Ministry for Primary Industries
Manatū Ahu Matua

ACVM Manufacturing Workshop

Wellington

www.mpi.govt.nz

AGENDA

Topic	Presenter	Time
Arrive and Network (08:30 - 09:00)		
➢ Welcome	Holly Jeboult-Jones	09:00-09:05
➢ ACVM Overview & Update	Glen Bradbury	09:05-09:15
➢ Quality Management	Christian Morales / Francie Olliver	09:15-09:50
➢ GMP Programme & Common Deficiencies	Holly Jeboult-Jones	09:50-10:10
➢ Manufacturing Admin & Submissions	Francie Olliver	10:20-10:30
Morning Tea (10:30 - 11:00)		
➢ GMP Update – Asia Pacific & Beyond	Bob Tribe	11:00-12:00
➢ VM Chem & Manufacture Information Req.	Awilda Baoumgren	12:00-12:30
Lunch (12:30 - 13:15)		
➢ Agricultural Chemical Manufacturing	Rafael Barbieri	13:15-13:35
➢ Validation (Concept, Process & Cleaning)	Christian Morales	13:35-14:20
➢ Requirements for Contract Manufacturing	Bob Tribe	14:20-15:00
Afternoon Tea (15:00 - 15:20)		
➢ Split into two groups - Questions & Case Studies		15:20-16:20
• Group 1: Vet Med, VTA, Ag Chem & Exempt Compound Manufacturers - Questions (20 mins) - Group Activities – Manufacturing related (40 mins)	HJJ, CM & GB	
• Group 2: Registrants & Regulatory Affairs - Questions (20 mins) - Group Activities – Data and information required when making applications (40 mins)	AB, FO & RB	
➢ Closing Summary	Glen Bradbury	16:20-16:30
Closing (16:20-16:30)		

Ministry for Primary Industries
Manatū Ahu Matua

Manufacturing Workshop
ACVM Group
Who we are and what we do

Glen Bradbury

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ACVM Act (1997)

Purpose:

Manage risks to:

- Public Health
- Trade in primary produce
- Agricultural Security
- Animal Welfare

Always in relation to agricultural compounds

- ➢ Avoid non-compliant residues in food
- ➢ Ensure sufficient consumer information

Agricultural Compound…

Any substance, mixture of substances, or biological compound used or intended for use in the direct management of plants and animals, or to be applied to the land, place or water on or in which the plants and animals are managed, for a listed purpose.

ACVM's Role – How we do it

To protect New Zealand's primary production sector through:

- Assessment and registration
- Post registration review, reassessment and response activities (including Pharmacovigilance)
- Audit and compliance monitoring and certification
- Development and review into policy and standards
- Border monitoring and clearance
- Ministerial communications and support (Media)
- Setting of limits and specifications (e.g.MRLs)
- Technical advice

ACVM Group – Changes in the last year

Glen Bradbury
Manager, ACVM Programmes & Appraisals

Agricultural Chemicals and VTAs Assessors
Bruce Nalder
Rafael Barbieri
Sarah Lester
Wayne Severn
Joy O'Connor

Veterinary Medicines Assessors
Alfredo Caicedo Caldas
Jennifer Doyle
Justin Mercier

Regulatory Programmes
Holly Jeboult-Jones
Francie Olliver
Christian Morales Orea

Food and Trade
Awilda Baoumgren

Warren Hughes
Principle Adviser ACVM R&A

Contractors
Paul Spencer (Chem)
Jennifer Moran (Vet)
Meg Moffat (Vet)
Richard McKinley (Vet)
Suzanne Lane (Vet)
Chris Boland (Projects)
Karen Booth (Reg Review)
Pip Cameron (Reporting)
Sarah De Barr (Procedures)

Maree Zinzley
Manager, Approvals Operations

Gina Armstrong
Vu Mpofu
Shaleen Narayan
Daniella Foote
Jessica Gautry
Sara Van Rooy

ACVM Priorities for 2017/2018

Projects

- Registration Review (completion and implementation of actions)
- Exemption Regulations Refresh
- GMP and Manufacturing Review (official initiation)

Ongoing matters requiring focus

- AMR
- Data Protection Bill

Guidelines/Information Requirements

- Vet Med Chemistry and Manufacturing
- Information Requirements

Why is Manufacturing an important aspect for ACVM products?

Minimise Harm

What if you get it wrong ?

Regulatory Programmes - Resourcing and Timeframes

- Additional resource
- Large scope of work
- Compliance issues, responses, recalls and Ministerials
- Plans to establish metrics going forward

GMP & Manufacturing Review – Initial Stages

- Revise categories of approval and GMP certification
- Revision of internal QMS and associated procedures
- Review ACVM Standard and Guideline
- Risk-based audit frequency (and length)
- MRA review of requirements
- Add Release for Sale entities and QC Labs
- Additional Standards (VTA, Feeds)

Expectations of Manufacturers Going Forward…

- Ongoing and open communications.
- Improved understanding and awareness
- Responsiveness and transparency
- Taking ownership
- Commitment to producing safe, pure, efficacious and consistent ACVM products.

Next up - Christian & Francie

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Manufacturing Workshop
Quality Management
Agricultural Compounds and Veterinary Medicines

Christian Morales and Francie Olliver

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Quality Management Systems (Origins)

1900-1920:

- Awareness of ensuring quality product, **customer satisfaction started to be a key factor**
- The practice of testing every item to ensure that it complied with product specifications was introduced; worked well when the volume of production was reasonably low. (Frederick W. Taylor, 1911, *Scientific Management*)
- **Mass production played** an important role around the world (WW). Testing every item become impossible
- Socio-psychological aspects of human behaviour in organisations started to gain attention (Productivity vs Quality)

Quality Management systems (Origins)

1930s:

- **Watler Shewhart** developed the methods for statistical analysis and control of quality. He introduced the concepts of control chart analysis.
  - Shewhart cycle or PDCA

- **W. Edwards Deming** introduced the sampling techniques in the industry.
  - 14 Principles for Managers

1950s:

- **W. Edwards Deming,** taught methods for statistical analysis and control of quality to Japanese engineers and executives. **This can be considered the origin of Total Quality Management (TQM).**

1968:

- The Japanese named their approach to total quality companywide quality control. It is around this time that the term Total Quality Management arises.

- **Kaoru Ishikawa's** application of the philosophy contributed to Japan's ascendancy as a quality leader.

What is Quality Management System?

"Quality Gurus" QMS Definitions:

- Something with the positive attribute of conformance **to specified standards.** Conformance to requirements (Crosby 1979)

- It is an approach representing a **new way of thinking about management.** To meet this goal, **everyone** in the company **must** participate in and **promote quality** control (Ishikawa 1985)

- A predictable degree of uniformity and dependability at a low cost with a **quality suited to the market** (Deming 1986)

- Avoidance **of causes of 'loss of product' to society** after being shipped other than any losses caused by its intrinsic function (Taguchi 1986)

- Product performance which results in customer satisfaction **'fitness for use'**(Juran 1988)

Quality Management Systems (Principles)

- **Everyone is involved in quality**
- **Quality is defined by customers' requirements**
- **Systematic analysis and continuous improvement**

Quality Management Systems (Today)

Definition:

- A quality management system (QMS) is **a collection** of internal documented processes and procedures focused on achieving the **quality policy and quality objectives of a company** (i.e., what the customer needs). This system defines how a company will achieve the creation and delivery of the product or service they provide to their customers

A QMS should:

- Ensure that the **product or service is consistent** with the established specifications
- Set direction and meet **customers' expectations**
- **Improve process control**
- Reduce wastage
- Increase market share
- Facilitate training
- **Involve staff**
- **Create engagement**

Tools to support a QMS:

- Good Manufacturing Practice (GMP)
- International Organisation for Standardisation (ISO)
- Lean-Six Sigma

QMS Central Aspects

The most central aspects of QMS are:

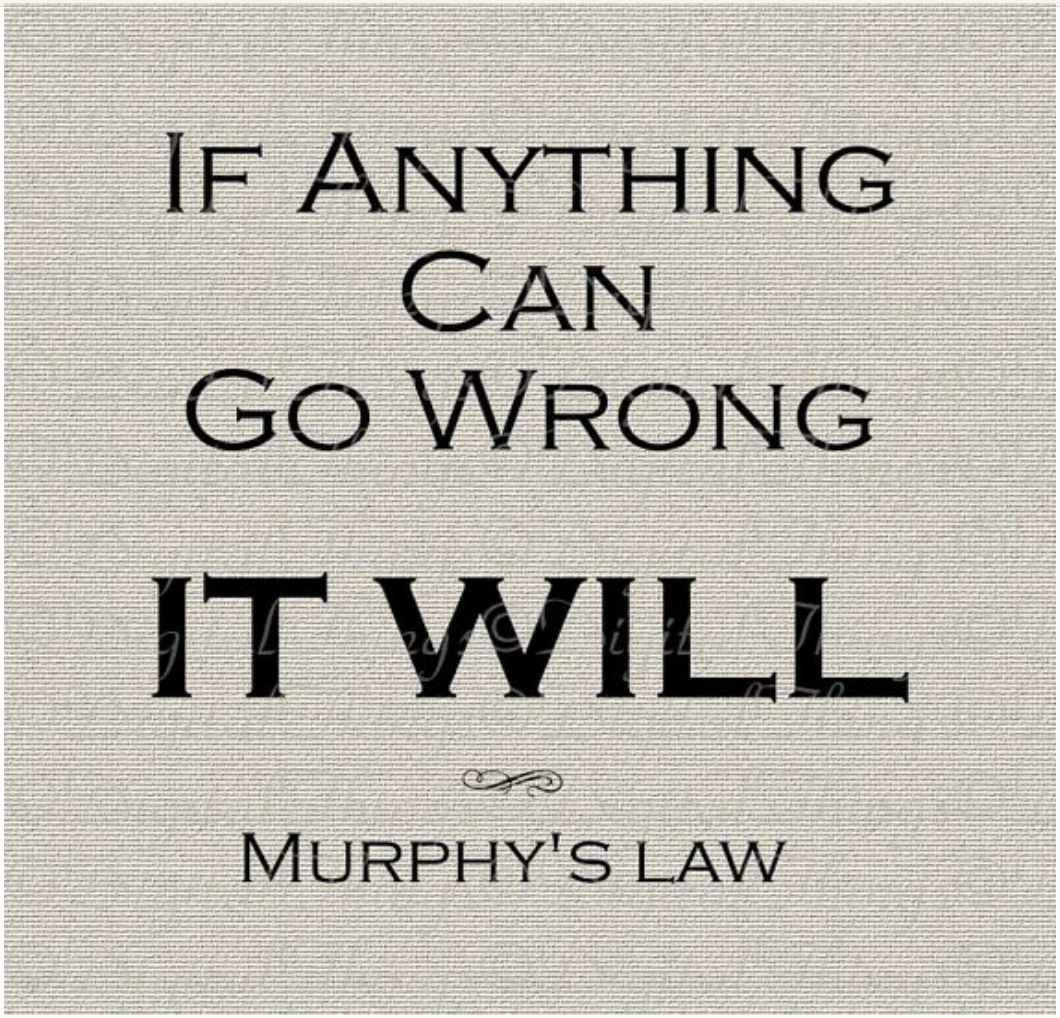
- **Traceability:** the ability to reconstruct or verify the history of a product
- **Accountability:** the ability to identify the person who has contributed to the process and when
- **Documentation:** is a critical tool for enabling QMS adherence (If it is not written down, it didn't happen)
- **Risk Management:** (criticality vs probability)
- **Data Analysis:** (Without data it is impossible to determine consistency and measure improvement)

Case Study

Japan, leader in TQM, always right the first time?

- Takata (Auto-parts manufacturer leader) 2016:
  - Defective airbags that could potentially explode during deployment.
  - 53 Million Vehicles recalled from 14 car manufacturers that had been affected.
  - 17 deaths and more than 100 hundred injuries were linked to this problem.
  - **Root Cause:** The use of ammonium nitrate propellant without moisture-absorbing desiccant combined with a poor inflator assembly that did not adequately prevent moisture intrusion.
  - Takata's competitors decided not to use ammonium nitrate because of the risks it involved. Takata was confident about its engineering and manufacturing expertise.
  - 25 Jun 2017 Takata files for Bankruptcy mainly because of the massive recall expenses and compensations. Some brands expanded their recall volumes because Takata **acknowledged inadequate records of quality control and batch manufacturing.**

QMS (Risk Management)



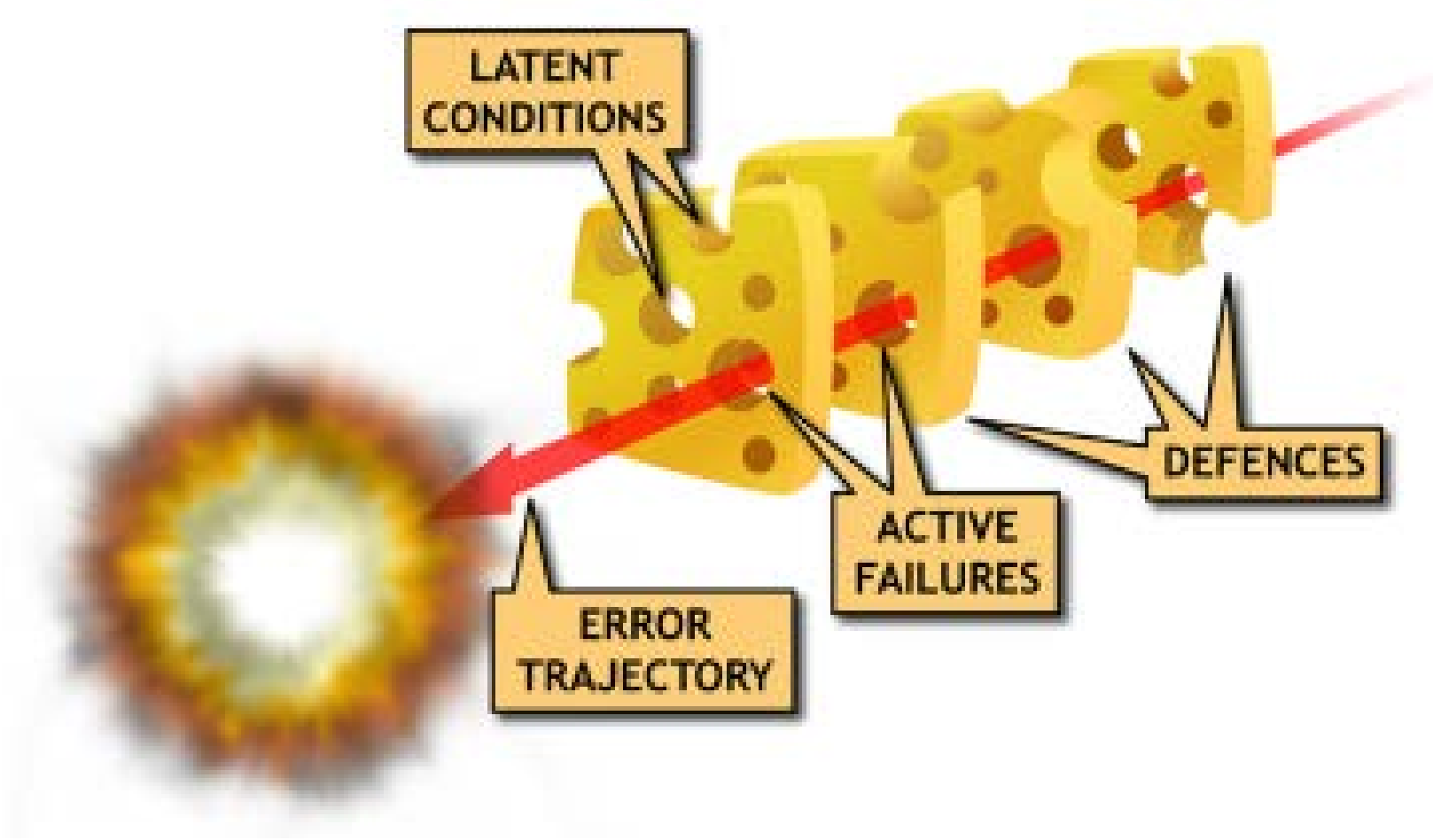
QMS (Risk Management)

Risk Management:

- **Risk**: Combination of the probability of occurrence of harm and the severity of that harm
- **Risk Management:** Is a systematic process for the assessment, control, communication and review of risks to the quality of the products across the product lifecycle
- **Risk Assessment:** A systematic process of evaluating potential risks
- **Tools:**

- Brainstorming
- Structured or semi-structured interviews
- Delphi method
- Checklist
- Preliminary hazard analysis (PHA)
- Hazard and operability study (HAZOP)
- Hazard analysis and critical control points (HACCP)
- Toxicity assessment
- Structured What If Technique (SWIFT)
- Scenario analysis
- Business impact analysis
- Root cause analysis
- Failure mode and effects analysis (FMEA)
- Fault tree analysis
- Event tree analysis
- Cause and consequence analysis
- Cause-and-effect analysis
- Layer protection analysis (LOPA)
- Decision tree
- Human reliability analysis (HRA)
- Bow tie analysis
- Reliability centered maintenance
- Sneak circuit analysis
- Markov analysis
- Monte Carlo simulation
- Bayesian statistics and Bayes nets
- FN curve
- Risk index
- Consequence/probability matrix
- Cost/benefit analysis
- Multi-criteria decision analysis (MCDA)

Risk Assessment (Swiss Cheese Diagram)



What is GMP?

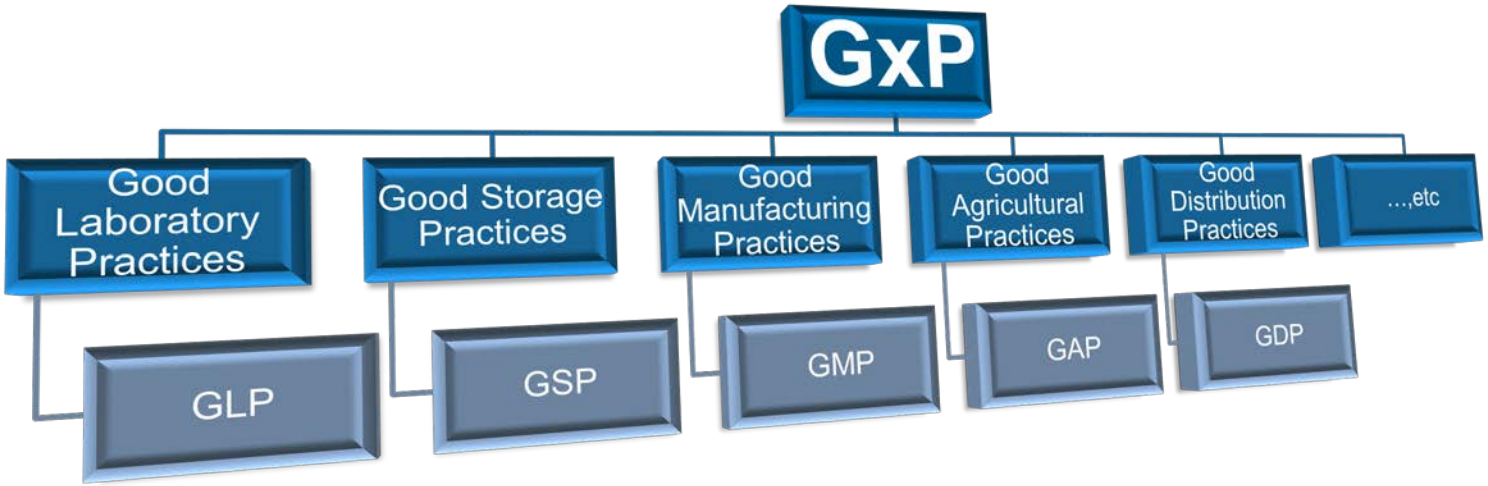
- **Practices that must conform to requirements imposed** by regulatory authority that controls the authorisation and licensing of products

- It **provides the minimum requirements** in order to ensure the products comply with the quality required by the customers (don't pose any risk to consumers)

- It is a system that ensures the **products are manufactured consistently and controlled** according to quality guidelines or requirements

GMP Structure

Other Good Practices (GxP)



Quality Management (GMP as a Tool)

Vet Med and VTA

- Vet Med and VTA manufacturers are audited to GMP to comply with the product registration conditions
- In order to allow for international recognition of NZ's GMP Programme, NZ is part of the EU Mutual Recognition Agreement

Ag Chem

- Ag Chem Product must conform to product registration conditions.

Exempt Products

- Exempt Product must conform to documented system - ACVM (E&PS) regulations 2011 (regulations 9 – 14)
- New ACVM Notice – Exempt Products to be published

The QMS must ensure that product meets regulations/conditions.

QMS Design – ACVM expectation

Quality Objective

Fit for purpose, comply with the product registration and do not place undue risks to *animals, trade, agricultural security or public health* due to inadequate safety, quality or efficacy.

- QMS design & implementation should be fully documented and its effectiveness monitored
- Actual QMS is dependent on products, activities performed, risks to be managed
- Ensuring Quality of Product

Elements of a QMS

- **Quality Manual (or SMF) and Procedures** or
- **Quality/Operations Manual** including Procedures

Consider:

- Quality Management/Policies
- Personnel
- Premises, Plant, Equipment
- Documentation
- Production/Manufacturing
- Quality Control
- Contract Manufacture
- Complaints and product recall
- Continuous improvement

QM – Personnel - Premises

- **Quality Management**
  - Quality objectives
  - Management & all staff committed to the QMS
  - Adequate resourcing (premises, staff, equipment)
- **Personnel**
  - Hygiene
  - Qualified - Ongoing training
  - Quality relies on people following processes
- **Premises and Equipment**
  - Must be appropriate for products manufactured
  - Prevent cross-contamination
  - Prevent adverse effects on product quality

Documentation

- Planned process
  - Procedures/instructions
  - Manufacturing formulae
  - Specifications – raw materials, finished products

- Records
  - Legible, true & accurate
  - Evidence of actions
  - Allow traceability

Procedures/Instructions

Purpose: ensure a process/activity is performed correctly and consistently

- Detailed, clear, easy to use
- Available to staff
- Current – regular review
- Consistency across

NOTE: Only effective if followed

Production

Follow defined procedures to ensure quality of product:

- **Processing steps** – formulation of bulk, intermediate & packing/labelling operations
- **Workflow** of product through premises
- **Incoming → Finished goods → Dispatch**
- **Starting materials** - actives, raw materials & packaging
- **Validation** – consistency of manufacture

Quality Control

Ensure that necessary & relevant tests are carried out, materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

- Sampling – incoming goods & final product
- Specifications
- Testing – validated test methods
- Retention samples
- Statistical Trending of results

Product Release for Sale

- **Formal evaluation** - fit for purpose (conforms to the requirements of the registration)

- **Release** – review of batch record, test results, release specifications & examination of final finished packed product (packaging, labelling & correct B+E)

- **Release steps documented** and retained with the batch record and test results.

Deviations & Non-conformances

Events or situations that depart from approved instructions, standards or policies – unexpected event.

Process for Handling:

- **Record:** Reporting, logging, tracking - traceability
- **Actions: Corrective** and **Preventative** - appropriate
- **Investigation:** Root cause determination (e.g. Who? When? How? What? Where?)
- **Quality Impact:** Risk Assessment to Product Quality
- **Regulatory Impact:** ACVM notification/approval?

