Challenges in Auditing Veterinary Manufacturers

(Some personal experiences)

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Some Background

- Part of original auditor group in 1997
- Initially industry education as much as auditing role – this has changed
- Code of GMP was focused on fundamentals + Manufacturing Principles
- APVMA GMP Inspectorate based in Armidale
- Currently ~ 10 auditors:
  - Eight approved for Cat 1**/ 2/ 3 and 4 (**biologics / sterile)
  - One specializes in Cat 4 – feedlots
  - Spread across NSW, Q'ld and Victoria
- National auditing - many are regional
- Many are small enterprises
- Scheme is not yet recognized by PICs – Export to EU requires TGA License

Our Patients

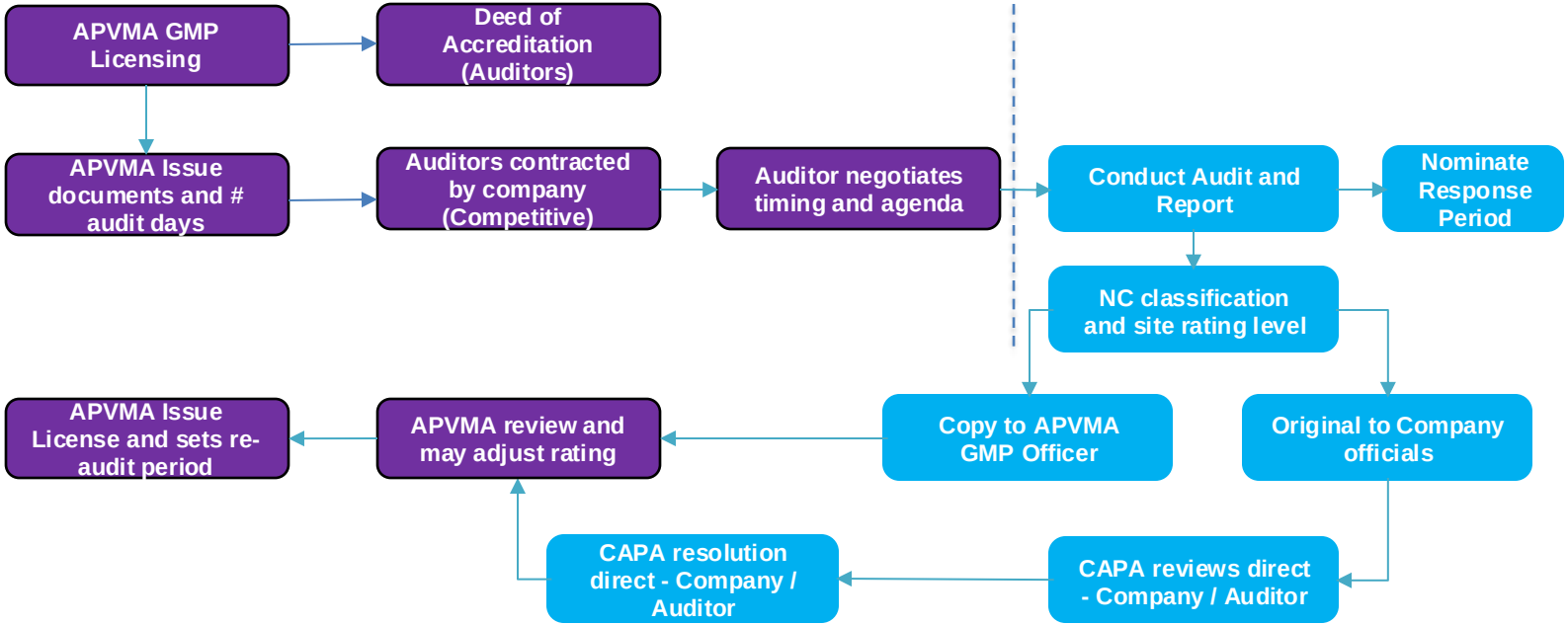





GMP Coverage

- Covers National manufacturers (~ 200 companies and laboratories)
- Mutual agreement with New Zealand regulator (ACVM)
- Covers importers of Veterinary Medicines
  - India, China, South Africa, South America, Japan, Mongolia, USA etc…
- 4 Main categories – Cat 1/ Cat 2/ Cat 3/ Cat 4
- Covers testing laboratories (Automatic if TGA)
- Excludes API manufacturers (not licensed)
  - Dealt with by Registered Particulars
- Allows for manufacture under Permit (equivalent to SAS scheme)
- Accept TGA Inspections and report - issue APVMA GMP License

How does the auditing scheme work ?



Step of Manufacture		Step of Manufacture	
Quality assurance (QA) of raw materials		Packaging	
Serum collection		Labelling	
Colostrum collection		**Or:** Secondary packaging	
Management and immunisation of donor animals		Secondary labelling	
Bacterial fermentation		Repackaging	
Fungal fermentation		Relabelling	
Virus cultivation		Strip, blister or sachet packaging	
Chemical synthesis		Tableting	
Formulation including Blending		Tablet coating	
Dry milling		Pellet extrusion	
Wet milling		Capsule filling from bulk	
Granulation		Aerosol filling from bulk	
Filling		Freeze-drying	
Aseptic filling		Spray-drying	
Sterilisation: a) Heat		Other type of manufacturing *(please specify)*	
b) Radiation			
c) Gas			
d) Filtration			
e) Chemical			
Microbiological reduction treatment:			
a) Heat			
b) Radiation			
c) Gas			
d) Filtration			
e) Chemical			
Analysis and testing:		***Comments:***	
Physical			
Chemical			
