GMP for Listed Medicines

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Topics

- Optional ‘onsite’ audits of listed medicine active material suppliers and manufacturers
- Control of impurities and allergens in listed medicines:
  - Elemental impurities (OSDs)
  - Residual solvents (OSDs)
  - Allergens

Onsite Audits of Listed API suppliers & manufacturers and/or QC laboratories (not mandatory for listed medicines)

New requirements introduced in PE-009-14 (1 July 2018)

‘...Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements...’

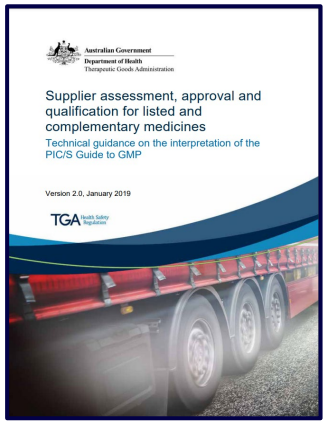
– Clause 5.29 PE-009-15

‘The medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials...’

– Clause 5.36 (ii) PE-009-15

Current acceptable approach for Supplier Approval and Material Qualification for Listed Medicines

- ✓ Appropriately completed and reviewed supplier questionnaire
- ✓ Establishment and agreement of relevant specifications
- ✓ Risk based period of re-evaluation
- ✘ No requirement for GMP/Technical Agreements
- ✓ System of material qualification, e.g., full testing of the first three batches, followed by ongoing rotational testing
- ✓ Once qualified, reduced sampling available on incoming listed medicine active ingredients
- Now, if 5.29 and/or 5.36 are followed there is scope for even further reductions in sampling and testing programs.



Sampling requirements for API pre/post qualification

Pre-qualification

Sample all containers

Post qualification

Apply $\sqrt{n} + 1$ *or reduced sampling

*Starting materials coming from a single product manufacturer or plant

PQ* **including onsite audit**

1 x sample

Testing requirements for API pre/post qualification

Pre-qualification

Full testing

Post qualification

Rotational Testing

PQ **including onsite audit**

Definitive ID testing

+ C of A review against specification

Pre-requisites and supplier maintenance requirements for ID only testing of Raw Materials (Annex 8 § 2)

- ✓ History of reliable test results (in house QC)
- ✓ If agents/brokers are used they must be audited also.
- ✓ Material comes directly from the manufacturer or in the manufacturer's sealed container

Ongoing maintenance

- Periodic full testing of the raw material and comparison against the suppler CoA
- Any discrepancies with supplier/lab CoA must be investigated!
- Re-audits with the periodicity based on risk

Additional considerations/Exemptions

Herbal raw materials

Minimum sampling requirements prior to qualification, must meet the requirements of the default standards:

- Ph. Eur. Method 2.8.20
- British Pharmacopoeia Appendix XI T
- USP <561>

Annex 7 (PE-009) requirements also apply

Intermediate & Bulk product

- Exempt from the supplier approval process
- Manufacturer/sponsor must hold a TGA GMP licence/certificate, or clearance respectively
- Technical/GMP Agreement required
- Container integrity checks
- Sample a minimum of one container

What areas should the audit/inspection cover?

- Raw material manufacturers:
  - Confirm information on the questionnaire is accurate!
  - Quality Management System
  - Manufacturing areas (inc. risk of cross contamination)
  - QC Laboratories
  - Supply chain traceability
- 3rd Party QC Laboratories:
  - Distribution controls
  - Applicable test methods/validation
  - Issuance and authorisation relating to Certificates of Analysis

Audits must be satisfactorily completed!

3rd party contractors can be used (see clause 2.23)

Effective remote inspections allowed

Summary/Key points

- Audits of active material suppliers is **optional** for manufacturers of **listed medicines**
- In addition to an onsite audit, the justification for reducing sampling and testing of incoming raw materials must be based on an established history of use with the supplier, with acceptable test results.
- Audits should be comprehensive, relevant to the material(s) supplied and ongoing.
- Effective remote inspections are permitted but must be equivalent to an onsite audit
- 'Full testing' must be performed periodically – frequency should be based on risk.

Updated guidance documents to be published later on this year!

Control of impurities and allergens in Listed Medicines

- Elemental impurities
  - Sources
  - Application of Quality Risk management
  - Methods of calculation
  - Case study
- Residual solvents
  - Overview
  - Requirements for testing/methods of calculation
- Allergens
  - Overview
  - Materials of concern
  - Control strategy
  - Example deficiency

Elemental Impurities – Overview

*Elemental impurities include catalysts and **environmental contaminants** that may be present in **drug substances**, **excipients**, or drug products USP <232>*

ICH Q3D adopted by TGA in 2019 as an 'international scientific guideline'.

