: +61 (0)2 6232 8412
Fax: +61 (0)2 6232 8426

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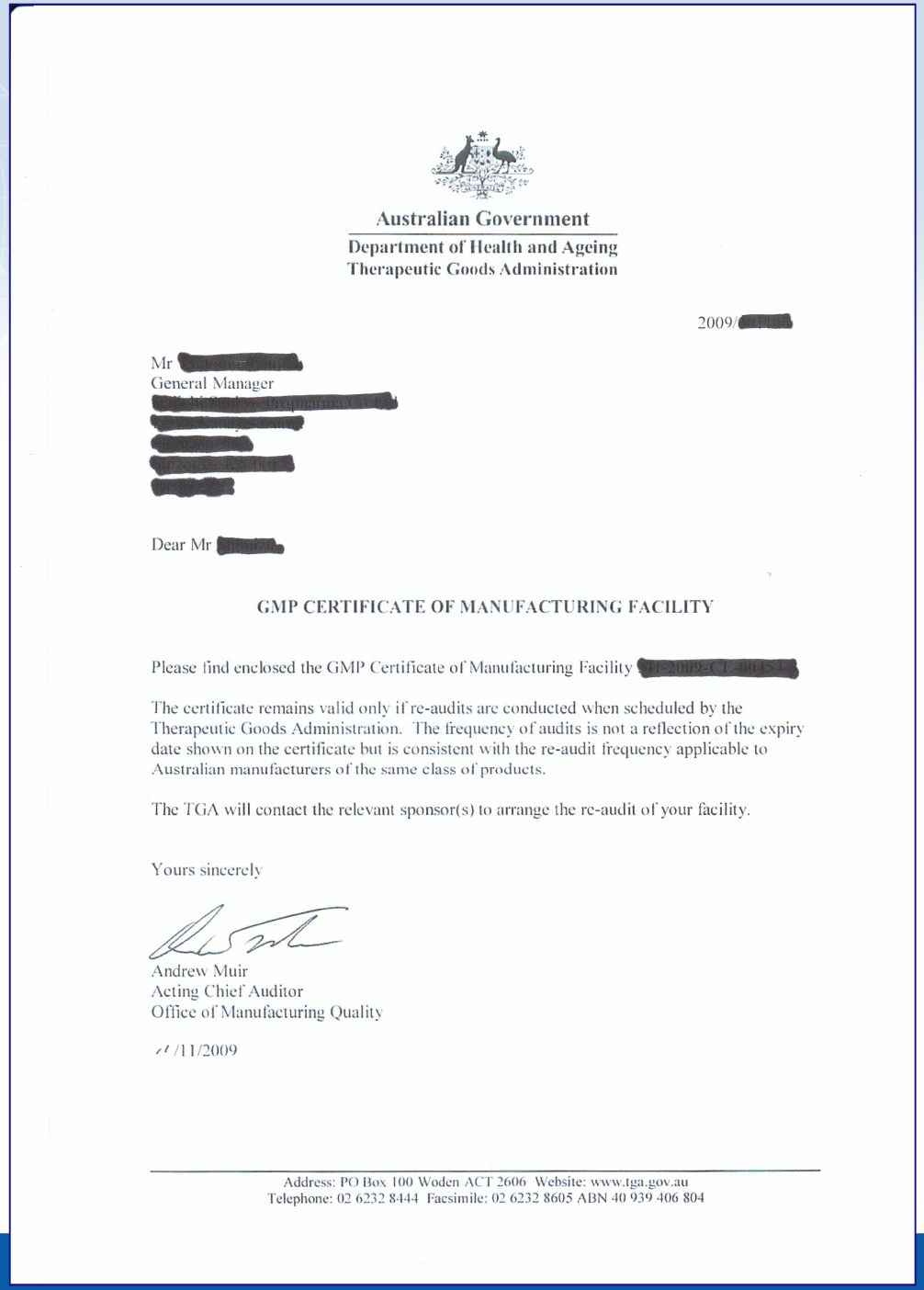
This certificate must not be reproduced except in full. It remains the property of TGA and must be returned upon demand.