Change Management (Change Control)

- **A system to ensure all changes made are controlled, evaluated, implemented and documented in a manner that prevents impact on the quality of the product.**
  - **Change Proposal:** evaluated by Management and Quality before the planning or implementation process begins
  - **Quality Impact:** impact to product quality assessed during the change proposal evaluation (Risk Assessment)
  - **Planning and implementation:** Controlled & documented – traceability
  - **Evaluation:** Effectiveness of the change monitored implemented.

Contracted Manufacture

- **Contract Giver** - ensure manufacturer is competent & adheres to quality requirements
- **Contract Acceptor** - no activity which may adversely effect quality of product

Important:

- **Responsibilities** – may be shared
- **Agreement** - duties of each party & manufacture controlled

Complaints and Recalls

Complaints: All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures.

Recalls: A process to recall promptly products known or suspected to be defective from the market.

Review effectiveness – Improvement

- Regular review for effectiveness of control
- Consider all aspects of QMS
- Improvement
- Focus on the detail

Reminder:

- Independence – fresh set of eyes
- Not just a paperwork exercise – actual processes
- Recalls - mock recall to establish capability

Summary - Quality Management

- **Ensuring Quality of the Product**
- **GMP / ISO/ Documented System**
- **Principles**
  - Traceability
  - Accountability
  - Documentation
  - Risk Management
  - Improvement

Next Up - Holly

Ministry for Primary Industries
Manatū Ahu Matua

Manufacturing Workshop
ACVM GMP Programme & Common Manufacturing Related Deficiencies
Agricultural Compounds and Veterinary Medicines

Holly Jeboult-Jones

ACVM Regulatory Programmes Team

- Holly Jeboult-Jones

- Francie Olliver

- Christian Morales Orea

Scope of Activities

- GMP Programme
  - International Vet Med & VTA approvals & Certificate recognition
  - Domestic Vet Med & VTA audits
  - International Vet Med audits (where required to support NZ registration
- Technical Manufacturing advice (to assessors / wider MPI)
- RVM Seller OP Programme (assessment & approvals)
- Compliance under the ACVM Act
  - NCRs & Rapid Alerts
  - Recalls
  - Complaints
  - Batch variations (for registered products)
  - Deviations, non-compliant product (exempt & registered), stability issues etc.
- International agreements (EU-MRA, MoUs etc.)
- QMS Maintenance

GMP Audit Programme

We currently have **63** NZ manufacturers and **2** International GMP Manufacturers (pending approval)

- Vet meds, VTAs, ONCs – for export
- **5** audited by Medsafe

Audits conducted every **2 years** to verify continued compliance

Audits range from **1 day** to **5 days**

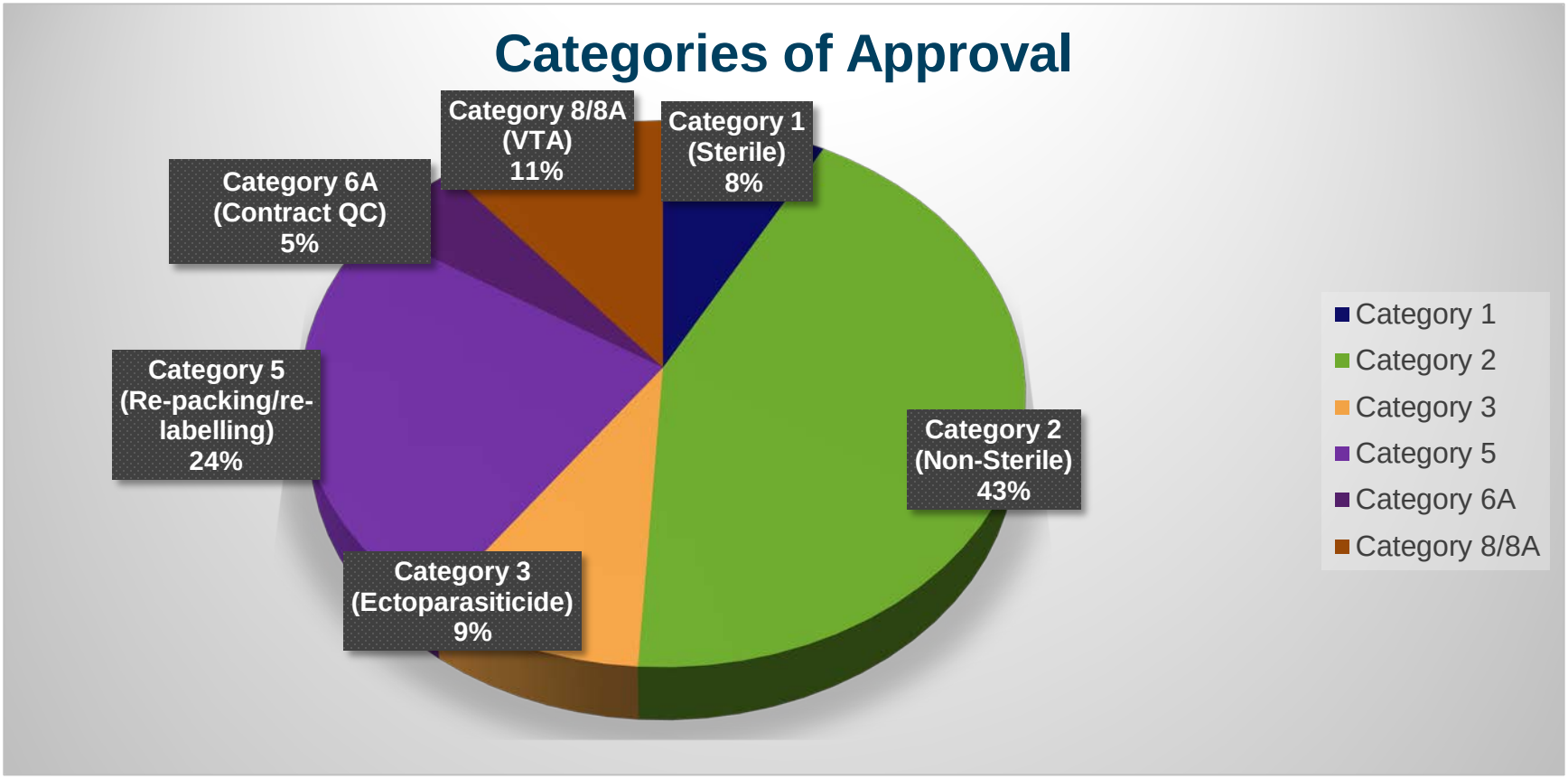
ACVM GMP Programme

Current Manufacturing Categories

- 1A Immunobiologicals
- 1B Steriles
- 2 Non-sterile veterinary medicines
- 3 Large Volume Ectoparasiticides (external application)
- 5 Re-packing/Re-labelling
- 6A Contract Testing
- 6B Contract Sterilisation
- 8 Vertebrate Toxic Agents
- 8A Vertebrate Toxic Agents (Re-packing/re-labelling)

NOTE: These categories are changing and will be reflected in the new GMP Certificate Format

NZ GMP Approved Manufacturers



NB: 18 of the 63 manufacturers are approved in multiple categories

Why a GMP and Manufacturing Review?

- Gaps identified
- Some sectors not covered
- Resource and focus needed to maintain QMS
- Compliance issues increasing
- Responsibilities in relation to maintaining equivalence
- Expectations raised internationally
- Advances in technology and changes to guidelines internationally

GMP and Manufacturing Review - Gaps

- Are the appropriate risks being managed in each sector?
- Is the scope of approval sufficient?
- Is GMP approval the best way of managing VTA manufacturers?
- Are the EU MRA and MoU with Australia working for industry and the ACVM Group, are we continuing to comply with expectations, is it cost effective?

GMP and Manufacturing Review - Gaps Cont.

- Timeframes sufficient and/or established?
- Are Guidance and Requirements current, fit for purpose and reflective of expectations?
- Do Guidance and Requirements incorporate advances in technology and changes to industry practices?
- Future state?

Initial Plans – Within 6 – 12 months

1. Review & amendment of internal procedures/policies (ongoing)
2. Establish metrics and commit to new timeframe for GMP audit reports (40 working days)
3. Roll out of revised GMP Certificate format
4. Review Deficiency Close-out Policies (incl. timeframes and process)
5. Review audit lengths & frequency
6. Introduce risk based audit frequency procedure
7. Review scope of GMP Programme

Common Observations that lead to deficiencies

- Poor Documentation Standards
- Inadequate Deviation Management
- Making changes without:
  - adequate change control assessment
  - or regulatory approval (where applicable)
  - validation (where applicable)
- Minimal information in Contracts/Quality Agreements

Poor Documentation Standards

Missing entries, lack of information in template, incomplete SOPs.

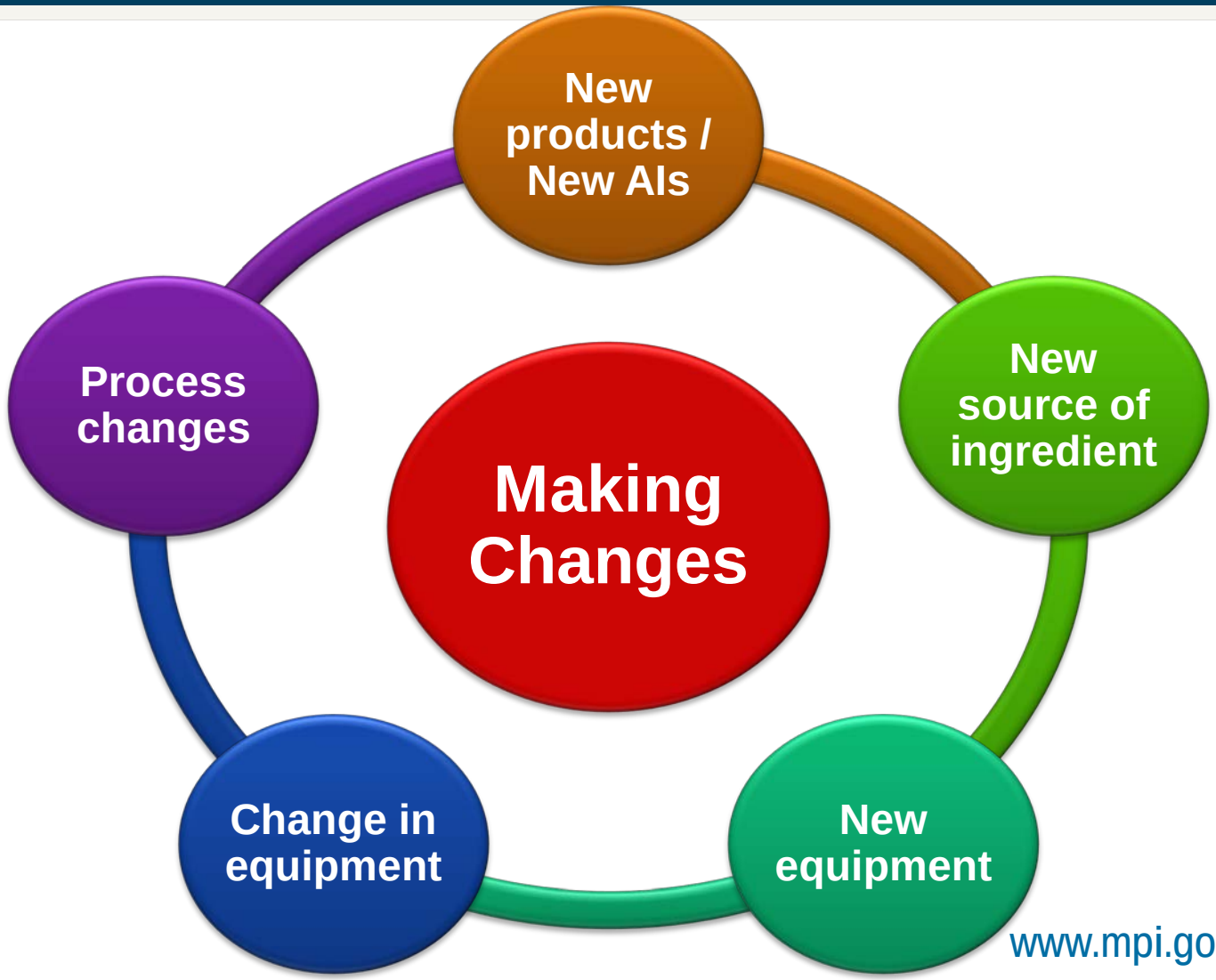
Things to consider

- Corrective Actions
- Preventative Actions
- Other Impact?

Inadequate Deviation Management

- Minimal System for documentation, investigation, risk assessment, justification and CAPA follow-up
- Incomplete or No Risk Assessment
- No thought about root cause or wider implications
- No CAPAs or incomplete CAPAs

Making changes without thought



Reports of Non-Compliance or Product Quality Issues – Registered Products

- Product separation during shipment and storage
- Product separation during filling
- Contamination
- OOS identified during ongoing stability trials
- Precipitation when arriving in NZ
- Incorrect Label used (old version)
- Unapproved process, AI manufacturer or pack size
- Labelled with unapproved SL
- Decanting into smaller unregistered pack sizes
- Inefficacy

Reports of Non-Compliance or Product Quality Issues – Exempt Products

- Not meeting conditions or scope of the exemption
- Label claims or claims in advertising
- Inadequate Label information e.g. misleading or incomplete
- Packaging not fit for purpose
- No documented system
- Contaminated Product not fit for purpose

Taking responsibility for Non-Compliance

Next up - Francie

Ministry for Primary Industries
Manatū Ahu Matua

Manufacturing Workshop
Manufacturing Administration & Submissions

Francie Olliver

Responsibilities

- **Registrant**
  - Overall responsibility for manufacture of product using appropriate quality standards and to product registration requirements

- **Manufacturer**
  - Manufacture according to a QMS and the product specifications provided by registrant

Conformance to Conditions of Registration

- **60 (AC +VM)…** product must, at all times, conform to the product and manufacturing specifications approved as part of registration….
- **62 (VM) ….** manufactured by a person specified to manufacture it….
- **2 VTA ....** manufactured …to the ….Chemistry & Manufacturing specifications provided by the registrant and approved as part of registration

Communication - Registration Conditions & Details

- **Registrant** – must supply all details to enable manufacture according to registration

- **Manufacturer** - cannot subcontract testing or any functions without approval from registrant (in contract with Registrant)

Product Registration

- **Product Data Sheet (PDS)**
  - Shelf life & Pack sizes (supported by stability data)
  - Manufacturers Formulated product & Active ingredients (VMs & VTAs only)
  - Formulation and Manufacturing Process
  - Release & Expiry Specifications
  - Test methods
  - Release for supply (entity responsible)

Registration must be kept current!

Variations to Manufacturing - Registration

- **MUST be approved prior to making change!**
- C2 Variations to Manufacturing:
  - C2 - Change to manufacturing process
  - C2 - Add/change AI manufacturing site
  - C2 - Add/change Formulated product manfuacturer, QC lab, relabeller etc

  Variations sent to: approvals@mpi.govt.nz

C2 - Manufacturing Changes

- **Manufacturing Process** – justification regarding impact on safety, efficacy etc
- **AI manufacturers** – accurate site address
  - ➢Physical site address included on CoA
- **FP manufacturer** – check category & scope
  - ➢Provide evidence of QMS (as needed)
    - eg GMP (Vet Meds)
  - ➢International GMP manufacturers – Current GMP certificate needed for all applications

ACVM GMP Manufacturer - Change in Scope or Premises

- Notify ACVM of intended change
  - allow for timing of Inspection (3 mths)
- Application form: ***Approval (or Variation of Approval) to Manufacture Veterinary Medicines and/or Vertebrate Toxic Agents ACVM 18*** (August 2014)
- New GMP certificate
  - with new scope/site

ACVM GMP Manufacturing - Name Change

- Provide verification/formal evidence
  - GMP Certificate - match legal name
- Application form: ***GMP Certificates: Request for Name Change ACVM 20 (July 2015)***
- **Notify registrants** to update product PDS
  - Ensure name on PDS matches GMP certificate

ACVM GMP Certificates - copies

- If additional copies of GMP certificates needed for international authorities
- Use the Application form ***Request for Additional Copies (ACVM 19) July 2015***
- **Email all GMP manufacturer applications to:**

  ACVM.ManufacturingAssurance@mpi.govt.nz

Adverse Event Reports (AERs)

- **AERs must be reported to ACVM -** required as condition of product registration

  - **Vet Meds - Condition 64**
  - **Ag Chems - Condition 82**
  - **VTAs - Condition 37**

- **Post-registration monitoring**
- **Product Stewardship**

Vet Medicine - Definition

An **adverse event** is any:

- negative physiological or pharmacological side effect
- target animal safety issue
- residue issue
- **lack of efficacy**
- or alleged interactions with other products or compounds

Vet Medicines – AERs

Includes all **unfavourable** and **unintended** events associated with the use of the product in an on-label or off-label manner.

- Residues – IS grades
- Suspected lack of efficacy (note: product may or may not be the cause)
- Multiple product use/interactions

Agricultural Chemicals - Definition

Any observation in target crop, species, claim or disease or non-target plants that is unintended, and that occurs after the use of an agricultural chemical. This may include:

- unintended effects
- unacceptable residues
- lack of efficacy
- Good Agricultural Practice (GAP) issues
- application issues (faulty sprayers, poor quality product, sedimentation, and compatibility issues).

VTAs - Definition

Any unexpected effect, associated with a product when used in accordance with the approved conditions placed on the registration

- unintended effects
- target animal welfare issues
- **lack of efficacy**
- non target animal events
- alleged interactions with other products or compounds.

Animal Feeds – Exempt Products

- Animal Feed AERs should also be reported to ACVM although not mandated

- Must be fit for purpose & not cause any harm...

  - *ACVM (E & PS) regs 2011; reg 7 & 8*

- Reporting form is on ACVM Website:

  www.foodsafety.govt.nz/industry/acvm/vet-medicines/using/something-goes-wrong.htm

AER Handling - Process

- **Record** - database of all cases
- **Investigate**
  - objective fact-finding, gather evidence, testing, assess significance, is there a quality issue, scientific rationale for conclusions
- **Corrective actions** - update to label warnings, change to manufacturing controls or specifications
- **Trend Analysis** – is there an increase in number or change in type of reports received?

ACVM Reporting – Requirements

- **Registrants are Responsible**
- Report the significance of AERs within **20 working days** to:

  ACVM-adverseevents@mpi.govt.nz

Serious AERs must be reported as soon as possible – within 1 working day!

New Information

- **New information – Notify ACVM!**
- **Examples:**
  - Manufacturing quality issue impacting product safety, efficacy, quality
  - Out of Specifications (OOS)
  - New trial work which contradicts registered information

    Condition 65 (AC + VM)

    Condition 37 (VTA)

Product Recalls

Voluntary or Mandated (35G ACVM Act)

- Contamination - microbial, chemical or particulate
- Low potency, formulation etc
- OOS within shelf life
- Incorrectly labelled/packed

Contact MPI asap within 24 hrs if recall is being considered - before it is implemented!

Request to Release Individual Batch

- Batch does not meet all registered release specifications or conditions
- Exception – Case by Case!

Information required:

- Summary of issue & request for release
- Risk assessment including justification
- All supporting data (including CoA)
- Comparison to other batches (if applicable)

MORNING TEA BREAK – 30 MINUTES

Morning Tea

Topic	Presenter	Time
Arrive and Network (08:30 - 09:00)		
➢ Welcome	Holly Jeboult-Jones	09:00-09:05
➢ ACVM Overview & Update	Glen Bradbury	09:05-09:15
➢ Quality Management	Christian Morales / Francie Olliver	09:15-09:50
➢ GMP Programme & Common Deficiencies	Holly Jeboult-Jones	09:50-10:10
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Morning Tea (10:30 - 11:00)		
➢ GMP Update – Asia Pacific & Beyond	Bob Tribe	11:00-12:00
➢ VM Chem & Manufacture Information Req.	Awilda Baoumgren	12:00-12:30
Lunch (12:30 - 13:15)		
➢ Agricultural Chemical Manufacturing	Rafael Barbieri	13:15-13:35
➢ Validation (Concept, Process & Cleaning)	Christian Morales	13:35-14:20
➢ Requirements for Contract Manufacturing	Bob Tribe	14:20-15:00
Afternoon Tea (15:00 - 15:20)		
➢ Split into two groups - Questions & Case Studies		15:20-16:20
• Group 1: Vet Med, VTA, Ag Chem & Exempt Compound Manufacturers - Questions (20 mins) - Group Activities – Manufacturing related (40 mins)	HJJ, CM & GB	
• Group 2: Registrants & Regulatory Affairs - Questions (20 mins) - Group Activities – Data and information required when making applications (40 mins)	AB, FO & RB	
➢ Closing Summary	Glen Bradbury	16:20-16:30
Closing (16:20-16:30)		

Ministry for Primary Industries
Manatū Ahu Matua

Manufacturing Workshop
Bob Tribe
GMP Update – Asia, Pacific and Beyond

www.mpi.govt.nz

GMP Update – Asia Pacific & beyond

Bob Tribe
Canberra, Australia

Overview

- Asia Pacific a major supplier of pharmaceuticals
- Problem areas in some Asia Pacific countries
- Growing influence of PIC/S in Asia Pacific region
- International regulatory convergence
- GMP Updates:
  - Australia
  - ASEAN countries
  - India
  - China
- Outlook for the future

A Changing World

Quotes from Dr Hamburg's speech to MHRA – 6 March 2014

- *"The world has changed. The idea of a wholly domestically produced drug is a fast fading reality"*
- *"Nearly 40% of drug products consumed in USA are made outside USA"*
- *"Nearly 80% of APIs used in USA are made outside USA"*
- *"China & India are each expected to see a more that 400% increase in product exports between now and 2020, with China accounting for nearly 20% of all global product exports by that time"*

Source: http://www.fda.gov/NewsEvents/Speeches/ucm388388.htm

24 Asia Pacific Countries

60% of the world's population lives in the Asia Pacific region

Fastest growing region of the world

Typical problem areas in some Asia Pacific countries

- "Guanxi" in China; "old boy network" in India *(business connections & relationships; reciprocal favours).*
- Companies operating "shadow factories" *(one as "showcase" factory; another operating at a lower standard).*
- Absence of deviations & complaints on record *(even after 5 years).*
- Data integrity *(recent increase in detection of data integrity breaches).*
- Site rules not observed *(e.g. cellphones; smoking).*
- Manufacture of counterfeit/falsified medicines:
  - *In Europe, 31% of counterfeited medicines originate from India & 20% originate from China* [1].
  - *Almost 15% of medicines in global supply chain are counterfeit* [2].