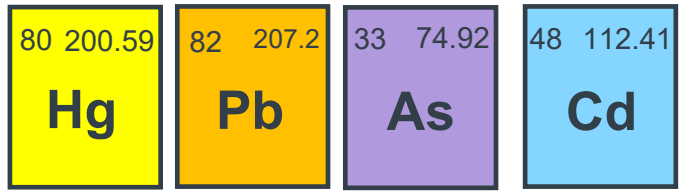
S6, TGO 101 introduced in 2021 (tablets capsules and pills) allows:

- **ICH Q3D**
- **USP <2232>**

General chapters include:

- BP and EP (general chapter 5.20) effectively defer to ICH Q3D
- USP<232> is the equivalent for non-dietary supplements

Any specific monograph with heavy metal limits takes precedence over a general chapter



…human toxicants that have limited or no use in the manufacture of pharmaceuticals. Their presence in drug products typically comes from commonly used materials (e.g., mined excipients)…. ICH Q3D

Other elements may also apply!

Sources of Heavy metals in complementary medicine ingredients

Sources of contamination

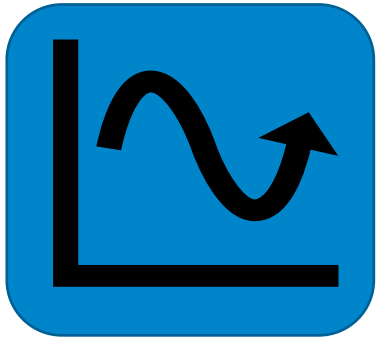
- **Drug substance/excipient**
- **Water**
- **Manufacturing equipment (wear and tear)**
- **Container closure system**

RISK (complementary medicines)

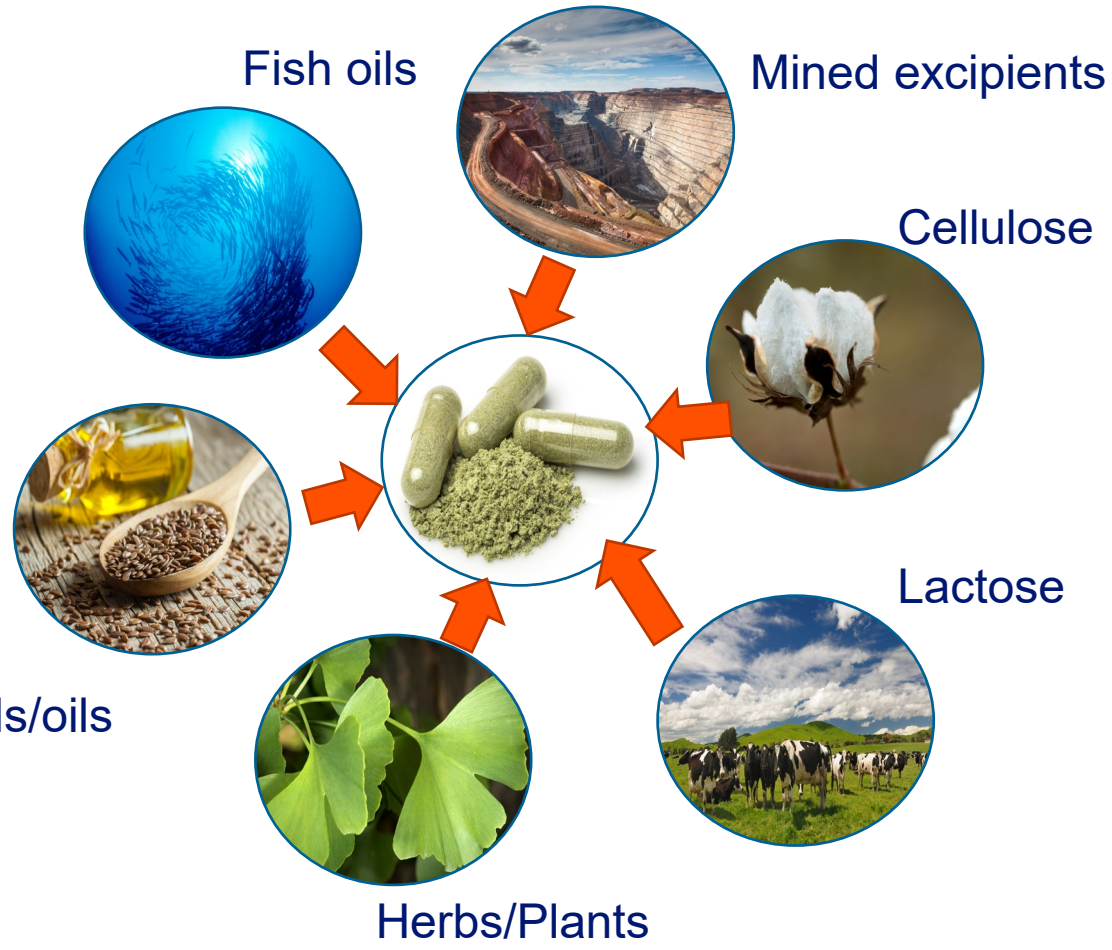
Other sources include:

- Traditional medicines (TCM, Ayurvedic)

Levels of elemental contamination found in natural materials are inherently variable!