Example of TGA GMP Certificate covering letter



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

2009/[redacted]

Mr [redacted]
General Manager
[redacted]

Dear Mr [redacted]

GMP CERTIFICATE OF MANUFACTURING FACILITY

Please find enclosed the GMP Certificate of Manufacturing Facility [redacted]

The certificate remains valid only if re-audits are conducted when scheduled by the Therapeutic Goods Administration. The frequency of audits is not a reflection of the expiry date shown on the certificate but is consistent with the re-audit frequency applicable to Australian manufacturers of the same class of products.

The TGA will contact the relevant sponsor(s) to arrange the re-audit of your facility.

Yours sincerely

Andrew Muir
Acting Chief Auditor
Office of Manufacturing Quality

/ /11/2009

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GMP Inspection Techniques

ENGINEERING PHARMACEUTICAL INNOVATION

Different Inspection Techniques

- Trace forward:
  - Most common approach.
  - Start with a raw material & follow production flow.
  - If time permits, start with an inspection of external surrounds.
- Trace backwards:
  - Review history of a specific batch of product.
    eg. final product ➡ processes ➡ raw materials.
  - Usually used to investigate cause of product defect leading to complaints and/or recall.
- Random:
  - Start from points that appear significant.
    eg. PQR ➡ Complaint ➡ CAPA ➡ Change Control ➡ Training.

The 5-Why +1 Exercise

- A good way to remember how to drill down to the level you need to get to in an inspection.
- However, inspector must:
  - be positive & constructive.
  - Give the inspectee the "benefit of the doubt".
  - Look for factual evidence that can be justified to the inspectee.
  - Not rely on "gut feeling" to report a deficiency.

    (but "gut feeling" can be useful to dig deeper to find the facts)

The 5-Why +1 Exercise

Question	Answer
1. Why is there water on the floor?	1. There is a leaking pipe.
2. Why does the pipe leak?	2. The fittings are leaking.
3. Why are the fittings leaking?	3. The seals are leaking.
4. Why are the seals leaking?	4. They are old and corroded.
5. Why have they not been replaced?	5. There is no one in charge of taking care of this.
6. Now we ask the SIXTH question: "What other systems are deficient because no one is assigned?"	6. ??

How to Take Notes (1)

- Detail and facts – trust, but verify
  - If operator says he cleaned a machine, look at documents and verify.
- Record specifics, not general impressions
  - eg. "atropine sulphate injection 1.2 mg/mL, batch X123, was stored in bulk store # 3 with no temperature control, monitoring or recording".
  - NOT: "atropine sulphate injection was stored in a bulk store where the temperature is not monitored".

How to Take Notes (2)

- Record detail as seen
  - Record what you see, not what you are told what you should see
- Ensure accuracy
  - Inaccurate statements & observations undermine credibility
  - If necessary, check facts to ensure accuracy
- Be open
  - No need to hide what you are recording

Use of Checklists

- PIC/S does not like to see check-lists being used.
- Concerns:
  - Can act as a set of blinkers or blinders (narrow focus)
  - Can reduce training value
  - Can be used as crutch instead of tool (tick the box approach)
  - May be too narrow to identify problem areas
  - May be intimidating to those being inspected
  - Some questions may be outdated quickly
  - Some questions may need more thorough investigation to answer

  However, may be OK for trainee inspectors.

Attributes of a Good Inspection Report

Tips:

- Write against standard used for the inspection
- Focus on deficient conditions; not people
- Include positive observations if deserved
- Use neutral tones, keep it simple & base it on fact – should be no ambiguities
- Use past tense – "The company did not validate XYZ".
- List deficiencies classified by criticality
- Cross-reference deficiencies to standard used for the inspection (eg. show relevant clause number of PIC/S GMP Guide)
- Provide a summary of the outcome of the inspection