[1] http://dgra.de/media/pdf/studium/masterthesis/master_strobl_seb.pdf

[2] http://www.cmpi.org/in-the-news/testimony/counterfeit-drugs-and-china-new/

Counterfeited Cialis Manufactured in Asia Pacific

(Source of slide: Mr Sia, Director of Audit & Licensing Division, HSA, Singapore)

Counterfeit: Lot: A041410 A052788

Authentic: Lot

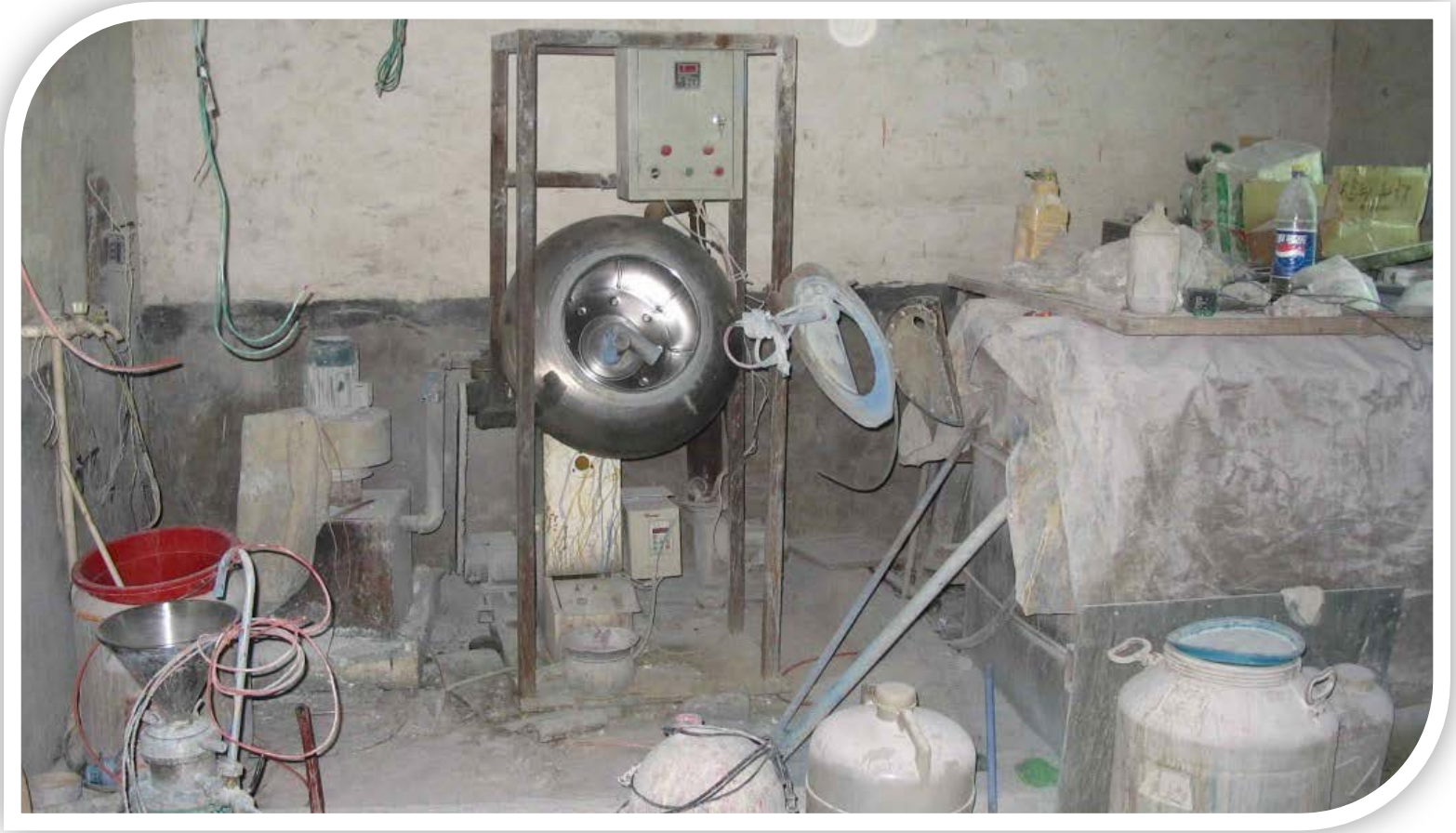
Counterfeit Manufacturer

Counterfeited Viagra Manufactured in Asia Pacific

(http://www.pbs.org/wgbh/nova/next/body/uncovering-counterfeit-medicines/)

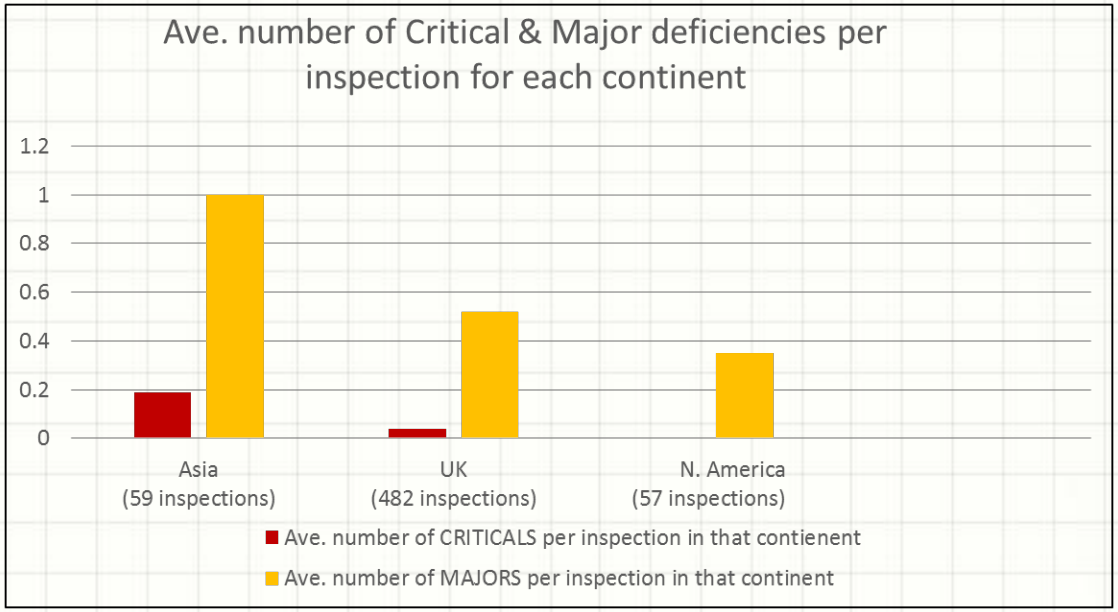
Manufacturer of Counterfeit Viagra tablets

(http://www.pbs.org/wgbh/nova/next/body/uncovering-counterfeit-medicines/)



Higher Proportion of Critical & Major GMP Deficiencies found in Asia

The relative number of Critical & Major GMP deficiencies raised per inspection by MHRA in 2014 was higher in Asia than other continents where MHRA inspections were carried out.

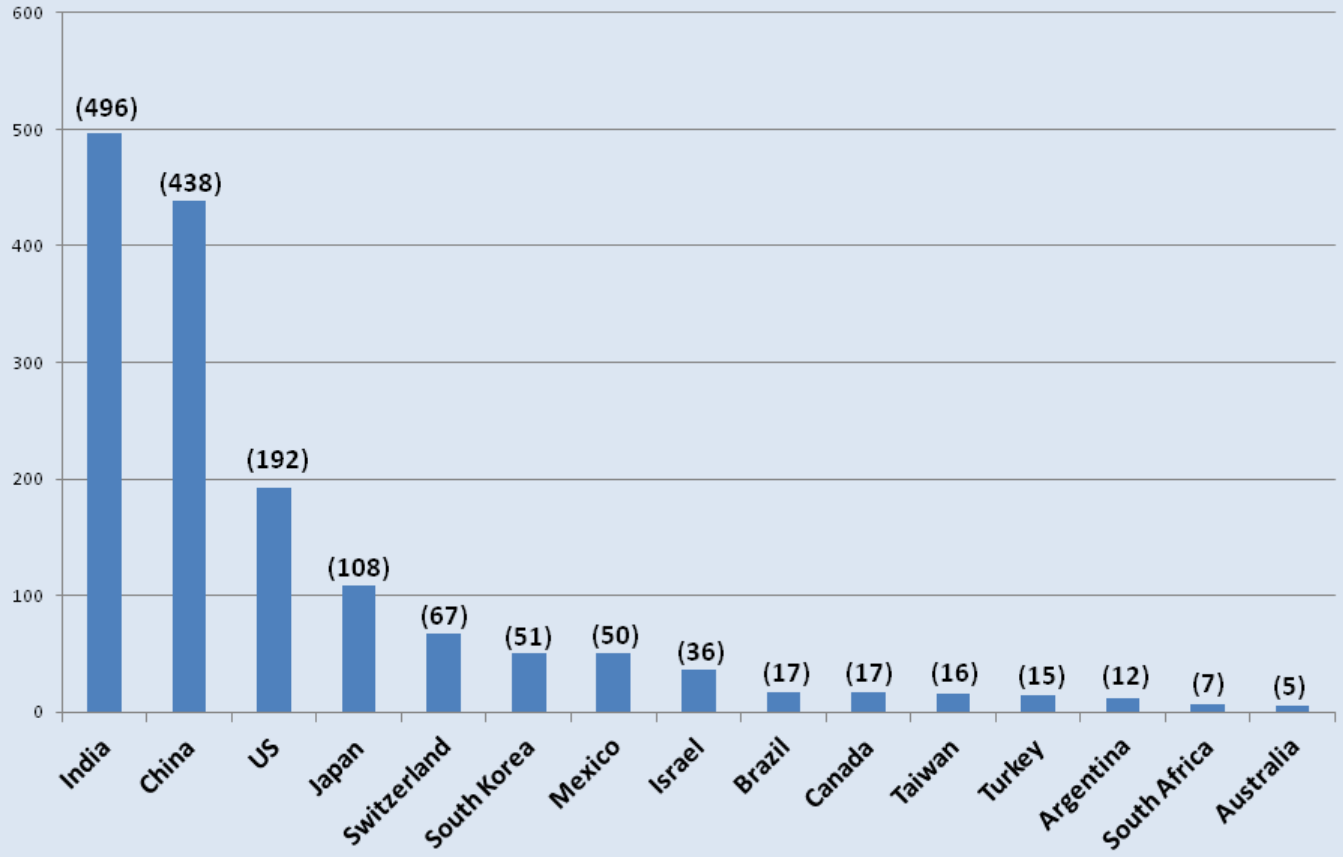


Source: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con464241.pdf

China – Getting Serious

Top 15 Countries Supplying API to EU by Number of Plants

(Source: Dr Gerald Heddell, Director of Inspection & Enforcement, MHRA, UK)



API Manufacture in India and China

- Most APIs in the global supply chain originate from India and China.
- History of poor GMP compliance at many sites.
- Europe now requires APIs entering Europe to be accompanied by a “written confirmation” of compliance to Q7 GMP requirements from the regulatory authority of country of origin*.

(under EU “Falsified Medicines Directive” 2011/62/EU - http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm)

* Switzerland, Australia, Japan, USA, Israel & Brazil are exempted from “written confirmation”.

Influence of PIC/S* in Asia Pacific

- Currently, the biggest GMP change in Asia Pacific is the growing influence of PIC/S.
- Of the 24 countries in Asia Pacific, 19 countries are being influenced in some way by PIC/S.
- Only Asia Pacific counties not yet influenced by PIC/S are:
  - Pakistan
  - Sri Lanka
  - Bangladesh
  - Nepal
  - Papua New Guinea

* Pharmaceutical Inspection Cooperation Scheme

Summary of PIC/S Influence in Asia Pacific

Asia Pacific Regulatory Authorities Regulatory authorities of:			
Current PIC/S Members **(at 1 August 2016)**		**Interested in joining PIC/S**	**Using the PIC/S GMP Guide**
Australia	*From January 1993*	P.R. China	Cambodia
Singapore	*From January 2000*	India	Laos
Malaysia	*From January 2002*	Bhutan	Myanmar
Indonesia	*From July 2012*	Brunei	
New Zealand	*From January 2013*	Vietnam	
Chinese Taipei	*From January 2013*	Philippines	
Japan	*From July 2014*		
South Korea	*From July 2014*		
Hong Kong	*From January 2016*		
Thailand	*From August 2016*		

PIC/S – Main Features

- Commenced operating in November 1995.
  - Previously existed as “PIC” (Pharmaceutical Inspection Convention) from 1971 as a legal treaty between 10 countries.
- Is an informal “Cooperative Arrangement” **between GMP regulatory authorities**; i.e. **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.
- PIC/S meetings & seminars are **not** open to industry.

www.picscheme.org

US FDA Commissioner, Dr. Margaret Hamburg, delivered a key-note address to the PIC/S 40th Anniversary Symposium (Geneva, 31 May, 2011).

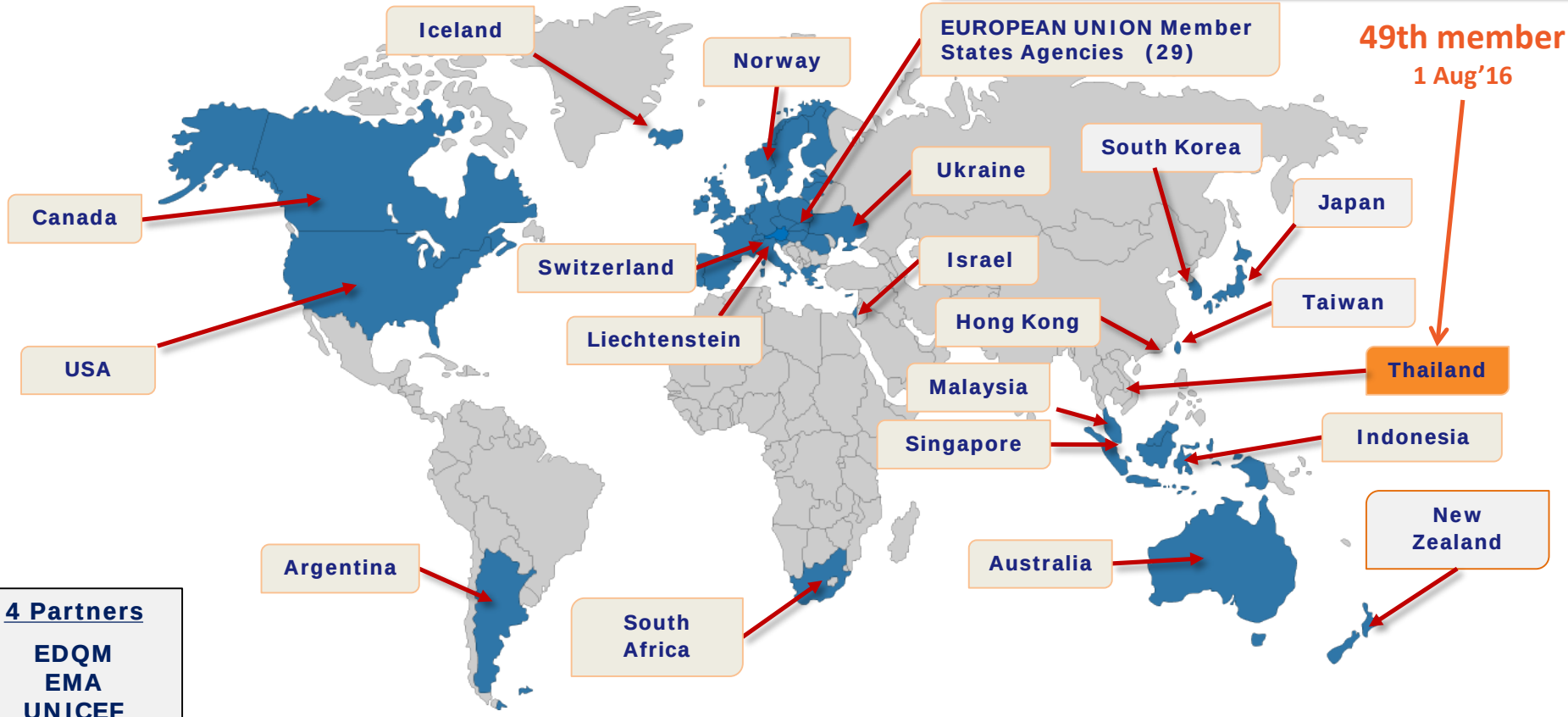
She said that **"PIC/S' main advantage over a Mutual Recognition Agreement is that it is not legally binding, thus allowing Participating Authorities to co-operate and share information informally while keeping complete control over imported medicinal products".**

49 PIC/S member authorities

(1 January 2017)

EUROPEAN UNION Member States Agencies (29)

Austria	Belgium	Croatia	Czech Rep(H&V)	Cyprus (H)
Denmark	Estonia	Finland	France (H&V)	Germany
Greece	Hungary (H)	Ireland	Italy	Latvia
Lithuania	Malta	Netherlands	Poland	Portugal
Romania	Slovak Rep.	Slovenia	Spain	Sweden
UK (H&V)				



4 Partners

EDQM
EMA
UNICEF
WHO

Candidates for PIC/S Membership

(at 1 January 2017)

Applicants
(Up to 6 years)

- Italy (vet)❶
- Brazil❷
- Mexico❷
- Turkey❷
- Iran❷

- ❶ *on-site visit due in 2017*
- ❷ *on-site visit done*

Pre–Applicants
(gap analysis by PIC/S)

- Belarus
- Kazakhstan

Interested

- Bulgaria
- Hungary (vet)
- Russia
- Nigeria
- China (CFDA)
- India (CDSCO)
- Saudi Arabia
- Vietnam
- Philippines
- Armenia

Note

Colour coding for different regions

Americas Asia
Europe
Africa

PIC/S GMP Guide

- PIC/S GMP Guide to GMP for Medicinal Products
  (PIC/S document PE 009-13, 1 January 2017).

- Similar to the EC GMP Guide:

  Main differences:
  - The term “authorised person” used instead of “Qualified Person” (QP).
  - No Annex 16 (QP) or Annex 18 (old API Annex) in PIC/S GMP Guide.

- Divided into 3 parts
  - Part I: PIC/S GMP Guide (general provisions).
  - Part II: GMP Guide for APIs (identical to ICH Q7).
  - Annexes 1 to 20.

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

Legal GMP requirements in different PIC/S member Agencies

PIC/S GMP Guide (11 Agencies)	EU GMP Guide (33 Agencies)	Canada GMP Guidelines	US FDA GMP Regulations	Korean GMP Standards	Japan GMP Guidelines
Argentina Australia Hong Kong Indonesia Malaysia New Zealand Singapore South Africa Taiwan Thailand Ukraine	28 EU Agencies Israel Iceland Liechtenstein Norway Switzerland	Canada	USA	South Korea	Japan

PIC/S Working Groups

(an indication of the future directions of PIC/S)

- EMA-PIC/S Joint drafting Group on revision of Annex 1 *(EMA = Chair)*
- Harmonisation of Classification of GMP Deficiencies *(TGA = Chair)*
- Advanced Therapy Medicinal Products *(ATMPs)*
- Steering Committee for the PIC/S Inspectors' Academy *(PIA)* *(HSA = Chair)*
- Unique Facility Identifiers (UFI). *(US FDA = Chair)*
- Controlling Cross-contamination in Shared Facilities

PIC/S Working Groups

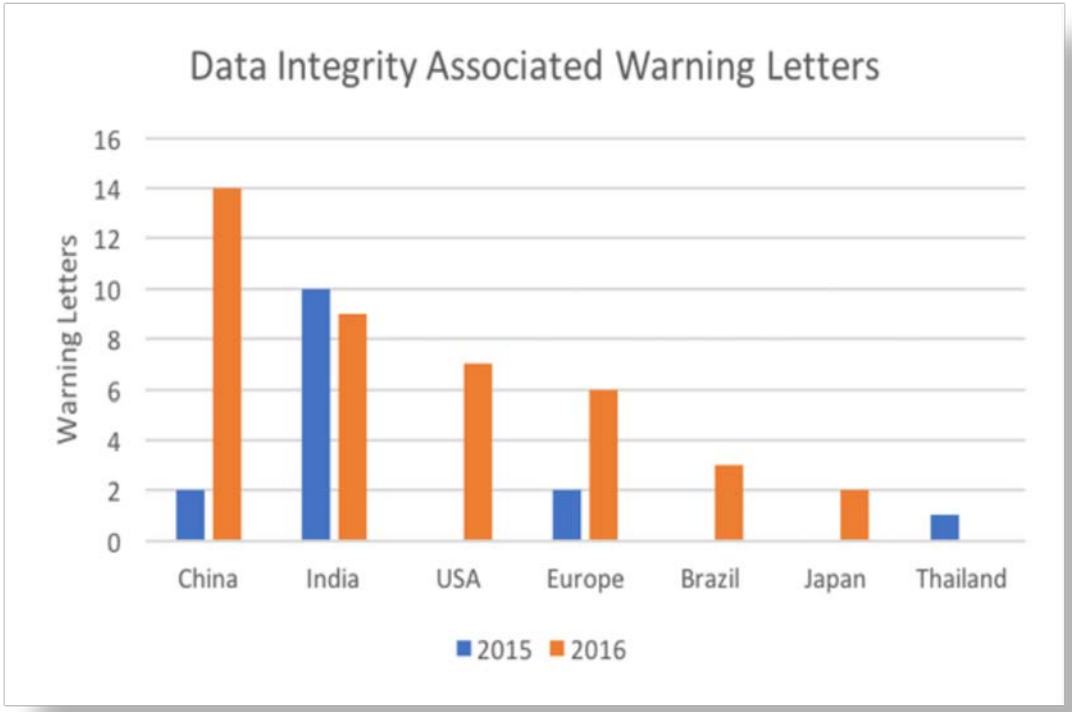
(an indication of the future directions of PIC/S)

- Revision of PIC/S Recommendations guideline on Validation.
- Good Clinical Practices *(GCP)* & Good Pharmacovigilance Practices *(GVP)*
- Q&A for APIs.
- Inspector Travel Safety.
- Strategic development (share lists of planned foreign inspections & promotion of joint inspections. Aim is to avoid duplicate inspections).
- Data Integrity – Inspectorate guidance *(TGA & MHRA = joint Chairs)*
- Strengthen cooperation with ICMRA.

“Data Integrity”
A hot topic for PIC/S Inspectorates

- Since mid-2013, data integrity has become a major focus of attention by all PIC/S Inspectorates.
- For example, many China & India manufacturers have received warning letters from US FDA because of serious data integrity breaches. Supply of products to USA halted.
- Similar experiences by MHRA, TGA, ANMS, etc. in various parts of the world, including Europe, USA & Asia.
- PIC/S Inspectorates now receive training on data integrity breaches & share experiences.
- MHRA has issued a *“Data Integrity Definitions & Guidance for Industry”* in January 2015 (updated in March 2015).
- PIC/S has issued a draft guidance on *“Good Practices for Data Management in Regulated GMP/GDP Environments”* (August 2016), as a guidance for inspectors.