Endotoxin testing			
Antibiotic assay			
Microbiological			
Sterility test			
Serological			
Immunological			
Other *(please specify)*			
Storage (in process/quarantine)			
Release from Manufacture only (partial release)			
Release for supply (final quality release of finished product)			

Scope of License

Particular Challenges

1. QA of starting materials
2. Sterility Test
3. Release from (Manufacture or Supply)
4. Stability / Shelf life

APVMA GMP Rating System

Audit Result		Audit Rating # *(please select one)*	Manufacturer eligible for closure by plan?
Number of Major NCs	**NC Score**		
0	0 to 4	☐ Audit Level 1	Yes
No more than 5	5 to 20	☐ Audit Level 2	Yes
No more than 10	21 to 40	☐ Audit Level 3	No
More than 10	Greater than 40	☐ Audit Level 4	No
Any critical NC	N/A ►	☐ Audit Level 4	No

- **Audit Level 1 -** no major NCs and the non-conformance score is 4 or less.
- **Audit Level 2 -** no more than 5 major NCs and their non-conformance score is between 5 and 20
- **Audit Level 3 -** no more than 10 major NCs and non-conformance scores of 21 to 40
- **Audit Level 4 -** more than 10 major NCs and/or a non-conformance score greater than 40, or any critical NCs.

Auditing Variety and Challenges

- One day to 5 – 6 days duration
- Only one auditor (+ APVMA observers sometimes)
- Cat 4 - Feedlot manufacturers (mostly small)
- Vaccine manufacturers (mostly large)
- Specialty manufacturers:
  - Snake antivenom, vaccines on permit, CMOs, single product / single line, sanitants, seasonal manufacturers, antibiotics in feedlots, flea powders etc…
- Can be a combination of on-site + remote (by approval)
- Auditing to Vet Code vs PICs/TGA Code GMP

Case #1 – Exporter to Europe

- Company has an APVMA License for local distribution
- Applies for a TGA license to export to EU for specified products
- TGA cGMP and standard substantially higher
- Mis-match of assessments can arise – Criticals vs Majors or Minors
- TGA may assume the APVMA audit was deficient (not the case)
- **Example:**
  - APVMA auditors are instructed to review internal audit reports as policy
  - TGA may or may not review these records
- **Example:**
  - APVMA APIs are often accepted on a C of A and sometimes identity
  - TGA require far more rigorous quality control