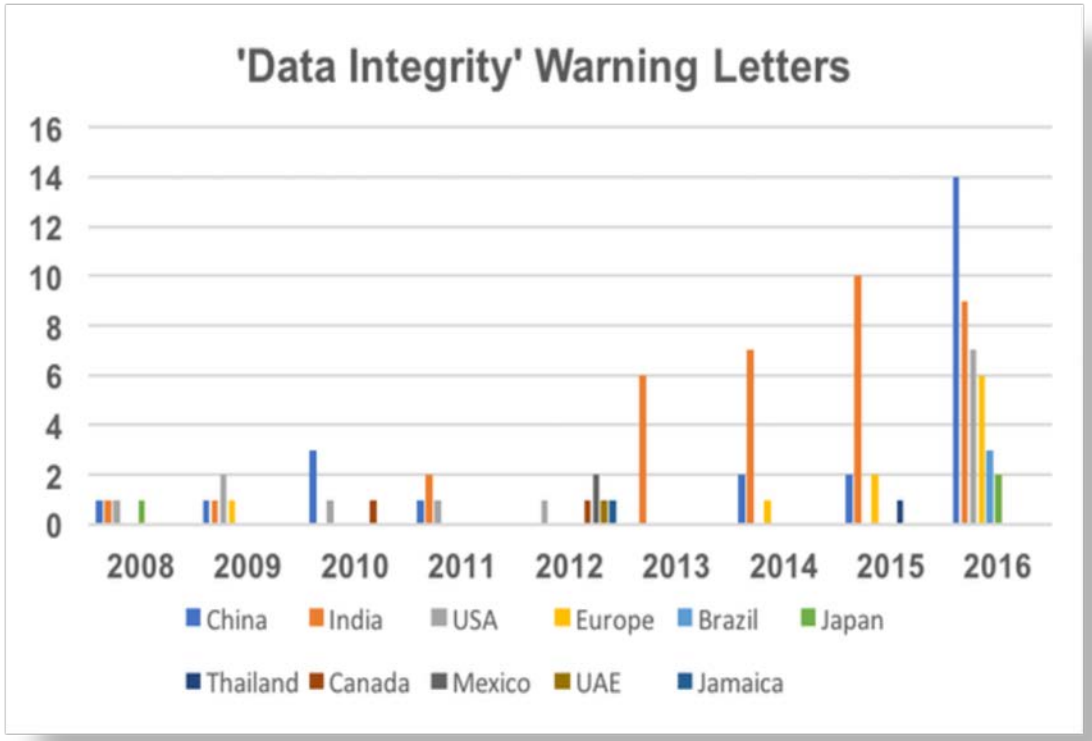
FDA Warning Letters – Data Integrity (2105 & 2016)



Comments

- USA 3rd on list in 2016
- 2 Japanese companies in 2016

FDA Warning Letters – Data Integrity (2008 to 2016)



Analysis

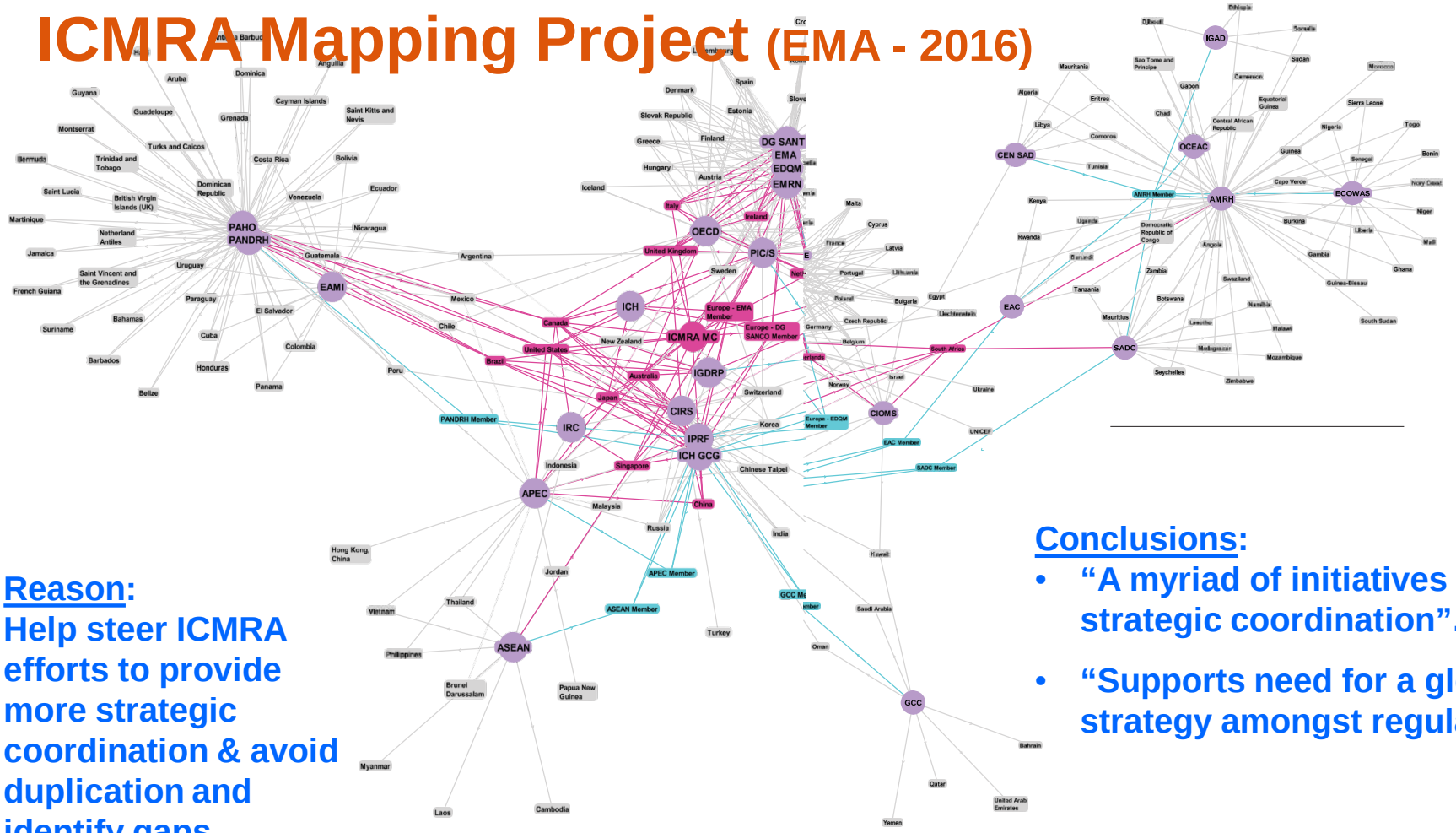
- Significant increases for China, Europe & USA in 2016.
- Slight decrease for India in 2016. Does this indicate a proactive industry?
- Should industry be running Data Integrity Seminars in China?

ICMRA – Main Features

(International Coalition of Medicines Regulatory Agencies)

- Formed in December 2013.
- First regulatory coalition at **agency head level.**
  - **Heads of Agency of 29 regulatory authorities + WHO & European Commission.**
- Provides strategic, high-level advocacy and leadership.
- Leverages existing efforts to maximise global impact.
- Initial priorities:
  - Better information sharing mechanisms between regulators
  - GMP inspection work sharing
  - Generic medicines convergence and work-sharing
  - Capacity building of emerging regulators
- **My Opinion:** Is the best entity to drive/coordinate regulatory convergence activities.

ICMRA Mapping Project (EMA - 2016)



Reason:
Help steer ICMRA efforts to provide more strategic coordination & avoid duplication and identify gaps.

Conclusions:

- **"A myriad of initiatives but no strategic coordination".**
- **"Supports need for a global strategy amongst regulators".**

http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2016/10/WC500214180.pdf

ICMRA – Current Initiatives

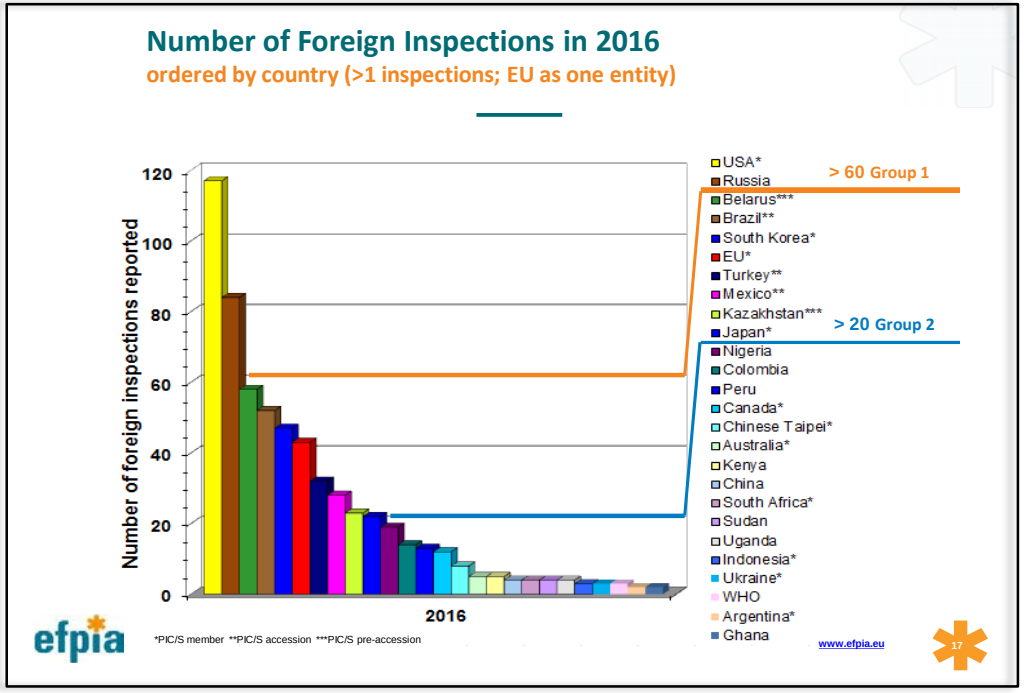
(www.icmra.info)

- Various work streams, including:
  - **GMP harmonisation**
  - Supply chain integrity
  - Pharmacovigilance
  - Crisis management
- ICMRA work stream on **GMP harmonisation** *(actioned by PIC/S)*.
  - Reliance on information in inspection reports of other countries for "same scope" inspections (i.e. desk top assessments) with the goal of **reducing duplication of inspections globally**.
  - Unique Facility Identifier (UFI).
- Good communication between ICMRA and PIC/S (*PIC/S delegate at ICMRA*).
- Limited information available publicly (*at present*).
- **My Opinion:** Industry needs to encourage & support ICMRA's efforts to lead regulatory convergence internationally, & advocate future work topics.

The Need for Better Work Sharing by Inspectorates

2016 GMP Inspection Data *(EFPIA member survey)*

Number of Foreign Inspections in 2016 undertaken by different regulatory authorities



Survey Outcome – 2016

- Most active inspectorates are Russia, US FDA, Belarus, Brazil, South Korea & EU.
- Fewer foreign inspections by EU, EU, China, Kenya & Uganda (from (from previous years).
- Increased involvement by Russia Russia & Belarus (from previous years).

Source: www.efpia.eu

Progress on MRA Between EU & USA

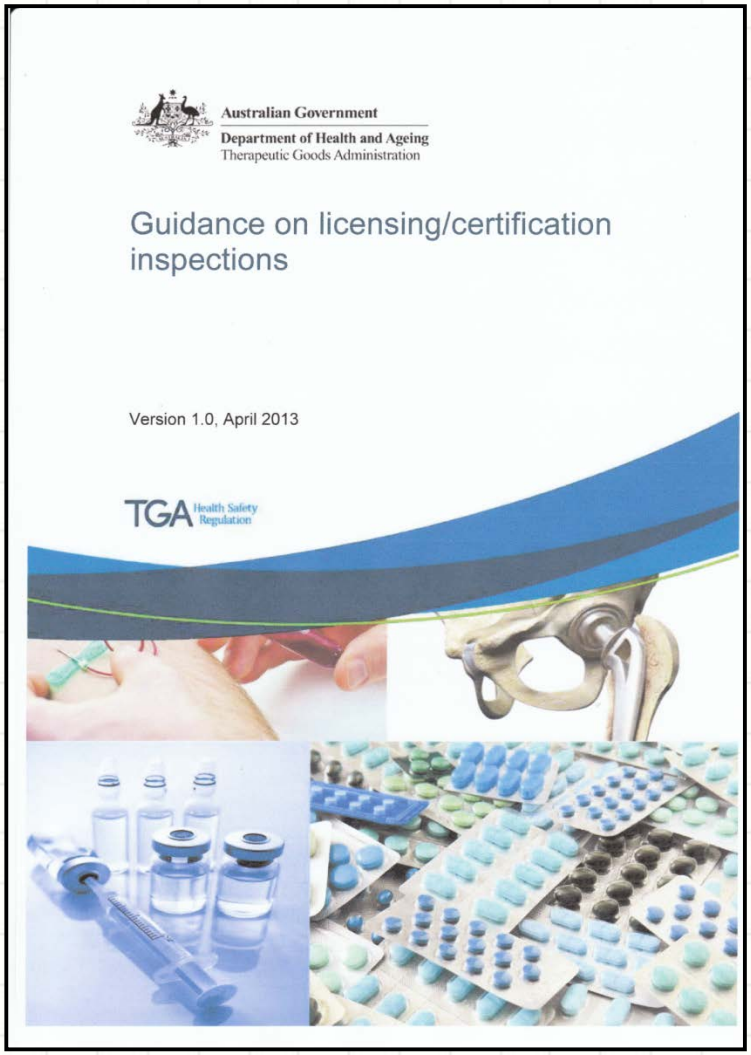
- Assessment of FDA completed by EU on 1 July'17. Assessment of 8 EU member states by FDA already commenced.
- Partial implementation of the MRA from 1 Nov'17, provided FDA completes assessments of at least 8 EU member states.
- Transitional phase of MRA from 1/11/17 to 15/7/19 when all other EU member states must be assessed by USA (JAP assessments done by EU, with FDA observing) .
- Imported batch testing of US medicines entering EU will not cease until all 28 EU member states are recognised by USA.
- Products included in MRA:
  - **Finished pharmaceuticals (human use), APIs, intermediates, medical gases, radiopharmaceuticals, herbals & homeopathic products**
- Products excluded or pending consideration:
  - **Human blood/plasma, human tissues/organs, veterinary immunologicals.**
  - **Veterinary products (decision by 1/7/19); vaccines for human use & plasma derived medicines (decision by 15/7/22)**

Australia

- Population: 24 million
- Land mass is same size as USA.
- Central “Federal” government in Canberra
- 6 State governments
- Regulator is “TGA” (Therapeutic Goods Administration)

TGA Australia - Recent Developments

- "ANZTPA" project abandoned *("Australia New Zealand Therapeutic Products Agency")*
  - Instead, an MRA on GMP inspections to be developed (between Australia & NZ).
- Guidance document on "Release for Supply" (January 2015).
  - Describes requirements & responsibilities of the "Authorised Person".
  - Includes a requirement for medicines entering Australia to be "released for supply" in Australia (already applies in NZ).
- Guidance document on "Licensing/certification inspections"(Apr'13)
  - Provides detailed description of TGA's inspection and licencing procedures for medicine manufacturers, including examples of GMP deficiencies (critical, major, minor).
  - TGA now uses the term "inspection" rather than "audit".
- TGA to adopt latest version of PIC/S GMP Guide (v13 Jan'17) later this year.
  - Current legal GMP requirement is v8 of Jan'09 (8 years out of date).



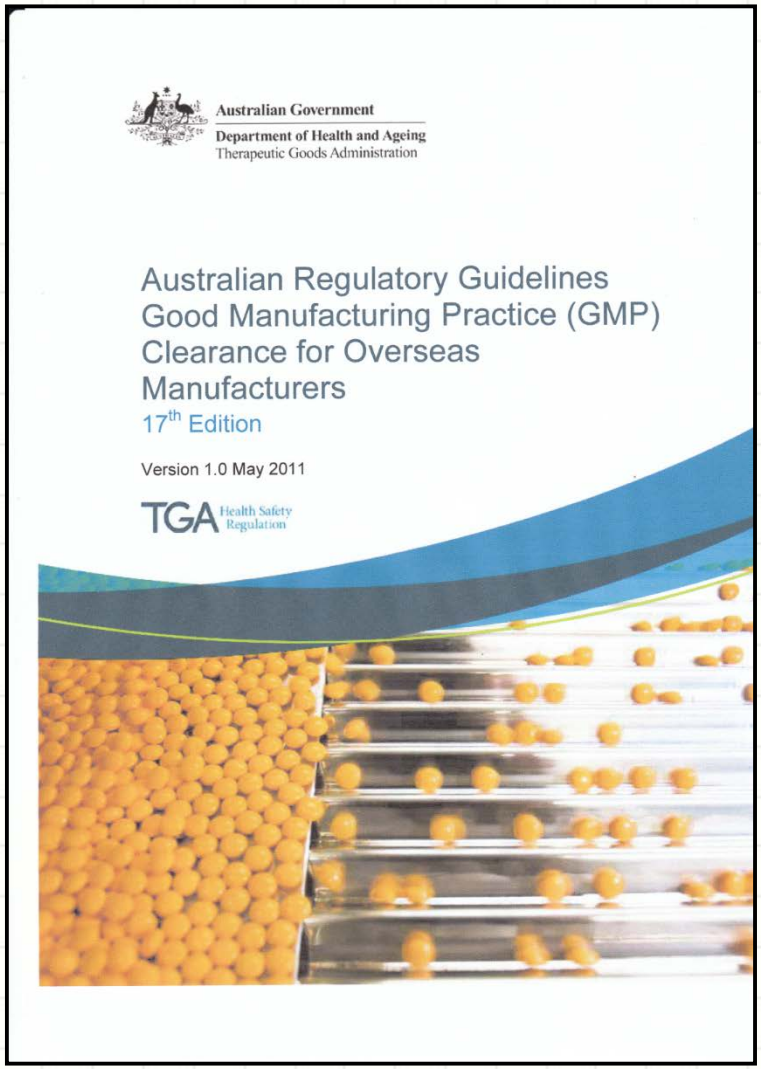
Available from:
www.tga.gov.au

TGA's GMP Controls for Imported Medicines

Medicines cannot be imported into Australia until evidence of GMP compliance is provided and a "GMP Clearance" is issued by the TGA.

Three types of evidence accepted:

1. A GMP inspection by an MRA regulator (EU, Canada, Singapore) in their own country. Always accepted.
2. A GMP inspection by:
   - an MRA regulator in third countries, or
   - an MOU or PIC/S regulator in their own or third countries, e.g. US-FDA & NZ. These are formal arrangements, but with option not to accept. Additional information may be required depending on product risk.
3. TGA inspection (full cost recovery, including inspection fee and travel costs).



Available from:
www.tga.gov.au

TGA web site (www.tga.gov.au)

GMP related information includes:

- Various Guidance documents.
- Report of the “Review of Medicines and Medical Device Regulation”.
- An overview of the TGA inspection/certification processes, including close-out procedure for on-site inspections.
- TGA’s risk-based approach to inspection frequency.
- Q & A on GMP requirements.
- Procedure for lodging complaints/disputes about TGA inspections and/or inspectors.
- List of licensed Australian manufacturers of therapeutic goods.

ASEAN: Association of Southeast Asian Nations

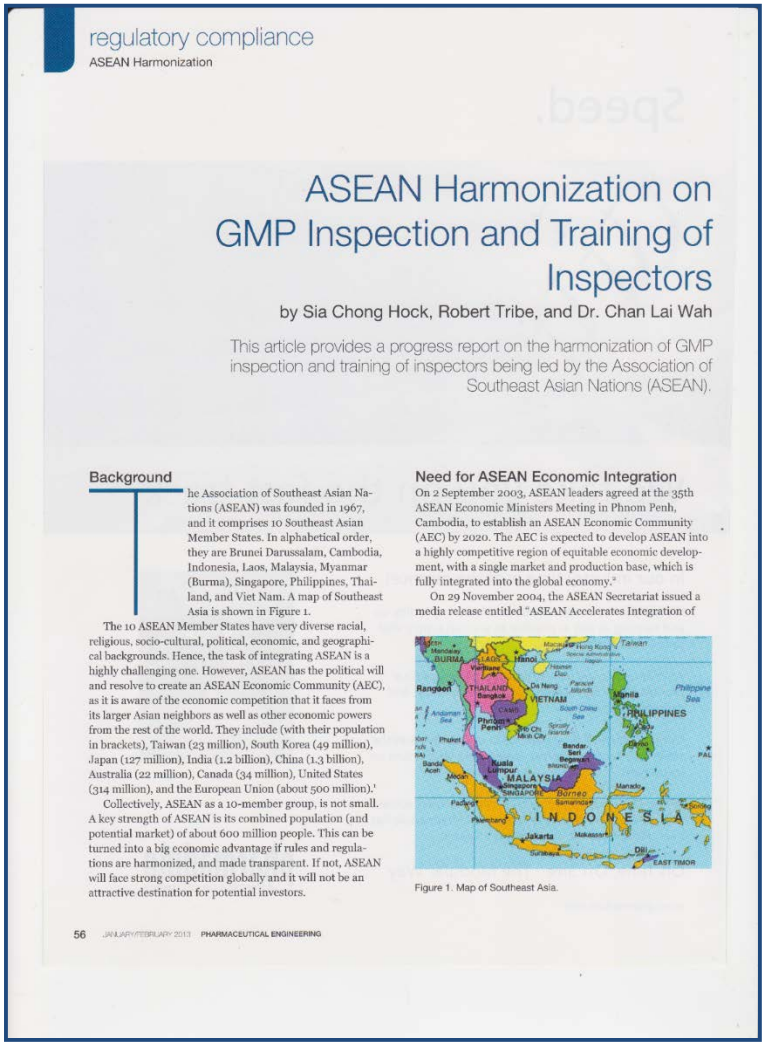
- Founded in 1967.
- Comprises 10 countries of South East Asia.
- Combined population of 650 million people.
- Will become 5th largest world economy by 2020.

ASEAN Harmonization

- **ASEAN Economic Community (AEC)** established in 2015, with harmonised regulations in place.
- An ASEAN Sectoral MRA on GMP inspection was signed in 2009.
  - Obliges each member country to have a PIC/S-equivalent GMP inspection framework.
  - Obliges non-PIC/S ASEAN countries to migrate towards adopting PIC/S GMP Guide & inspection framework.
  - Covers medicinal products only *(the MRA presently excludes APIs, biologicals & herbals).*
- ASEAN is collaborating with PIC/S, ISPE & other parties to assist with training & developing equivalency.
- Only Singapore, Malaysia, Indonesia & Thailand are PIC/S members.
- Those countries listed as ***"ASEAN accepted inspection services":***
  - Singapore, Malaysia, Indonesia & Thailand (through their PIC/S membership).
- FDA Philippines currently being assessed as an *"ASEAN accepted inspection service".*

Benefits of ASEAN MRA on GMP

- Avoids duplication of GMP inspections within ASEAN.
- Savings of time, resources & costs for regulators & industry.
- Facilitates trade in medicinal products across ASEAN.
- Quicker access to medicines by patients within ASEAN.
- Increased competitiveness of ASEAN countries.
  (viz-a-viz India, China & other large industrialized countries)



regulatory compliance
ASEAN Harmonization

ASEAN Harmonization on GMP Inspection and Training of Inspectors

by Sia Chong Hock, Robert Tribe, and Dr. Chan Lai Wah

This article provides a progress report on the harmonization of GMP inspection and training of inspectors being led by the Association of Southeast Asian Nations (ASEAN).

Background

The Association of Southeast Asian Nations (ASEAN) was founded in 1967, and it comprises 10 Southeast Asian Member States. In alphabetical order, they are Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar (Burma), Singapore, Philippines, Thailand, and Viet Nam. A map of Southeast Asia is shown in Figure 1.

The 10 ASEAN Member States have very diverse racial, religious, socio-cultural, political, economic, and geographical backgrounds. Hence, the task of integrating ASEAN is a highly challenging one. However, ASEAN has the political will and resolve to create an ASEAN Economic Community (AEC), as it is aware of the economic competition that it faces from its larger Asian neighbors as well as other economic powers from the rest of the world. They include (with their population in brackets), Taiwan (23 million), South Korea (49 million), Japan (127 million), India (1.2 billion), China (1.3 billion), Australia (22 million), Canada (34 million), United States (314 million), and the European Union (about 500 million).[1]

Collectively, ASEAN as a 10-member group, is not small. A key strength of ASEAN is its combined population (and potential market) of about 600 million people. This can be turned into a big economic advantage if rules and regulations are harmonized, and made transparent. If not, ASEAN will face strong competition globally and it will not be an attractive destination for potential investors.

Need for ASEAN Economic Integration

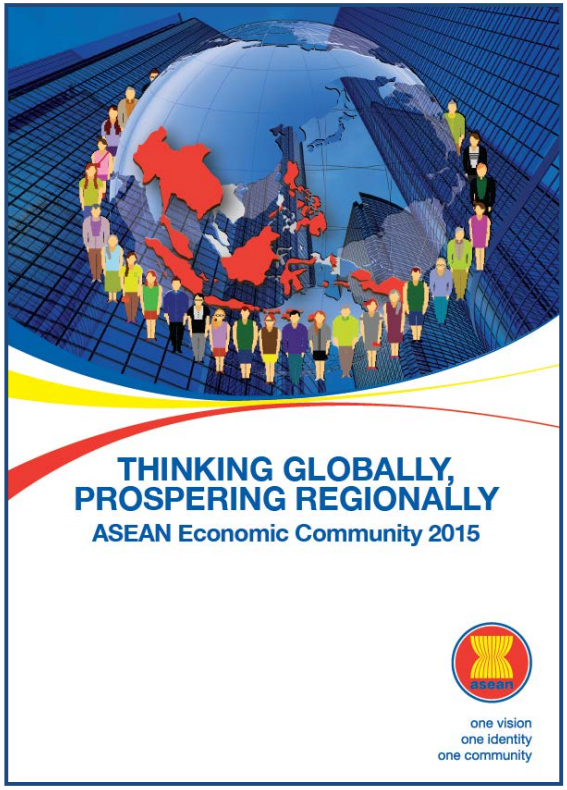
On 2 September 2003, ASEAN leaders agreed at the 35th ASEAN Economic Ministers Meeting in Phnom Penh, Cambodia, to establish an ASEAN Economic Community (AEC) by 2020. The AEC is expected to develop ASEAN into a highly competitive region of equitable economic development, with a single market and production base, which is fully integrated into the global economy.[2]

On 29 November 2004, the ASEAN Secretariat issued a media release entitled "ASEAN Accelerates Integration of

Figure 1. Map of Southeast Asia.

Further information:

"ASEAN Harmonization on GMP Inspection and Training of Inspectors". *Pharmaceutical Engineering, Jan/Feb 2013 2013: 56-62, Sia Chong Hock, Robert Tribe, Dr. Chan Lai Wah*



India

- Population: 1.2 billion
- World's largest democracy.
- 29 State governments
- Regulator is "CDSCO" (Central Drugs Standard Control Organization)

GMP Regulatory Controls - India

- GMP requirements ("Schedule M") issued by CDSCO (Central Drugs Standard Control Organization).
  - "Schedule M" modelled on WHO GMP, but not equivalent to WHO or PIC/S GMPs.
  - "Schedule M" can be found at: http://cdsco.nic.in/html/GMP/ScheduleM(GMP).pdf
- Responsibility for GMP is divided between Central and State governments (some joint inspections of "high risk drugs" undertaken):

Central government (CDSCO)	State governments
Laying down standards for drugs.	Inspect & license drug manufacturers.
Issue market authorization new drugs.	Pre & post licensing inspections.
Regulate imported drugs, including some overseas inspections.	Inspect & license drug testing laboratories.
License manufacturers of "high risk drugs" such as LVPs, vaccines, sera.	Coordinate drug recalls.
Testing of drugs by Central Drugs Laboratories	Investigation & prosecution of breaches of legal provisions.

Issues Specific to India

- Lack of patent protection.
- 40% of OTC & generic prescription medicines consumed in USA come from India. About 550 sites approved by US FDA.
- US FDA investigators are currently blitzing Indian drug plants.
- Data integrity fraud is a major problem in India.
- Half of all US FDA warning letters in 2014 were for Indian drug manufacturers supplying USA.
- WHO has estimated that 1 in 5 drugs made in India are counterfeit or fake.
- Convictions of drug counterfeiters in India are extremely rare.

Sources: *Gardiner Harris, The New York Times, 14 February 2014.*
Vikas Danekar, The Gold Sheet, 30 January 2014.

China

- Population: 1.35 billion
- 22 Provinces
- 5 autonomous regions
- Regulator is “CFDA” (China Food & Drug Administration)

China – Getting Serious about GMP

- Director of SFDA (Zheng Xiaoyu) was **EXECUTED** in July 2007.
  - Accepted bribes in exchange for drug production licences.
  - Resulted in patient deaths from fake/substandard medicines.
- Powerful message to regulators & companies that corruption will not be tolerated.
- On the day after the execution:
  - A stricter approval process for new drugs introduced.
  - Drug approvals made by special panel (not one person).
  - Greater transparency (companies have access to approvals).
- Gradual introduction of other reforms to bring China's regulatory controls closer to international levels.
- Nationwide crackdowns on sale of fake & counterfeited medicines.

But Fraudulent Activities Re-emerging

- CFDA investigations in 2016 found 80% of data used in clinical trials of new drug products had been fabricated
- Fraudulent behaviour at all levels:
  - Adverse side effects hidden or deleted from records
  - Tampering of data that did not meet desired outcomes
  - Data fabrication
- 80% of current drug applications cancelled by CFDA in 2016

New China GMPs

- China Good Manufacturing Practice (2010 version)
  - Came into operation in March 2011.
  - Is a combination of PIC/S and WHO requirements.
- Five Annexes:
  - Annex 1: Sterile Medicinal Products
  - Annex 2: Active Substances Used as Starting Materials
  - Annex 3: Biological Products
  - Annex 4: Blood Products
  - Annex 5: Chinese Traditional Medicines
- The new China GMP & Annexes not yet equivalent to PIC/S, but currently work being done (draft Annexes) to bring closer to PIC/S.

Recent GMP Issues in China (1)

- New GMP Annexes (1 July 2014)
  - Prepared slices of Chinese Crude Drugs
  - Medicinal Gases
  - Sampling
- Draft GMP Annexes.
  - Qualification and Validation
  - Computerized systems
  - Risk Assessment Management
- Un-announced inspections in China (from 1 Sept'15).
  - To investigate complaints, product quality risks, spot checks, etc.
  - Inspection team to carry cameras, photocopiers & recording devices.

Recent GMP Issues in China (2)

- Aim of CFDA is to apply for PIC/S membership, starting with an application for a pre-accession audit (not known when this will be).
- Decentralization of GMP inspections.
  - From 2016, all GMP inspections within China are conducted by provincial FDA inspectors.
- GMP controls over APIs recently strengthened.
  - GMP compliant API manufacturers issued with a drug licence.
  - However, still limited controls over brokers.
- Foreign inspections commenced (from 2013).
  - Requires key documents, including SMF (in PIC/S format).
  - 49 foreign inspections in 2016.

Recent Contamination Scares in China

- Heparin (2008)
  - >230 deaths; >900 adverse reactions.
  - Heparin injection contaminated with the synthetic chemical “OCSC” (over sulphated chondroitin sulphate).
  - Intentional adulteration by some Chinese factories to save costs.
- Melamine (2008)
  - 6 deaths; 54,000 babies hospitalised.
  - Synthetic melamine added to milk powder to increase nitrogen content.
  - Sanlu Milk Products, China (own by Fonterra, NZ).
  - Helen Clark, then NZ Prime Minister pressed Beijing officials to total recall.
  - Top two company officials executed in late 2009 as punishment.
- Chromium in hard shell capsules (2012)
  - No deaths.
  - Empty hard shell gelatin capsules contaminated with high levels of chromium.

Chromium Contamination

(empty hard shell gelatin capsules)

WANG MIN / XINHUA

Huge piles of substandard leather scraps at the warehouse of Xueyang Gelatin and Glair Factory in Hengshui, Hebei province, were used to make gelatin that was sold to capsule makers.

China Daily (Beijing 18.4.12)

Companies pull tainted medicines

By CHEN XIN
chenxin@chinadaily.com.cn

Three pharmaceutical companies have recalled their chromium-contaminated drug capsules after authorities suspended sales of 13 types of problematic medicines.

Tonghua Yuson Pharmaceuticals in Northeast China's Jilin province said the company decided to recall all tainted products made since 2010.

"Pharmaceutical producers do not possess the capability to examine capsules, so we just simply checked the quality report provided by capsule suppliers and then let them go," an anonymous official with the company's product quality department was quoted as saying by stcn.com, a website run by Securities Times.

But the company said the producer of the problematic capsules was a Zhejiang-based company and was not among those exposed by media.

China Central Television revealed in an investigative program on Sunday that nine pharmaceutical companies after an investigative TV program on Sunday claimed that capsules for 13 types of medicine were made by illegal industrial gelatin that contained an excess amount of chromium.

A netizen posted an entry on Sina Weibo with photos, teaching netizens how to take medicine without eating the capsule. "First, get hot and soft steamed bread," it said. "Steamed stuffed buns and sponge cakes are also OK. Then pull a piece from it, press it flat, and fill it with the medical particles from the capsule. After that, make it into a round ball suitable for swallowing. After that, you can take it safely."

But doctors warned patients "not to take the risk".

"The coating on capsules

CCTV, but "those products were not problematic because they were produced in 2009 and they accorded with the standards set in related code released in 2000".

The Chinese Pharmacopoeia, amended in 2010, permits no more than 2 milligram of chromium per 1 kilogram of medicine. Before that, the cap was 5 mg per 1 kg for heavy metal, but it had no specific stipulation about chromium, said the announcement.

The company's products were found with 3.54 mg of chromium per 1 kg of medicine.

Dandong Tongyuan Pharmaceutical in Northeast China's Liaoning province also announced the recall of its chromium-contaminated products, according to China News Service.

Xiuzheng Pharmaceutical Group in Jilin said in a statement on its website that the company has suspended sales of the problematic products but said "the capsule suppliers we pick are quality firms that meet all the country's standards and we are re-examining those

DOCTORS WARN AGAINST OPENING CAPSULES

Fearing chromium-contaminated capsules, some patients have begun to explore new ways to take medicine — and not always beneficial ways.

On Monday morning, a 60-year-old woman in Hangzhou, Zhejiang province, rushed to hospital after she removed the coating of three capsules and swallowed the medicinal powder directly. She later felt extreme pain in her throat.

"I caught a cold recently and have to take many medicines, but most of them are capsule medicines," the woman, surnamed Huang, told Hangzhou-based newspaper City Express.

A doctor said Huang's esophagus was burned by the powder. "I worried that medicine cap-

Industrial gelatin widely used in drugs

Panic grows over capsule scandal

Global Times (Beijing 18.4.12)

By Liu Meng

Analysts warned yesterday that ineffective supervision and inadequate production of edible gelatin left room for manufacturers to use industrial gelatin in medical capsules, as exposed in the latest public scandal.

The Hebei Xueyang Glair and Gelatin Factory in Fucheng county, Hebei Province, had been selling its industrial gelatin to capsule producers in Zhejiang Province and in the cities of Beijing, Changzhou and Xiamen, the Xinhua News Agency reported, citing investigators.

The company's head has been detained for trying to destroy evidence. The firm was exposed for having used scraps of leather to produce gelatin.

Graphics: GT

The probe was launched after the State Food and Drug Administration (SFDA) issued an emergency notice Sunday halting the sale and consumption of 13 drugs packed in capsules confirmed to contain excessive levels of chromium.

A press officer with the Beijing Drug Administration told the Global Times that they had found four of the 13 drugs on sale in Beijing but these had been taken off the shelves.

2
Poor
See also
Page 12

Media reports

Global Times, Beijing, 18.4.12

China Daily, Beijing, 18.4.12

Chromium Contamination
(empty hard shell gelatin capsules)

- Involved high levels of chromium contamination in empty hard shell gelatin capsules.

Cause:

- A gelatin factory in Hebei Province in China used leather scraps (including discarded shoes) to make gelatin.
- This industrial-grade gelatin sold to capsule manufacturers throughout China *(medical-grade gelatin is made from animal bones).*
- Many drug recalls in China.
- The Managing Director of the factory detained by police as he was suspected of setting fire to his factory to eliminate evidence.
- Gelatin & gelatin capsules added to SFDA list of 28 high risk excipients.

Messages:

- Audit your suppliers of empty gelatin capsules (*if imported from China*).
- Carry out QC testing on empty gelatin capsules & include a test for chromium.

Outlook for the Future

By 2027 (10 years from now)

- Asia Pacific will be the main supplier of APIs and medicines to the rest of the world.
- PIC/S will have at least 60 member authorities:
  - Including Russia, China, Brazil, Turkey, Saudi Arabia, Philippines.
  - India will struggle to join PIC/S (because of lack of patent protection & lack of uniform national approach to regulating medicine manufacturers).
- Less foreign inspections for medicine manufacturers because of:
  - The MRA between EU and USA.
  - An increase in work sharing amongst PIC/S member Inspectorates.
- Improved regulatory convergence through the efforts of ICMRA (less duplication/overlap of regulatory requirements for medicines).

Thank you

Questions?

Ministry for Primary Industries
Manatū Ahu Matua

Manufacturing Workshop

Guidance for the Chemistry and Manufacture of Veterinary Medicines

Agricultural Compounds and Veterinary Medicines

Awilda Baoumgren

www.mpi.govt.nz

Chemistry and Manufacture of Veterinary Medicines

1. Overview of current VM Chemistry and Manufacturing Requirements

2. Information Requirements Review

3. Restructure to Chemistry and Manufacturing Guidance

4. Overview of Guidance Content

VM Registration Standard and Guideline

- Current Requirements: *ACVM Registration Standard and Guideline for the Chemistry of Veterinary Medicines*

- Outlines information and data required to register a veterinary medicine TNP
  - Establishing the formulation
  - Active and excipient ingredients
  - Manufacturing processes and manufacturers
  - Product and packaging specifications
  - Stability

VM Registration Standard and Guideline

- Current Requirements: *ACVM Registration Standard and Guideline for the Chemistry of Veterinary Medicines*
  - Out of date: 10+ years old
  - Minimal detail in all sections
  - No information or guidance on varying existing registrations
  - No information specific to immunobiological products
  - No information on distribution or post-registration product management

VM Registration Standard and Guideline

- Current Requirements: *ACVM Registration Standard and Guideline for the Chemistry of Veterinary Medicines*
  - International and domestic risks have changed
  - Current standard does not reflect ACVM Expectations
  - As documents become more outdated, requested information and assessments become more variable
- **C+M guidance material needed review and update**

Review of the Veterinary Medicine Chemistry and Manufacturing Information Requirements

- Used existing NZ Standard and Guideline as a baseline
  - Reviewed current assessment criteria vs. current Standard content

- Reviewed and compared requirements in the EU, Australia, U.S. and Canada
  - What information required and how it is presented
  - Other guidance

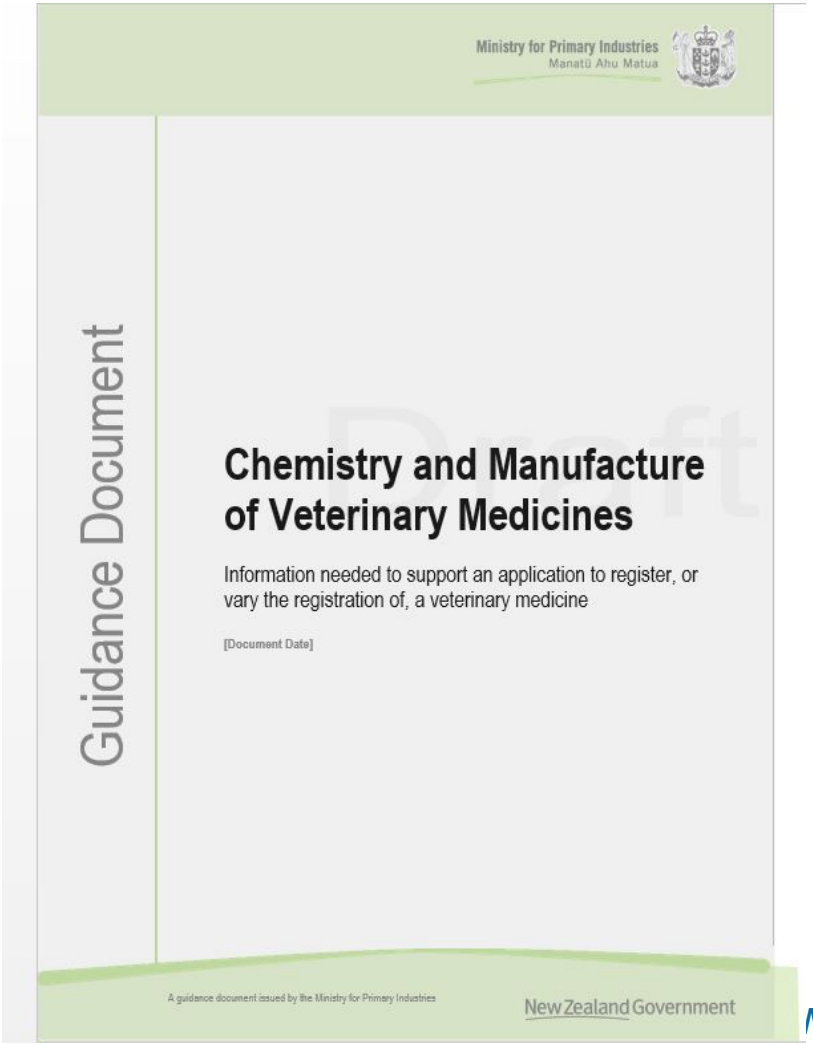
Review of the Veterinary Medicine Chemistry and Manufacturing Information Requirements

- Need to align manufacturing information expectations with GMP requirements
- Define ongoing registrant responsibilities
- ACVM Changes
  - Change in how information requirements are structured
  - Shifting from “standard and guideline” to “guideline”
    - Old: list of information to be provided
    - New: risk management aspects to be covered

Chemistry and Manufacture of Veterinary Medicines

- **Emphasis on risk assessment and risk management rather than ticking boxes**
- More detail
- First draft currently in consultation

Guidance Document: Chemistry and Manufacture of Veterinary Medicines



Chemistry and Manufacture of Veterinary Medicines

- Guidance now split into four main sections
  - Registration of a new TNP
  - Variations to a registered TNP
  - Registration of a new immunobiological TNP
  - Variations to a registered immunobiological TNP
- Expanded definitions and abbreviations section
- Revised guidance on product type, formulation type, and expected formulated product specifications

C & M Guidelines: New Registrations

- Formulated product description
- Starting Materials
- Formulation of the product
- Finished product specifications
- Formulated product batch analyses
- Product packaging
- Formulated product stability
- Final release for sale
- Product distribution
- Post-registration monitoring

C & M Guidelines: New Registrations

- Formulated product description
  - Product development information
  - If the product needs further alteration (e.g. reconstitution), this must be detailed
  - Pharmcodynamic, pharmacokinetic, and physico-chemical properties affecting RP
- Starting Materials
  - Active ingredients: multiple manufacturers
  - Raw material specification for AIs
  - Excipients and their role in the formulation and RP
  - Critical components

C & M Guidelines: New Registrations

- Formulation of the product
  - Justification of overages with respect to RP of the product
  - FP Manufacturers: release for supply entities
  - Manufacturing Process
    - Site-specific processes
    - More emphasis on critical process parameters
    - Justifying batch sizes
  - More detail on expectations around process validation
  - Post-production storage procedures must be identified

C & M Guidelines: New Registrations

- Finished product specifications
  - More emphasis on justification of the specifications
  - Specify QC labs performing each test
  - Updated appendix outlining expected parameters

- Formulated product batch analyses
  - Specific requirement to report all results including NC
  - Stated requirement for multiple analyses if needed for AI equivalence

C & M Guidelines: New Registrations

- Product packaging
  - Identification of current NZ-marketed pack sizes as part of the approval
  - Identification of attachments and devices, and discussion relative to RP
  - Guidance on gaining approval to use recycled packaging

- Formulated product stability: Unbroached
  - More defined detail around expectations
  - Justification needed for specifications and shelf life
  - Ongoing stability expected

C & M Guidelines: New Registrations

- Formulated product stability: In-Use
  - Specific requirement for in-feed and in-water stability
  - Requirement for in-use stability for ALL multi-dose products
  - Ongoing stability expected

- Final release for sale
  - Specific stated requirement for the release for sale process to be provided in the dossier
  - Must be the process conducted by the release for supply entity
  - Further detail to be determined after consultation

C & M Guidelines: New Registrations

- Product distribution
  - Guidance on providing information on storage and transportation of product after manufacture
    - Cold chain management
    - Other product-specific risk management

- Post-registration monitoring
  - Expectations of the registrant related to ongoing product management
    - Pharmacovigilance programme
    - Ongoing stability programme

C & M Guidelines: Variations

- General guidance for all variations
- Specific guidance and expectations for each variation application type
  - Formulation details (C1)
  - AI manufacturing (C2)
  - Excipient and critical component manufacturing (C2)
  - Formulated product manufacturers (C2)
  - Manufacturing processes and quality control (C2)
  - Finished product specifications (C3)
  - Product packaging (C3)
  - Stability/shelf life (C3)
  - Product distribution details

C & M Guidelines: Immunobiologicals

- New Registrations
  - Developed to provide guidance specific to immunobiologicals
  - Greater emphasis on starting materials and unique risk profile associated with AI development
  - Adjuvants will now be treated as critical components
  - Other aspects similar to guidance for other TNPs, with adjustments specific to immunobiological RP
- Variations
  - Similar to other TNP structure, adjusted for RP
- Some repetition – allows for ease of reference

Updated Annexes and Appendices

- New Appendix: Product Types
- Annex 1: Definition of formulation types
  - Now Appendix 2: Formulation types
- Annex 4: Recommended chemical and physical parameters for stability studies based on dosage form
  - Now Appendix 3: Expected specifications by product and formulation type

What's NOT in the new VM guidelines

- Two sections removed:
- Annex 2: Ingredient specifications for cited chemicals
- Annex 3: Shelf life exemptions (and appendix)

- **Must be risk assessed and addressed by the registrant and not defined by MPI as a "given"**

Key Points: New Guidance Document

- **Emphasis on risk assessment and risk management rather than ticking boxes**
- More guidance on specifics of the chemistry and manufacturing information to be provided
  - Additional detail required likely already held – R&D, post-registration pharmacovigilance, international dossiers
- New guidance on variations and immunobiologicals
- Shifting from “standard and guideline” to “guideline”
  - Old: list of information to be provided
  - New: risk management aspects to be covered


Thank you!

Lunch

Topic	Presenter	Time
Arrive and Network (08:30 - 09:00)		
➢ Welcome	Holly Jeboult-Jones	09:00-09:05
➢ ACVM Overview & Update	Glen Bradbury	09:05-09:15
➢ Quality Management	Christian Morales / Francie Olliver	09:15-09:50
➢ GMP Programme & Common Deficiencies	Holly Jeboult-Jones	09:50-10:10
➢ Manufacturing Admin & Submissions	Francie Olliver	10:20-10:30
Morning Tea (10:30 - 11:00)		
➢ GMP Update – Asia Pacific & Beyond	Bob Tribe	11:00-12:00
➢ VM Chem & Manufacture Information Req.	Awilda Baoumgren	12:00-12:30
Lunch (12:30 - 13:15)		
➢ Agricultural Chemical Manufacturing	Rafael Barbieri	13:15-13:35
➢ Validation (Concept, Process & Cleaning)	Christian Morales	13:35-14:20
➢ Requirements for Contract Manufacturing	Bob Tribe	14:20-15:00
Afternoon Tea (15:00 - 15:20)		
➢ Split into two groups - Questions & Case Studies		15:20-16:20
• Group 1: Vet Med, VTA, Ag Chem & Exempt Compound Manufacturers - Questions (20 mins) - Group Activities – Manufacturing related (40 mins)	HJJ, CM & GB	
• Group 2: Registrants & Regulatory Affairs - Questions (20 mins) - Group Activities – Data and information required when making applications (40 mins)	AB, FO & RB	
➢ Closing Summary	Glen Bradbury	16:20-16:30
Closing (16:20-16:30)		

Ministry for Primary Industries
Manatū Ahu Matua

Manufacturing Workshop
Agricultural Chemicals – manufacturing and conditions of registration

Rafael Barbieri
Adviser (Agricultural Compounds)

www.mpi.govt.nz

What is an agricultural compound?