Case #2 – Equine Drench Manufacturer

- Rat droppings in raw material store
- Mixing in a rusty cement mixer
- No SOPs
- No formula
- No batch record

- Outcome – license refusal

Case #3 – Snake Antiserum Manufacturer

- Sideline for local Veterinarian – knows what he is doing
- No employees
- Does everything (Production, QA, QC)
- Simple quality system and simple batch record
- 2 batches per year of approx. 1000 units
- Cleanroom is rudimentary - Grade C into Grade A (barely)
- Lack of aseptic technique and poor media fills

Challenges

- Does not meet code standards but is an “essential medicine”
- Cannot afford cleanroom upgrade
- Product has formalin in formulation
- Should they continue ?

Case #4 – Overseas Manufacturer of Injectable

- Holds no GMP licenses - local GMP Vet. standards non-existent
- Large local manufacturer of vet. medicines
- Has an extensive quality system but only local language
- Manufacture is simple – only one sterilizing filter
- Have solid validation programs, tests validated, extensive QC labs and stability programs
- Production areas are average standard but clearly defined cleanrooms
- Sterilisation processes are not to standard

Outcome: Corrective actions are in place and likely license – would not meet PICs

Case #5 – CDMO Manufacturer – Sterility Assurance

- Rotating QA Management (now stable)
- Basic cleanrooms and poor materials transfer programs
- Turned off HVAC on weekends
- EM program not validated and poorly constructed
- Contract test lab. does sterility testing
  - Most sterility tests not validated
  - Failed a terminally sterilized batch ? No lab error considered
  - Laboratory refused company audit – done by 3rd party

Outcome – all micro testing now in house / upgraded materials handling/ HVAC on

Case #6 – Manufacturer of Vaccines on Permit

- Manufacture under GMPs but no product registration (under annual permit system). Reporting from vet back to the manufacturer;
- Isolate organisms from client farms and deliver vaccine back to that farm (autologous);
- Create a master cell bank – bacterial fermentation of crude vaccine;

GMP Situation

  - Renovated cleanrooms with good design and containment system
  - Have excellent history of sterility tests + media fills + EMs
  - Well developed eQMS quality system + testing programs
  - Improvement mindset

Challenges in CMO Release for Supply Responsibility

- RFS is a step of manufacture – requiring a license
- Some CMO manufacturers are unclear on their obligations
- Some sponsors conduct RFS without a license (maybe unaware)
- GMP Contract agreements lack specificity in some cases
- Auditors are asked to check the QTAs and release authorities

Challenges in QA of Starting Materials

- CMOs often rely upon Sponsor to supply “Approved” Materials with C of A
- API suppliers not required to hold any licenses or accreditations
- Registered Particulars (RPs) require site of API manufacture to be nominated during registration and informed if a change;
- Manufacturers often receipt on C of A only and compare to specification;
  - C of As and internal specifications sometimes mismatch
  - Some test all incoming APIs, some don’t;
  - Very little supplier assurance programs in place. No site audits.
- C of As sometimes come from the broker / agent – not the manufacturer
- Brokers reluctant to reveal their sources

Other Challenges

- Product mix ranges from very very low risk to high risk – how to apply cGMPs ? ;
- Stability trial assessments;
- Process validation;
- Validation of Computer Systems;
- Potential for cross-contamination and cleaning validation limits;
- No requirement for Risk Management program;
- No formal requirement for PQRs yet;

Industry is improving !

- Manufacturers know their products and care about quality
- Substantial improvement over the last 5 years
- Quality Systems are more extensive and some eQMS systems in place
- Manufacturers receptive to issues identified
- APVMA has provided clear(er) expectations to industry

Always a balance around what is a reasonable requirement – partly risk based application of GMPs.

Thank You!

Questions ?