*"…any substance, mixture of substances, or biological compound, used or intended for use in the **direct management of plants and animals**…"*

- Agricultural Chemicals (manage plants)
- Veterinary Medicines (manage animals)
- Vertebrate Toxic Agents (manage vertebrate pests)

If the product fits the definition of an Agricultural Compound, it requires an authorisation under the ACVM Act to be imported, marketed, distributed, sold or used in New Zealand.

Risk Management under the ACVM Act (1997)

Purpose of ACVM Act

"The purpose of this Act is to—

(a) prevent or manage risks associated with the use of agricultural compounds, being—

(i) risks to public health; and

(ii) risks to trade in primary produce; and

(iii) risks to animal welfare; and

(iv) risks to agricultural security:

(b) ensure that the use of agricultural compounds does not result in breaches of domestic food residue standards:

(c) ensure the provision of sufficient consumer information about agricultural compounds."

Risk Management under the ACVM Act (1997)

What is the starting point of a risk analysis?

- **Product identity**
- **Confidence that the product conforms to the product identity**

Authorisations under the ACVM Act

Exempt from Registration – PASSIVE REGULATORY OVERSIGHT

ACVM (Exemptions and Prohibited Substances) Regulations 2011 and *subject to the conditions in Regulations 7 to 15 and Schedule 2*.

Authorisations under the ACVM Act

ACVM (E&PS) Regulations 2011; Reg. 9:

"..product must be manufactured in accordance with a documented system for the manufacture of that product.."

"..specifications for the product and specific processes to be followed are required to be met.."

"..a nominated person to monitor compliance with the requirements of the documented system.."

Authorisations under the ACVM Act

Registration Pathway – ACTIVE REGULATORY CONTROL

Applicant obtains authorisation under section 21 of the ACVM Act for importing, manufacturing, selling and using an agricultural trade name product in New Zealand. *Authorisation is subjected to conditions*.

Ag. Chem. – Conditions of Registration

Main conditions of registration specifically addressing product manufacturing:

- Condition 60: *"the manufacture of the product must, at all times, conform to the product and manufacturing specifications approved as part of this registration"*

- Condition 61: *"the product must be labelled in accordance with the product and manufacturing specifications approved as part of this registration"*

Ag. Chem. – Conditions of Registration

- Condition 63: *"persons responsible for the product at each stage throughout its distribution must maintain the product in a manner that ensures it conforms to the approved product and manufacturing specifications through to the product's retail sale."*

- Condition 108: *"the registrant must provide sufficient consumer advice about the on-going stability of the product for use if requested by any purchaser of the product. The registrant must withdraw the product from the market place where evidence shows it is no longer capable of meeting its expiry specifications prior to its use, when stored in line with the manufacturers recommendations."*

Ag. Chem. – Conditions of Registration

In summary, conditions 60, 61 and 63 are imposed to ensure that PRODUCT complies with the ACVM approved specifications throughout shelf-life and retail sale.

Note: product specifications are the information provided in the Product Data Sheet (PDS) and Chemistry & Manufacture Dossier

Ag. Chem. – Conditions of Registration

In summary, condition 108 is imposed to ensure the PRODUCT complies with the ACVM approved specifications throughout the product's retail sale.

- As long as the product is on the shelf, the product must comply with the approved specifications
- The registrant should have processes in place to ensure that the product meets the shelf life requirements

Note: if the registrant cannot ensure the product meets the shelf-life requirements by any means – expiry date should be provided

Ag. Chem. – Conditions of Registration

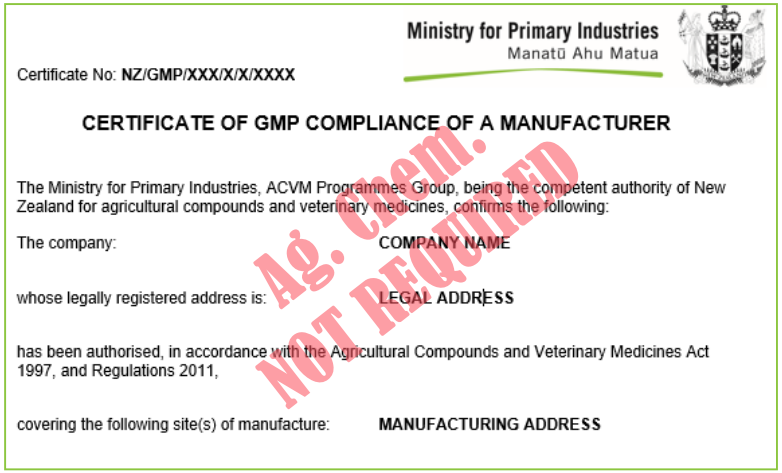
Examples of how shelf life could be managed without a label statement to ensure compliance with condition 108:

- testing batches of the product already in the market place
- establish an ongoing product stability programme, where manufactured samples are retained and re-tested

Note: requires keeping track record of the batches sold to distributors, so batches of the product in the market place likely to be out of specification are not available to end users

GMP Approval

- GMP approval is not enforced for Agricultural Chemicals manufacturers
- Conditions of registration for Agricultural Chemicals reflect expectations of GMP



Ministry for Primary Industries
Manatū Ahu Matua

Certificate No: **NZ/GMP/XXX/X/X/XXXX**

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Ag. Chem. NOT REQUIRED

The Ministry for Primary Industries, ACVM Programmes Group, being the competent authority of New Zealand for agricultural compounds and veterinary medicines, confirms the following:

The company: **COMPANY NAME**

whose legally registered address is: **LEGAL ADDRESS**

has been authorised, in accordance with the Agricultural Compounds and Veterinary Medicines Act 1997, and Regulations 2011,

covering the following site(s) of manufacture: **MANUFACTURING ADDRESS**

<u>Note:</u> in order to meet the conditions of registration it is expected that manufacturers operate under some form of quality management system. QMS could be implemented in different forms according to the product type and associated risks

Compliance with conditions of registration

Registration:

- Chemistry & Manufacture Guidance
- Setting of limits and specifications (*e.g.* AI Purity)
- Impose conditions of registration

Post-registration:

- Audit and compliance monitoring

  (*e.g.* target audits, AER, MRLs-FRSP)
- Post registration review and reassessment
- Development and review of guidance and requirements

Manufacturers Audit 2017 (initial findings) – Agricultural Chemicals only

Overall aim:

- to investigate Registrants and Operators' controls in the Manufacture of Agricultural Chemicals
- Shelf life management of registered products (compliance with Condition 108)

Methods:

- Use of an audit form to ensure consistency across all audit locations
- Various registrants' locations (*e.g.* importation, manufacture, distribution, sales)

Manufacturers Audit 2017 (initial findings) – Agricultural Chemicals only

Registrants and Operators' Controls in the Manufacture of Agricultural Chemicals

- Where warehousing and logistics are contracted to third parties – registrants tend to exercise close supervision and stock control

- Where product manufactured overseas by a third party, CoA are generally requested from source – some also perform additional crosscheck analysis using an independent NZ based laboratory.

Manufacturers Audit 2017 (initial findings) – Agricultural Chemicals only

Registrants and Operators' Controls in the Manufacture of Agricultural Chemicals

- Some registrants have robust recall procedures in place supported by full batch traceability – some have a recall procedure but have never challenged the procedure.

- Some registrants have very tidy manufacturing environments – some have manufacturing environments not as tidy as others (could potentially result in cross-contamination)

<u>Overall:</u> Registrants have quality management systems in place, but there was variability – some doing better than others

Manufacturers Audit 2017 (initial findings) – Agricultural Chemicals only

Shelf life management of registered products (compliance with Condition 108):

- Registrants receive few queries relating to shelf life from users
- Few registrants were found to keep formal registers of shelf life queries
- Some registrants were found to keep extensive post manufacture samples tested every 5 years as part of an ongoing product stability programme

<u>Overall:</u> Registrants mostly comply with Condition 108, but there was variability – some doing better than others

Manufacturers Audit 2017 (initial findings) – Agricultural Chemicals only

AER: not all registrants were aware of ACVM's AER notification system

Approvals Operations Group
Regulation and Assurance
Ministry for Primary Industries
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Ministry for Primary Industries
Manatū Ahu Matua

Adverse Event Report: Agricultural Chemicals
ACVM 23 (February 2016)

Adverse event: Any unexpected effect, which is thought to be associated with a formulated trade name product when used in accordance with the approved conditions placed on the registration or exemption from registration.
This may include side effects, target animal/crop safety issues, lack of efficacy, or alleged interactions with other products or compounds.

- Send the completed report electronically to the Ministry for Primary Industries (ACVM-adverseevents@mpi.govt.nz).
- **Registrants/distributors:** Attach a detailed report (if available) including action taken or proposed.
- **All other reporters**: We recommend that you send a copy of this report to the registrant/distributor.
- Refer to the Privacy Act 1993 and Official Information Act 1982 notices at the end of this form regarding collection of information by the Ministry for Primary Industries.

AER – Agricultural Chemicals

Condition 82: *"For the purposes of this condition, an adverse event is any event that brings into question the relevance or reliability of information provided at the time of registration and upon which the decision to register the product was made.*

The registrant must notify Ministry for Primary Industries of an adverse event in relation to the product, immediately upon becoming aware of the event, where the event has or may have significant implications for the continued use of the product."

Final Remarks

- Conditions of registration imposed on Agricultural Chemicals do not outline how registrants are expected to perform to ensure compliance, however, it is expected that manufacturers operate in line with GMP principles

- Use the messages from this workshop to improve QMS and implement sound product stewardship

- Once audit report is finalised there may be some recommendations that ACVM may consider

Thanks

Next Up Christian

Ministry for Primary Industries
Manatū Ahu Matua

Manufacturing Workshop Validation Practices

Agricultural Compounds and Veterinary Medicines

Christian Morales

www.mpi.govt.nz

What is Validation?

Definition

- Critical activity that provides a **high degree of confidence** and assurance that the system, method or process consistently produces product that meets **predetermined specification** and **quality expectations**
  - High degree of confidence: Scientific evidence supporting the quality of the product
  - Predetermined specification: Registered Product Specifications
  - Quality expectations: Quality attributes of the product (e.g., identity, purity, performance, etc)

What is Validation?

Definition

- Should not be viewed as a one-off event. Validation incorporates a **lifecycle** approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production
  - Product Lifecycle: All phases in the life of a product from the initial development through marketing until the product's discontinuation

What is Validation?

Validation Key Points

- A risk assessment approach is needed and should be used to establish the **scope of the validation**
- Validation activities must be planned (Validation Master Plan)
- Product critical quality attributes **(CQA)** must be identified along with the Critical process parameters **(CPP)**
- The number of validation runs or batches made should be sufficient to provide enough data for evaluation. Generally **three consecutive runs or batches** within specified acceptance criteria is considered enough for a proper validation

Validation Key Points

- Validation practices need successful completion of **prerequisite** steps (e.g., User Requirement, Qualification, Design Qualification)
- Worst case or “Bracketing” can be applied
- All evidence must be documented (e.g., Protocols, Validation Report, Batch Records)
- Standard operating procedures (SOP) should be in place to support the process or system to be validated

Validation Definitions

- **Validation Master Plan:** Defines the process, methods and systems to be validated, provides a written schedule to be followed and describes the controls for ensuring operations are maintained in a validated stage

- **Protocol:** A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment and decision points on what constitutes acceptable test results

- **Report:** Document reporting the validation activities, the validation data and the conclusions drawn

Example

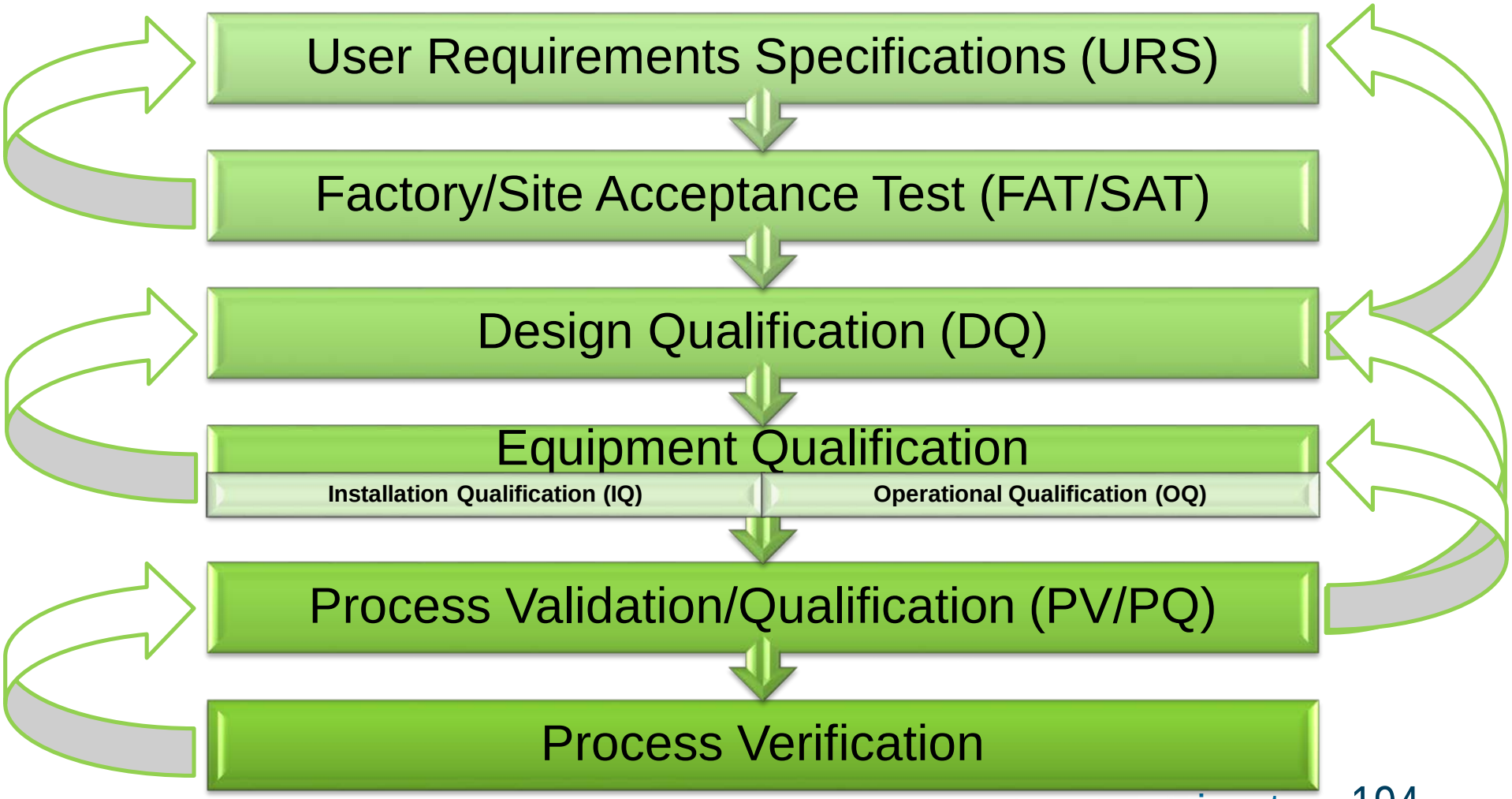
Validation Definitions

- **Worst Case:** Set of conditions that pose the greatest chance of process or product failure when compared with the ideal or normal conditions

- **Critical Quality Attributes (CQA):** A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH)

- **Critical Process Parameter (CPP):** A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH)

Validation Flow chart



Process Validation Prerequisites

User Requirements Specification (URS):

- Contains clear, measurable and detailed requirements of the system, equipment or utilities affecting the product specifications and performance of the manufacturing process

Factory/Site Acceptance Test (FAT/SAT):

- Test performed to the equipment or system that ensure that it was built or prepared in accordance to client's URS

Design Qualification:

- Verification that ensures that the general design is addressing each requirement stated in the URS

Equipment Qualification

Definition:

- Action of proving that any equipment works correctly and actually leads to the expected results
- Installation Qualification (IQ):
  - Documented evidence that the equipment or system is installed correctly and supplied with the adequate utilities and services (e.g., electricity, steam, etc). This qualification may include the need to qualify the room and other services
- Operational Qualification (OQ):
  - Documented evidence that the equipment or system operates according to all anticipated operational ranges established in the URS

Process Validation/Qualification

Definition:

- Action of proving, that any procedure, process, equipment, material, activity or system actually leads to the expected results
- Combines the actual facility, utilities, equipment, manufacturing process and the trained personnel with the commercial manufacturing process, control procedures and components to produce commercial batches

Requirements:

- Finished product release specification
- Details of analytical methods
- In-process controls (or CPP) proposed with acceptance criteria
- Sampling plan - where, when and how the samples are taken
- Methods for recording and evaluation of results (protocol and reports)

Example

Process Validation Approaches

- Two basic approaches:
  1. Evidence obtained through testing (prospective and concurrent validation), and
  2. Analysis of accumulated (historical) data (retrospective validation)

- Whenever possible, prospective validation is preferred

Re-Validation/Re-Qualification

- Ensures that the Processes and procedures **remain capable** of achieving the intended results
- It should be considered as a **Periodic activity** and a must after **changes** made to the system or process
- Should be included in the **VMP**
- Frequency and extent should be determined using a **risk assessment**

Changes requiring revalidation

Changes requiring revalidation should be defined in the validation master plan:

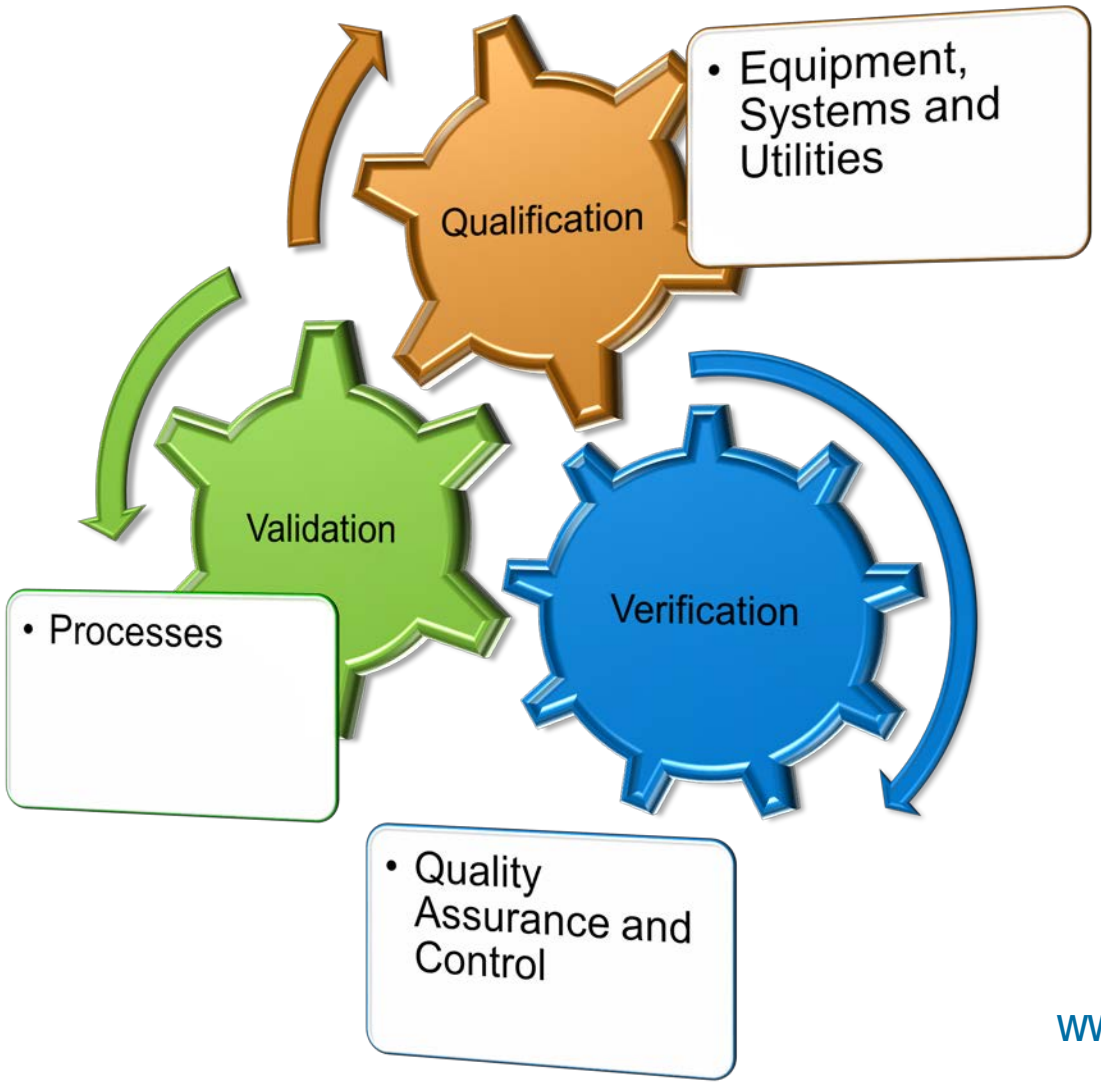
- Changes in starting materials
- Change of starting material manufacturer
- Transfer of processes to a different site
- Changes of primary packaging material
- Changes in the manufacturing process
- Changes in the equipment (e.g., “like for like”)
- Production area and support system changes
- Changes to any CQP or CPP
- Deviations

The rationale to re-validate (or not) following a change should be documented on a change control or a risk assessment

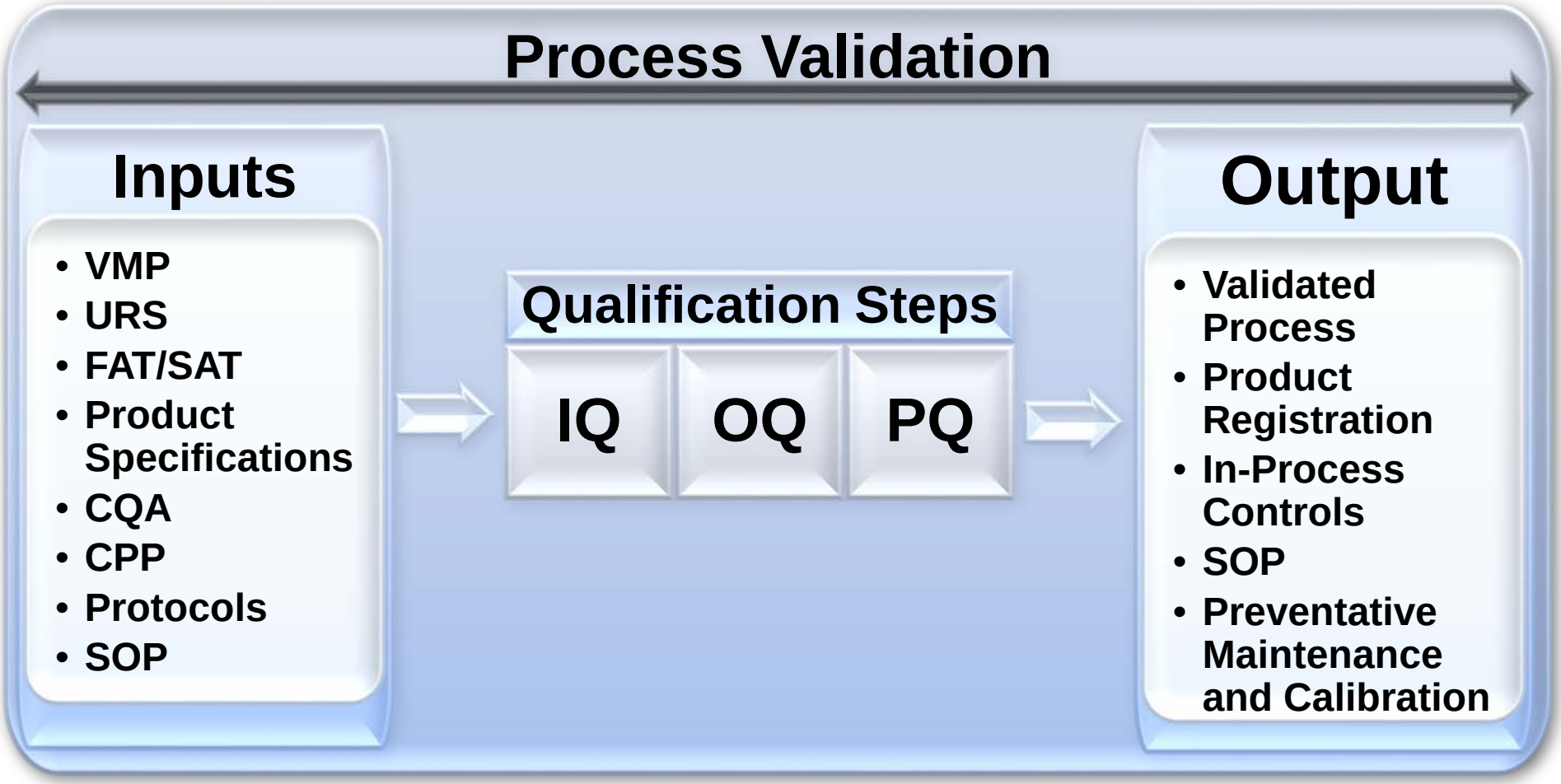
Process Verification

- Ensures that the process maintained a validated state during commercial manufacturing
- Ensures a continuous monitoring and sampling of CQA and CPP
- Detection of process variability:
  - Out of Specifications
  - Customer Complaints
  - Yield Limits
  - Batch Records
  - Inwards specifications
- GMP tools used for Process Verification:
  - Deviation Management
  - Change Management
  - Quality Control Laboratories
  - Self-Inspection

Qualification vs Validation vs Verification



Process Validation Summary



Cleaning Validation

Definition:

- Cleaning validation is documented evidence that an intended **cleaning procedure** will **reproducibly remove** the previous product or cleaning agents used in the equipment below the scientifically set maximum **allowable carryover level**
  - Cleaning procedure: A procedure should be documented before validation activities are executed.
  - Reproducibly remove: Consistently prevents Cross contamination (e.g., microbes, product, cleaning agents, etc.)
  - Allowable carryover level: Acceptance Limits. Should be practical, achievable and verifiable

What to validate

- Typically, only cleaning procedures for **product contact surfaces** of the equipment need to be validated
- Consideration should be given to non product contact surfaces
- It is usually not considered acceptable to **"test until clean"**
- In some cases of Batch-to-batch production it is not necessary to clean after each batch. Length of a campaign (maximum number of “batch to batch” or time between cleaning) should be established

Cleaning Validation Requirements.

Equipment and Facility Design

Equipment:

- Dedicated Equipment
- Product Contact surfaces
- Hard to reach-Hard to clean
- Movable or fixed
- Mechanical areas
- Semi and Fully automated systems (e.g., CIP)

Facilities:

- Cleaning activities should be part of an SOP
- Operating areas (e.g., aseptic finishes)
- Services and supporting equipment (e.g., vacuums)
- Surroundings

Example

Personnel

- Trained Personnel must be in place to perform the procedures
- Manual activity (inherently variable), operators should be involved in on-going training and monitoring

Holding Times

- The influence of the time between manufacture and cleaning (Dirty Hold Time or DHT) and the time between cleaning and use (Clean Hold Time or CHT)
- DHT:
  - Longer hold time increase the difficulty to clean.
  - Potential change in residues physical or chemical properties
- CHT:
  - Following cleaning and establish how long the equipment can remain clean.
  - Not related to residues or cross contamination but to storage conditions

Sampling

Condition	Swab	Rinse
Sampling material should be considered	Yes	No
Physical Removal	Yes	No
Invasive	No	Yes
Hard to reach locations	Yes	No
Large surfaces can be covered	No	Yes
Controlled area	Yes	No
Adaptable to irregular surfaces.	Yes	Yes
Technique and Handling should be considered	Yes	No

- Combination of the two is most desirable
- Use appropriate sampling medium and solvent

Sampling

Considerations for sampling locations:

- Hard to clean locations (Hard to reach, hard to clean)
- Locations that might contribute residue to the next product
- Materials of construction or surface finishes
- Representative surfaces that are likely to lead to build-up or difficult to remove

Solvent/Detergents

- Detergent **effectiveness and appropriateness** should be determine
- The **composition** of detergents should be identified
- The efficiency of cleaning procedures for the removal of previous product and detergent residues remaining from the cleaning should be evaluated
- **Acceptable limits** should be defined for levels of detergent after cleaning
- The manufacturer should ensure that their are notified by the detergent supplier of any critical changes in the formulation of the detergent

Analytical Methods

- The analytical method must be appropriately **validated**
- Should be **capable of detecting** the residue or contaminants being tested
- Must be sufficiently **sensitive to detect** the established acceptable level of the **residues** or contaminants
- May be specific to the substance to be assayed or non-specific (e.g., conductivity, pH testing, TOC)

Acceptance Criteria

The approach for setting limits can be:

- Grouping into product families and choosing a "worst case" product
- Grouping into groups of risk (e.g. very soluble products, similar potency, highly toxic products, difficult to detect)

Limits must be:

- Practical, achievable and verifiable
- Logical, based on knowledge of materials

Acceptance Criteria

There should be no detectable residue from:

- Previous product
- Reaction by-products and degradants
- Cleaning process itself (e.g., detergents or solvents)

Types of limits

- **Visually clean:** No residue visible on equipment after cleaning. Spiking studies to determine the concentration at which most active ingredients are visible
- Limits associated with the **percentage of contamination** (No more than 10 ppm will appear in another product)
- Limits associated with the **nature of the substance being cleaned** (No more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product)

Documentation

- Cleaning validation should be part of the validation master plan
- Cleaning procedures in place to be validated. (e.g., SOP, Batch Records)
- Protocols and validation report
- Cleaning Records and program should be established (e.g., Logs, templates)

Verification

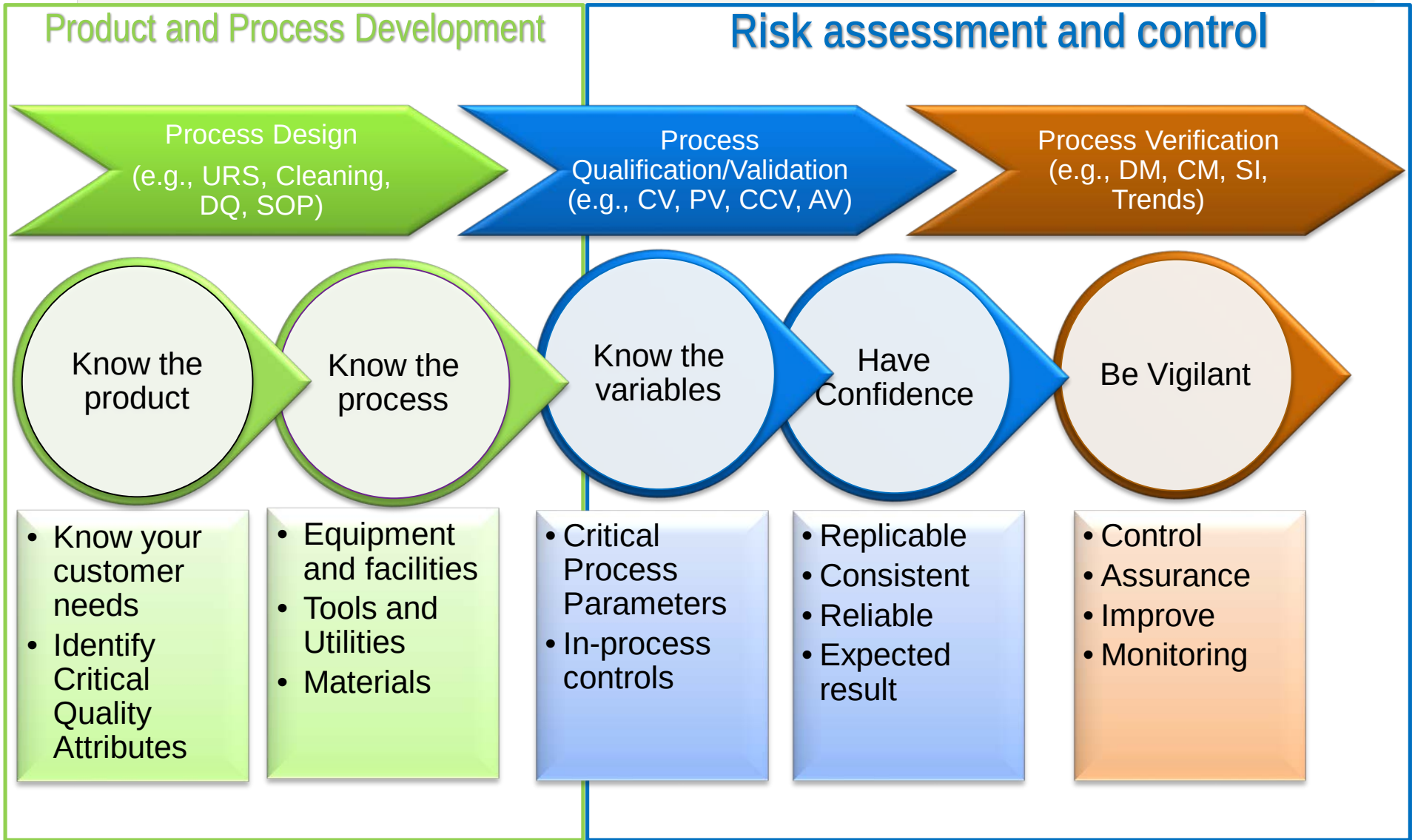
- To ensure the cleaning procedure is **still achieving** the intended results
- Provides **additional reassurance to the visual** assessment or other verification performed with each cleaning
- Consistent with the **lifecycle** approach to validation
- The extend and characteristics of the monitoring should be defined and include in a SOP or the VMP

Re-Validation

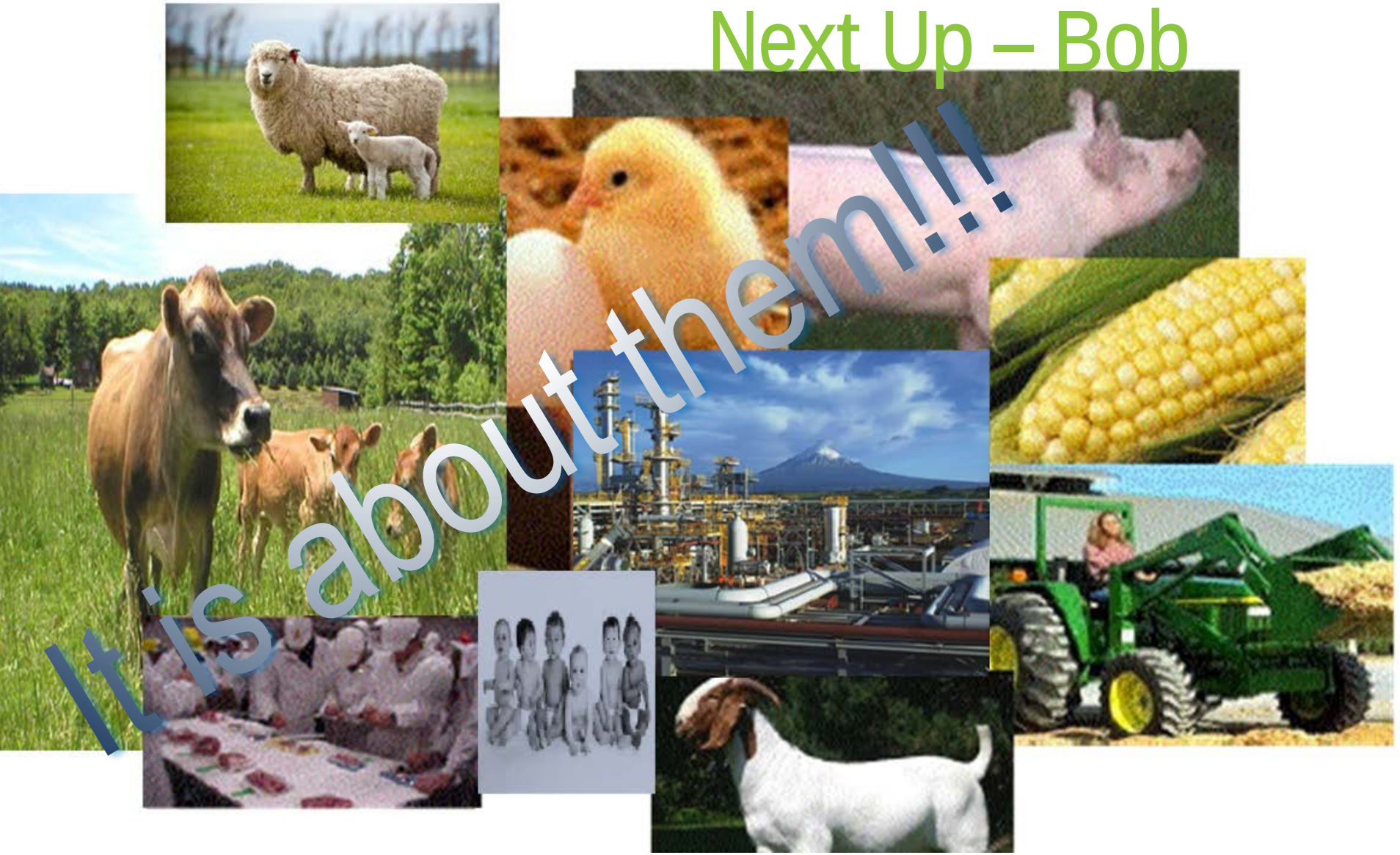
- Ensures that the Processes and procedures **remain capable of achieving the intended results**
- It should be considered as a **Periodic activity and a must after changes** made to the system or process
- Should be included in the **VMP**
- Frequency and extent should be determined using a **risk assessment**
- Changes requiring revalidation:
  - Processing equipment
  - Significant changes in cleaning equipment
  - Cleaning detergent/solvent
  - Cleaning procedure
  - Location of the equipment

Cleaning Validation Flow Chart

Validation Summary– Quality by Design (QbD)



Next Up – Bob



Ministry for Primary Industries
Manatū Ahu Matua

Manufacturing Workshop
Bob Tribe
Key Regulatory and Compliance Issues for Contract Manufacturers

www.mpi.govt.nz

Key Regulatory and Compliance Issues for Contract Manufacturers

Bob Tribe
Canberra, Australia

Overview

- A case study
- PIC/S Requirements (Chapter 7)
- Typical GMP Agreements
  - Contract manufacture.
  - Contract analysis.
- Summary.

Case Study*

- In January 2003 serious adverse reactions were reported to the TGA by consumers taking Travacalm tablets, which had been made by Pan Pharmaceuticals, Sydney.
  - Travacalm: a travel sickness tablet.
  - Contained 200 micrograms Hyoscine hydrobromide as one of the active ingredients.
  - 87 adverse reactions, including hallucinations; 19 persons required hospitalisation.
- Product sponsor was Key Pharmaceuticals, who had contracted Pan to make five batches (for 1st time).
- TGA testing revealed content of Hyoscine varied from 0% to 700%. All five batches involved.

* Based on publicly available information

Case Study*

- An urgent unannounced inspection of Pan by TGA was carried out on 30-31 January 2003.
  - TGA inspection team was the most experienced available, including a specialist analyst (HPLC).
- This inspection confirmed:
  - The TGA-approved wet granulation method of manufacture (as specified in Marketing Authorisation) had not been used.
  - A dry blend mixing process had been used instead.
  - Very poor mixing validation studies.
  - The particle size of the Hyoscine hydrobromide active ingredient used by Pan was too large to be mixed uniformly throughout the batch.

* Based on publicly available information

Case Study*

- Most disturbingly, the inspection revealed:
  - Systematic & intentional manipulation & fabrication of analytical test results for the five batches of Travacalm tablets to give the impression that the batches met specifications:
    - by eliminating "oos" results, and
    - by manipulating HPLC data on the computer.
  - Apparent destruction of computer records in an attempt to hide the data manipulation.
  - company blamed a "rouge analyst" (who was subsequently jailed).

Very serious data integrity breaches

* Based on publicly available information

Case Study*

- Pan's manufacturing licence was immediately amended to prevent the manufacture of micro-dose products (products containing active ingredients that are less than 2mg per tablet or capsule).
- A company-wide TGA inspection undertaken several weeks' later confirmed serious GMP problems throughout the company, including manipulation of QC data for other products.
- Pan's manufacturing licence suspended on 28 April 2003.
- All products made by Pan recalled:
  - 1800 products recalled in Australia and overseas.
  - Largest medicine recall ever undertaken.
- Licence suspension and product recalls were undertaken on the advice of an independent Panel of Experts.

* Based on publicly available information

Case Study*

Contract Manufacturing Issues:

- A GMP Agreement had been exchanged between Pan and Key for the contract manufacture of Travacalm tablets.
- However, Pan had:
  - Used a method of manufacture different to that specified in the Marketing Authorisation.
  - Apparently not advised Key of this different manufacturing method.
  - Apparently not advised Key of the QC testing problems (oos, etc).
  - Not complied with clause 7.11 of PIC/S GMP Guide
    (ie. **Authorised Person** did not check that the batches complied with Marketing Authorisation).
- Also, Key had:
  - Not monitored or audited Pan (important since this was the first time that Pan had made Travaclam for Key).
  - Not checked the quality of the final product.

* Based on publicly available information

Chapter 7 of PIC/S GMP Guide

Contract Manufacturing Issues:

- If both companies had followed the requirements of Chapter 7 of the PIC/S GMP Guide, this crisis and this very large recall may have been avoided.
- Chapter 7 of the PIC/S GMP Guide covers the requirements for "Contract Manufacture and Analysis".
- In Chapter 7:
  - The ***Contract Giver*** is usually the product sponsor or product owner.
  - The ***Contract Acceptor*** is usually the contract manufacturer.

The Authorised Person

Main Responsibility covered in "clause 1.4, xv" of the PIC/S GMP Guide (v13, Jan'17)

- *A Pharmaceutical Quality System 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.*

Chapter 7 of PIC/S GMP Guide

(renamed "Outsourced Activities" in Jan'17 edition)

Main Principles (Principle section):

- Contract manufacture must be defined, agreed & controlled to avoid misunderstandings which could result in product or work of unsatisfactory quality.
- There must be a written contract between the Contract Giver and the Contract Acceptor clearly establishing the duties of each party.
- The contract must state the way in which the **Authorised Person** releasing each batch exercises his/her full responsibilities.
- All arrangements for manufacture (& any changes) must be in accordance with the Marketing Authorisation for the product.

Chapter 7 of PIC/S GMP Guide

Contract Giver's responsibilities (Clauses 7.4 – 7.5):

- Assess competence of Contract Acceptor to carry out successful work, including ability to comply with requirements of the GMP Guide.
- Provide Contract Acceptor with all necessary information, including Marketing Authorisation.
- Make Contract Acceptor aware of any problems that could pose a hazard to premises, equipment, personnel, other materials or other products.
- Ensure that each batch received complies with specifications or has been released by an **Authorised Person**.

Chapter 7 of PIC/S GMP Guide

Contract Acceptor's responsibilities (Clauses 7.6 – 7.10):

- Must hold a manufacturing licence for the product to be made under contract, and have adequate premises, equipment, knowledge, experience & competent personnel for the job.
- Ensure all products or materials delivered for the job are suitable for their intended purpose.
- Should not pass work to a third party without the Contract Giver's prior approval.
- Refrain from any activity which may adversely affect the quality of the product manufactured.
- Understand that outsourced activities such as contract analysis may be inspected by the competent authorities.

Chapter 7 of PIC/S GMP Guide

The Contract (Clauses 7.11 – 7.14):

- Technical aspects should be drawn up by a competent person knowledgeable in pharmaceutical technology and GMP.
- Should set out the respective responsibilities of each party in relation to manufacture and control of the product, including:
  - An indication that manufacture and analysis must be in accordance with the Marketing Authorisation for the product.
  - An indication of the way in which the **Authorised Person** releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the Marketing Authorisation.
  - Specify responsibilities for:
    - Purchasing, testing and releasing of materials
    - Undertaking production, QC, sampling and analysis
    - Retention of manufacturing & QC records, & retention samples.
  - Indicate that any records relevant to quality of product in event of complaint/recall must be accessible to Contract Giver.
  - Contract Giver be allowed to visit premises of Contract Acceptor.

Chapter 7 of PIC/S GMP Guide

Written Contract v GMP Agreement

- Whilst Chapter 7 refers to the need for a “Written Contract”, GMP regulators will usually accept a less formal “GMP Agreement”.
- However, it is prudent to have in place:
  - A commercial contract, and
  - A GMP agreement (linked to each other and cross referenced).
- The value of having both documents in place:
  - Ensures more accurate costing.
  - Because commercial side of company involved, helps detection of undercharging and overcharging.
- The legally prepared commercial contract, containing price, indemnity, etc., could contain a confidentiality clause requiring non-disclosure of the contract to the GMP regulator.
- Using this approach, only the technically prepared GMP agreement would be shown to the GMP regulator.

Chapter 7 of PIC/S GMP Guide

Responsibilities of the **Authorised Person**

- There must be an **Authorised Person** designated in the GMP Agreement to release the contract manufactured product. This person:
  - Usually employed by the Contract Acceptor.
  - Can be employed by the Contract Giver if that company holds a manufacturing licence.
  - Can be a person holding a “release for sale” manufacturing licence (in Australia).
- The **Authorised Person** must be suitably qualified & have experience necessary to undertake the responsibilities of release for sale.
- The **Authorised Person** must obtain a copy of the Marketing authorisation in order to fulfil his/her responsibilities.

Chapter 7 of PIC/S GMP Guide

Responsibilities of the Authorised Person

- The GMP Agreement should indicate:
  - the duties of the **Authorised Person** in relation to the contracted work.
  - how release for sale will be undertaken.
  - that the **Authorised Person** will have access to production and laboratory areas prior to and during production.
- Where more than one manufacturing/testing site is involved, the **Authorised Person** must approve each step for the next stage.
- The **Authorised Person** must verify:
  - That manufacturing processes & analytical tests have been validated.
  - That specifications, expiry dates, test procedures and processes are based on data from validation studies.
  - All relevant documentation before certifying release for sale.

Chapter 7 of PIC/S GMP Guide

Subjects **NOT** covered in Chapter 7

- Complaints & recalls.
- Stability testing.
- Reprocessing.
- Change control.
- “Fit & Proper” person (Australian legislation).
- Period of time to keep:
  - Manufacturing and analytical records.
  - Retention samples of materials and products.

But important to cover these in the GMP Agreement in order to protect both parties.

Chapter 7 of PIC/S GMP Guide

General Comments

- Difficult for a GMP regulator to require Contract Givers to comply with Chapter 7 since they are often not licensed manufacturers and not usually subject to GMP requirements.
- Similar principles of documentation and GMP Agreement should apply to any analysis carried out under contract.

Example of a

GMP Agreement for contract manufacturing

(Page 1)

GMP AGREEMENT

1. In order to comply with the Australian Code of Good Manufacturing Practice for Medicinal Products August 2002 (the 'Code') and relevant sections of the Therapeutic Goods Act 1989 (the 'TG Act') and Therapeutic Goods Regulations 1990, the following agreement is entered into between:

1.1 Contract Giver: **Client Limited (Hereafter called Client)**

and

1.2 Contract Acceptor: **XXX Pty Ltd**
TGA Licence Number: 1234

2. **GENERAL**

2.1 Contract Acceptor agrees to manufacture and supply finished unit packed product to Client. The product and its associated specifications are included in Schedule 1 attached. The product will be sampled and transported in accordance with the attached SOP's/instructions included as Schedule 2.

2.2 Contract Acceptor agrees to manufacture, test, release and supply unit packed product in accordance with the Code, and Product Specification supplied (refer to Schedule 1) by the Client Quality Assurance Manager.

2.3 Contract Acceptor is responsible for the step(s) of manufacturing and any associated chemical, and physical testing (if applicable).

2.4 Contract Laboratory ABC is responsible for undertaking all associated microbiological evaluations of both the raw material and the finished product. Contract Laboratory ABC is a TGA approved microbiological testing facility whose licence has been attached as Schedule 3 of this agreement.

2.5 Client is responsible for ensuring that the microbiological test method PRO SOP 1018 is validated and transferred to Contract Laboratory ABC in accordance with approved protocols. Client shall ensure compliance with the Letter of Assurance provided to Contract Acceptor and attached to this agreement as Schedule 4.

2.6 Client is responsible for all steps covered after product is released by Contract Acceptor.

2.7 All products must comply with the microbiological limits specified in Schedule 5.

2.8 Formulations and Product Specifications cannot be changed except by the prior authorisation of Client's Regulatory Affairs Officer and Contract Acceptor's Quality Manager.

2.9 Contract Acceptor will not sub-contract to a third party any of the work entrusted to them by Client without the latter having evaluated the arrangements and given written consent. Any arrangement made with a third party shall be in accordance with the requirements of the Code and a similar technical agreement must be authorised by Contract Acceptor. Details of the third party's GMP status together with full address, ABN and contact person must be made available to Client.

2.10 With due notice and in accordance with Sec 40(4) of the TG Act, Contract Acceptor will permit Client or its nominated assignee to carry out periodic audits of their facility to ascertain that the requirements under the Code are being met and that the operations are being carried out in the agreed manner. Contract Acceptor will provide access to all relevant documents upon request during any such audit.

Example of a
GMP Agreement for
contract manufacturing
(Page 2)

2.11 Contract Acceptor shall supply unit packed product to Client in appropriate unit packs and bulk shippers labelled with all agreed information on the batch and its status. An original signed Certificate of Analysis shall be supplied for each batch of product, which has results for all of the agreed tested actives on the approved specification.

2.12 Upon request, Contract Acceptor shall provide information to Client relating to reprocessing of batches and batches containing product residues to enable meaningful stability studies to be carried out by Client.

2.13 Contract Acceptor must at all times maintain a valid TGA licence for manufacture of the type of products made for Client. Contract Acceptor must ensure that 'fit and proper' personnel are responsible for Contract Acceptor's manufacturing licence in accordance with Sec 38 of the TG Act.

3. **TESTING**

3.1 Test methods (other than those executed by Contract Laboratory ABC) will be held by Contract Acceptor and made available to Client and the TGA if so requested.

3.2 Microbiological test methods used by Contract Laboratory ABC for Client will be established. All results must be reported and all deviations monitored by both Client and Contract Acceptor.

3.3 Contract Laboratory ABC will advise and request approval from Client to change any test methods. Changes initiated by Contract Laboratory ABC will necessitate Contract Laboratory ABC and Client to undertake validation of these methods and to provide documented evidence to Contract Acceptor that this has been completed.

3.4 Where testing is undertaken by a contract laboratory Client must ensure that all arrangements and responsibilities are clearly specified in an appropriate agreement and that all test methods, method validation and results be made available to Contract Acceptor as required.

4. **REPORTING TEST RESULTS**

4.1 Contract Acceptor will provide Client with a Certificate of Analysis (in accordance with approved testing as per the approved specification) for all products manufactured. The Certificate of Analysis shall include:

Date:
Name of Product:
Batch Number:
Results:
Authorised signature:

4.2 Contract Acceptor will keep all product and testing records for Client products for a minimum period of 7 years from the date of manufacture in a secure manner. These records will be available for inspection by Client and the TGA if required.

5. **RETENTION SAMPLES**

5.1 Contract Acceptor will retain an adequate portion of all product manufactured to allow for repeat testing or inspection at a later date.

Example of a
GMP Agreement for
contract manufacturing
(Page 3)

6. ASSIGNED RESPONSIBILITIES

		Contract Acceptor	Client
6.1	**Starting Materials**		
	6.1.1 Purchase		Client
	6.1.2 Preparation of specifications	Contract Acceptor	
	6.1.3 Approval of specifications	Contract Acceptor	
	6.1.4 Quality Control testing (excipients)	Contract Acceptor	
	Quality Control testing (active)	Contract Acceptor	
	6.1.5 Retention samples	Contract Acceptor	
	6.1.6 Approval for use	Contract Acceptor	
6.2	**Packaging materials and labelling**		
	6.2.1 Purchase	Contract Acceptor	
	6.2.2 Preparation of Specification/designs-bulk	Contract Acceptor	
	Preparation of Specification/designs-unit		Client
	6.2.3 Approval of Specifications/designs	Contract Acceptor	
	6.2.4 Approval for Use	Contract Acceptor	
6.3	**Formulae and Processing Instructions**		
	Preparation of documents	Contract Acceptor	
6.4	**Safety or Hazard Information** (if indicated)	Contract Acceptor	
6.5	**Product Specifications**		
	6.5.1 Preparation of specifications	Contract Acceptor	
	6.5.2 Approval of specifications	Contract Acceptor &	Client
6.6	**Quality Control**		
	6.6.1 In-Process Quality Control	Contract Acceptor	
	6.6.2 Product Quality Control		
	6.6.2.1 Preparation of specification	Contract Acceptor	
	6.6.2.2 Approval of specifications	Contract Acceptor &	Client
	6.6.2.3 Quality Control Testing (Physical)	Contract Acceptor	
	Quality Control Testing (Microbiological)	Contract Acceptor	
	6.6.2.4 Retention samples of finished product	Contract Acceptor	
	6.6.2.5 Approval of finished product for release to Client	Contract Acceptor	
6.7	**Batch Reprocessing/Product Residues**		
	6.7.1 Authority to reprocess out of spec batches	Contract Acceptor &	Client
	6.7.2 Authority to include product residues	Contract Acceptor &	Client
6.8	**Finished Unit Packed Product**		
	Release from Manufacture	Contract Acceptor	
	Final release for sale[1]	Contract Acceptor	
6.9	**Stability Testing of Finished Product**		
	Stability trial		Client
	Allocation and approval of expiry date		Client
6.10	**Consumer Complaints**		
	6.10.1 Response to customer		Client
	6.10.2 Assistance with manufacturing related investigation	Contract Acceptor	

Example of a
GMP Agreement for
contract manufacturing
(Page 4)

6.11	**Retention Samples**	
	6.11.1 Starting materials	Contract Acceptor
	6.11.2 Finished product	Contract Acceptor & Client
6.12	**Documentation Retention**	
	6.12.1 Starting materials	Contract Acceptor
	6.12.2 Manufacturing	Contract Acceptor
	6.12.3 Packaging	Contract Acceptor
	6.12.4 Product	Contract Acceptor & Client
6.13	**Product Recalls**	Client
6.14	**Adverse event reporting of finished product**	Client

7. **CONFIDENTIALITY**

7.1 Contract Acceptor undertakes to treat all information supplied by Client as confidential. No such information will be supplied to a third party without the permission of Client, except where required for regulatory purposes.

7.2 Client undertakes to treat all results and method details supplied by Contract Acceptor as confidential. No such information will be supplied to a third party without the permission of Contract Acceptor, except where required for regulatory purposes.

8. **REVISION OF ATTACHED DOCUMENTS**

8.1 All attached Schedules are to be reviewed and updated as required.

9. **EXPIRY OF AGREEMENT**

9.1 This agreement will be valid for 36 months from the date of signing or at a time as agreed by both signatories.

9.2 It is the responsibility of both Contract Acceptor and Client to review this agreement and to enter into a new agreement prior to the expiry of this agreement or as otherwise determined.

10. **MARKETING AUTHORISATION / AUTHORISED PERSON**

10.1 A person(s) at Contract Acceptor is the 'authorised person' as defined by the Code.

10.2 Contract Acceptor's authorised person must verify and certify that the manufacturing processes and test methods used have been properly validated or an appropriate protocol to undertake validation has been prepared and agreed to. The Contract Acceptor authorised person is responsible for release for sale, which will include relevant checks for compliance with the Marketing Authorisation.

10.3 Client is the holder of the Marketing Authorisation for the products listed in Schedule 1. Client will provide copy of current Marketing Authorisation to the Authorised Person for use in the release for sale step.

10.4 Any changes that may impact the Marketing Authorisation must be communicated by the change originator to the other party

10.5 Client as the product sponsor has responsibility for the product whilst it is in the marketplace.

Example of a
GMP Agreement for
contract manufacturing
(Page 5)

11. **UNINTENDED HARMFUL EFFECTS**

11.1 Contract Acceptor will advise Client of any information that would indicate that the use of any product in Schedule 1, in accordance with the recommendations for their use, might have an unintended harmful effect

12. **UNACCEPTABLE QUALITY, SAFETY AND EFFICACY**

12.1 Contract Acceptor must refrain from any activity which may adversely affect the quality of the product and / or testing

12.2 Contract Acceptor must ensure that product is securely transported and transported appropriately so as to protect product from adverse environmental conditions.

Notes:

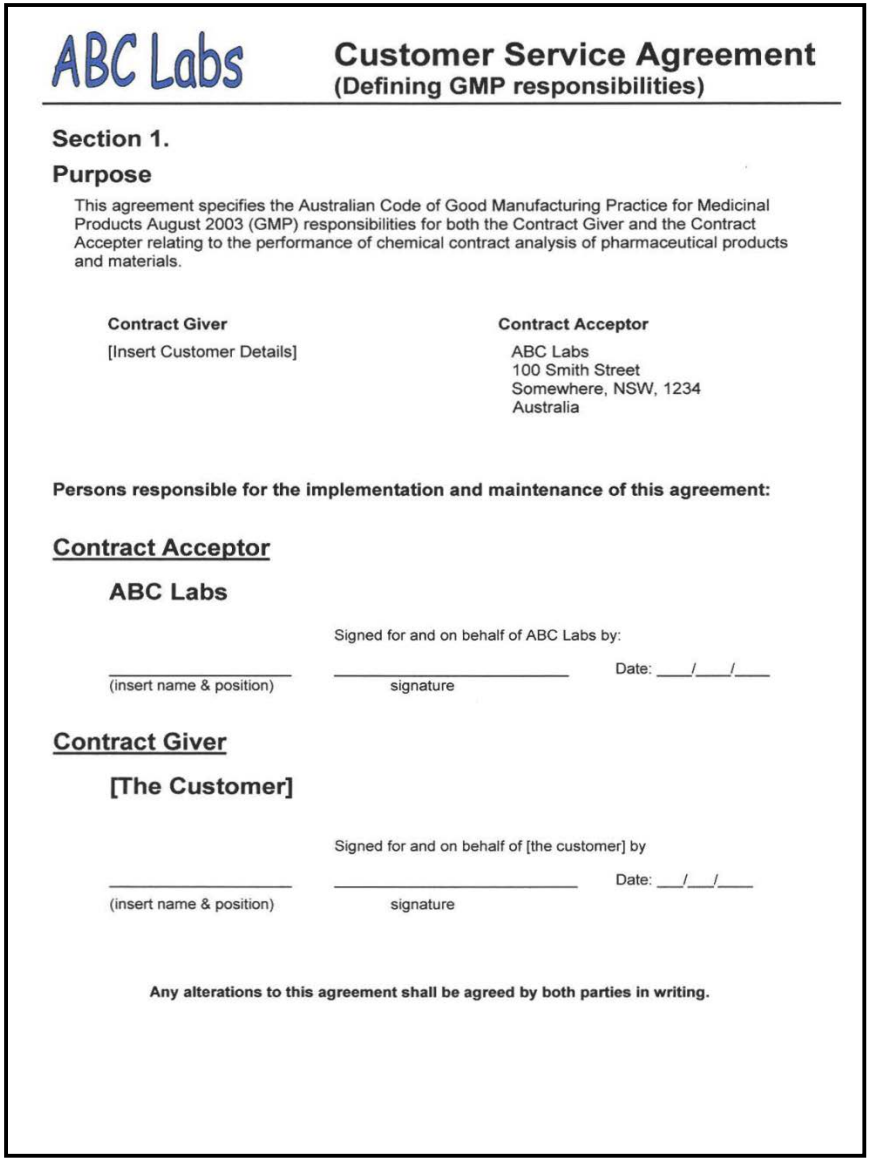
1 Contract Acceptor as the nominated authorised party responsible for release for sale of the product(s) listed in Schedule 1 to this agreement must ensure that stability studies have been undertaken or are under way by the sponsor and that the sponsor has justification for the claimed shelf life appearing on the label. Contract Acceptor will release the product against the approved Contract Acceptor product specification and in the knowledge that the marketing authorisation has been granted against this approved document. Any changes to the approved specification must be communicated to both parties at all times and the marketing authorisation updated accordingly by the product sponsor.

Signed:	Signed: .....
Name:	Name: .....
Title:	Title: .....
Date:	Date: .....
Company: Client Limited	Company: Contract Acceptor

Alternative Layout for a GMP Agreement (one of many pages)

RESPONSIBILITIES	CONTRACT GIVER	CONTRACT ACCEPTOR
Analytical, Laboratory, Sampling & Control		
Retaining and storing of all materials,samples, in-process samples, components and Bulk Drug Substances	✓	
Sampling, analysis and release of Raw Materials	✓	
Sampling o f Bulk Drug Substance	✓	✓
Testing according to Contract Specifications by CMC	✓	
Analysis and release of Bulk Drug Substance		✓
Sampling, analysis and release of Packaging Materials and Components	✓	
In-process analyses for manufacture	✓	
Reference standards for laboratory analysis		✓
Provide stability data and storage conditions		✓
Quality Assurance Activities		
Preparation and review of the master batch record	✓	Review, approval
Approval of master batch documents.	✓	✓

Example of a
GMP Agreement for
contract analysis
(Page 1)



ABC Labs

Customer Service Agreement
(Defining GMP responsibilities)

Section 1.

Purpose

This agreement specifies the Australian Code of Good Manufacturing Practice for Medicinal Products August 2003 (GMP) responsibilities for both the Contract Giver and the Contract Accepter relating to the performance of chemical contract analysis of pharmaceutical products and materials.

Contract Giver

[Insert Customer Details]

Contract Acceptor

ABC Labs
100 Smith Street
Somewhere, NSW, 1234
Australia

Persons responsible for the implementation and maintenance of this agreement:

Contract Acceptor

ABC Labs

Signed for and on behalf of ABC Labs by:

_____ (insert name & position)

_____ signature

Date: ____/____/____

Contract Giver

[The Customer]

Signed for and on behalf of [the customer] by

_____ (insert name & position)

_____ signature

Date: ___/___/____

Any alterations to this agreement shall be agreed by both parties in writing.

Example of a
GMP Agreement for
contract analysis
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Section 2. Responsibilities:

Item	Requirements
Sampling	*ABC Labs is responsible for:* ▪ Providing access to ABC Labs Analysis Request Form (FRM002) – Copy provided in appendix 1. *The [Contract Giver] is responsible for:* ▪ Completing and submitting Analysis Request Form (FRM002) for each request. ▪ Sampling according to in-house procedures. ▪ Samples being provided in appropriate containers suitable for transportation and analysis.
Sample transportation	*ABC Labs is not responsible for:* • any sample transportation requirements. *The [Contract Giver] is responsible for:* ▪ Ensuring the sample(s) are packed to ensure correct conditions are maintained during transportation. ▪ Cold-chain validation requirements (if required).
Inspection upon receipt	*ABC Labs is responsible for:* ▪ Verifying condition of sample(s) upon arrival and confirming that paperwork matches sample(s) supplied. ▪ Acknowledging receipt via e-mail to the Contract Giver or other agreed method. ▪ Clarifying discrepancies with the Contract Giver. *The [Contract Giver] is responsible for:* ▪ Clarifying discrepancies (if applicable)
Storage of samples at ABC Labs	*ABC Labs is responsible for:* ▪ Storage of samples at appropriate conditions upon receipt to completion of analysis (includes storing samples as retention samples post analysis). *The [Contract Giver] is responsible for:* ▪ Notifying ABC Labs when storage conditions are modified.

Example of a
GMP Agreement for
contract analysis
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Retention sample storage	*ABC Labs is responsible for:* ▪ Retaining samples for 6 months after completion of testing or as otherwise agreed. *The [Contract Giver] is responsible for:* ▪ Long term sample retention as per own requirements.
Analytical Method	*ABC Labs is responsible for:* ▪ Following the documented method (controlled copy) supplied by the Contract Giver. *The [Contract Giver] is responsible for:* ▪ Ensuring the method is fully validated to GMP requirements. ▪ Providing a controlled copy of the validated method to ABC Labs. ▪ Providing a new controlled copy of the method if updated.
Training	*ABC Labs is responsible for:* ▪ Training analysts to perform the relevant analytical method(s). *The [Contract Giver] is responsible for:* ▪ Providing additional training if required.
Reference Standard	*ABC Labs is responsible for:* ▪ Storage and control of reference standard at appropriate conditions. *The [Contract Giver] is responsible for:* ▪ Providing a reference standard of certified purity. ▪ Providing sufficient reference standard to perform analysis.
Analytical report format requirements	*ABC Labs is responsible for:* ▪ Where requested an interim non certified electronic analytical report will be provided. ▪ Final approved analytical report is provided in hard copy via mail. *The [Contract Giver] is responsible for:* ▪ [Complete as required]
Product Specification (Test Limit)	*ABC Labs is responsible for:* ▪ [Complete as required] *The [Contract Giver] is responsible for:* If applicable, providing specifications and limits (See Section 3)

Example of a
GMP Agreement for
contract analysis
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Quality Records Archiving:	*ABC Labs is responsible for:* ▪ Storage of all quality records in relation to analysis for a minimum of 10 years. *The [Contract Giver] is responsible for:* ▪ [Complete as required]
OOS Investigation	*ABC Labs is responsible for:* ▪ In the event of an Out-of-Specification (OOS) result, perform a laboratory error investigation only. ▪ Contacting the Contract Giver immediately upon verifying a valid OOS result. ▪ Documenting the investigation findings as part of the analytical report. *The [Contract Giver] is responsible for:* ▪ All other OOS investigations (eg. Production records etc.).
Stability Testing	*ABC Labs is responsible for:* ▪ [Complete as required] *The [Contract Giver] is responsible for:* ▪ [Complete as required]
Error Correction (Report recall)	*ABC Labs is responsible for:* ▪ Notifying Contract Giver immediately upon identification of error. ▪ Recalling incorrect report and issuing a new corrected report. *The [Contract Giver] is responsible for:* ▪ Returning or destroying incorrect analytical report version upon request.
Monitoring	*ABC Labs is responsible for:* ▪ Control Charting (if required).
Final Release	*The [Contract Giver] is responsible for:* ▪ The entire final release process.

Summary

- Chapter 7 of the PIC/S GMP Guide is a mandatory requirement for all licensed medicine manufacturers.
- A GMP agreement must be in place specifying the responsibilities of each party involved in the contract arrangements.
- A key person in any contract manufacturing arrangement is the **Authorised Person** who has important responsibilities including the release for sale of each batch of product.
- Failure to comply with Chapter 7:
  - Is a breach of the PIC/S GMP Guide & the conditions of the manufacturing licence.
  - Could result in costly consequences such as product recall and put manufacturer's licence in jeopardy.

Fate of Pan Pharmaceuticals

- Manufacturing licence was reinstated in late 2003 for soft gelatin capsules only.
- However, Pan went into liquidation around mid-2004.
- Another company purchased the factory and immediately used another company name (Sphere Pharmaceuticals).
- The many court cases that have taken place since 2004:
  - TGA prosecuted Company Directors of Pan (criminal charges relating to fraud, counterfeiting & destruction of computer records) – TGA successful for counterfeiting; TGA unsuccessful for others.
  - Analyst who manipulated HPLC data - prosecuted and jailed.
  - Managing Director of Pan sued TGA – he was successful.
  - ASIC sued Pan (share trading anomalies) – ASIC was successful.
  - Class Action Cases by Pan's customers against TGA (in an attempt to recover financial losses) – Class Action was successful.

Thank you

Questions?

Afternoon Tea

Topic	Presenter	Time
Arrive and Network (08:30 - 09:00)		
➢ Welcome	Holly Jeboult-Jones	09:00-09:05
➢ ACVM Overview & Update	Glen Bradbury	09:05-09:15
➢ Quality Management	Christian Morales / Francie Olliver	09:15-09:50
➢ GMP Programme & Common Deficiencies	Holly Jeboult-Jones	09:50-10:10
➢ Manufacturing Admin & Submissions	Francie Olliver	10:20-10:30
Morning Tea (10:30 - 11:00)		
➢ GMP Update – Asia Pacific & Beyond	Bob Tribe	11:00-12:00
➢ VM Chem & Manufacture Information Req.	Awilda Baoumgren	12:00-12:30
Lunch (12:30 - 13:15)		
➢ Agricultural Chemical Manufacturing	Rafael Barbieri	13:15-13:35
➢ Validation (Concept, Process & Cleaning)	Christian Morales	13:35-14:20
➢ Requirements for Contract Manufacturing	Bob Tribe	14:20-15:00
Afternoon Tea (15:00 - 15:20)		
➢ Split into two groups - Questions & Case Studies		15:20-16:20
• Group 1: Vet Med, VTA, Ag Chem & Exempt Compound Manufacturers - Questions (20 mins) - Group Activities – Manufacturing related (40 mins)	HJJ, CM & GB	
• Group 2: Registrants & Regulatory Affairs - Questions (20 mins) - Group Activities – Data and information required when making applications (40 mins)	AB, FO & RB	
➢ Closing Summary	Glen Bradbury	16:20-16:30
Closing (16:20-16:30)		

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Break-Out Sessions
Group 1:
Manufacturers and Manufacturing Staff
Group 2:
Registrants and Regulatory Affairs Staff

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ACVM Manufacturing Workshop
Closing and Summary
Agricultural Compounds and Veterinary Medicines

Glen Bradbury

Summary – What did we learn?

1. ACVM Overview and Update
2. Quality Management
3. Regulatory Programmes, Managing Compliance, Dealing with deficiencies & administration activities
4. Manufacturing Administration
5. GMP Update – Asia Pacific & Beyond
6. AIs and Critical Components
7. VM Chemistry & Manufacturing Guidance Changes
8. Ag Chem Manufacturing
9. Validation
10. Contract Manufacturing
11. Break-out Sessions

Any Questions?

We welcome your feedback

- Please complete the Feedback Questionnaire and place in the Question Box on your way out. Alternatively, take one and email the completed form to:

ACVM.ManufacturingandAssurance@mpi.govt.nz

Thank you for coming!!