All mined excipients and plant/marine/animal based materials are at risk from potential heavy metal uptake from the environment



Risk Assessments for Elemental Impurities

- Risk assessment must be wholistic but for Listed Medicines the focus of the assessment should be on the raw materials.
- Take into account the maximum daily intake of the medicine and the % wt. of each ingredient in the finished dosage form.
- Utilise any information provided by the supplier (e.g., supplier questionnaire, agreed limits on specifications) Test results must be qualified (see clause 5.36)
- Given the typical composition of complementary medicines, unlikely that no testing will be required – Batchwise testing is not expected

Available methods for calculation Elemental impurity content

USP <2232>

'Dietary Supplement'
- Analysis of finished product
- Max. daily intake
- (µg/day)

'Individual Component'
- Elemental analysis of each RM
- NMT 10g
- (µg/g)

'Summation'
- The sum total mass (µg) of each measured element from each RM
- **(µg/day)**

ICH Q3D

'Option 1'
- Analysis of raw materials
- NMT 10g
- (µg/g)

'Option 2a'
- Analysis of raw materials
- Max. daily intake
- (µg/g)

'Option 2b'
- Analysis of raw materials
- Specified amount
- **(µg/day)**

'Option 3'
- Analysis of finished product
- Max. daily intake
- (µg/g)

All methods directly/indirectly calculated from published Permissible Daily Exposure values (PDE) (µg/day)

Testing for Elemental Impurities – How much is required?

Scope and frequency of testing

Established test history of results **well within limits – Scope and frequency of testing can be reduced**

High results
OOS/OOT/~CoA

New Supplier/raw material source

Ongoing Testing

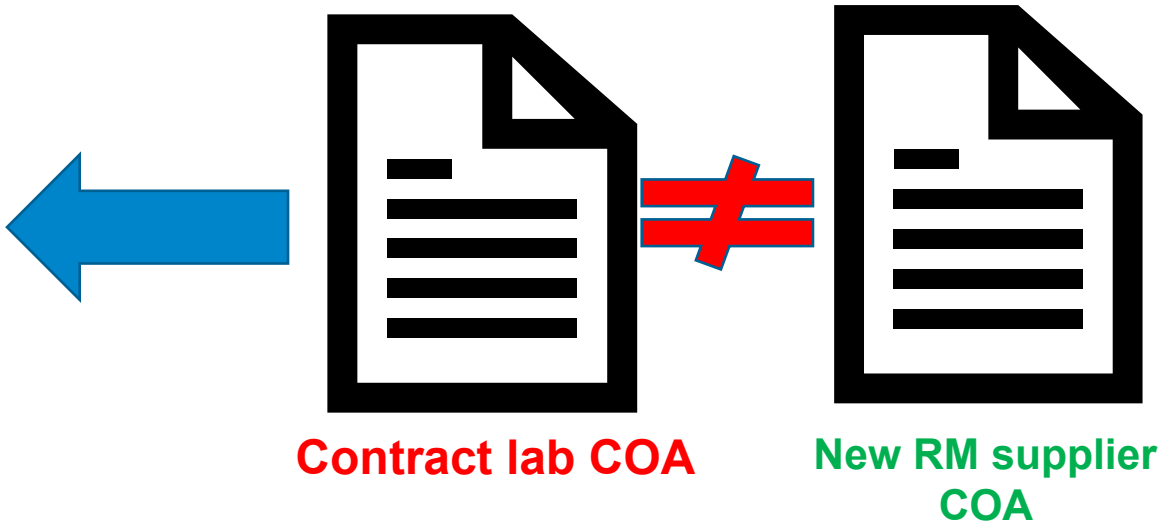
Limited history and test results

Extensive history and test results

Case Study: Raw material OOS for Cadmium

- Raw material procured through a broker
- New source of flaxseed oil identified during CoA review (including acceptable heavy metal levels)
- **Full testing initiated** (inc., residual solvents and heavy metals)
- **High limits of cadmium identified**

Element	Individual Component Limits (µg/g) USP <2232>	CoA results
Arsenic (in.)	1.5	0.20 (µg/g)
Cadmium	0.5	**0.77 (µg/g)**
Lead	0.5	0.02 (µg/g)
Mercury	1.5	0.70 (µg/g)
Methylmercury	0.2	0.02 (µg/g)



Case Study: Raw material OOS for Cadmium

- Company follows USP – **'Dietary Supplement'** or **'Summation'** methods available
- Maximum daily intake <10g, therefore **'Summation'** method followed
- Heavy metal analysis performed on other batch components of the finished product.
- **PDE for cadmium = 5µg/day**
- The amount of cadmium present in the FP per daily intake found to be less than PDE – Batch approved for manufacture
- EI analysis performed on subsequent batches of flaxseed indefinitely

1 tablet = **0.5g**; Max. serving = **4 tablets (2g)**; Number of servings a day = **2**

Ingredients	Mass per Unit (g)	Mass per Serving (g)	Max Daily Intake (g)	Cd (µg/g)	Total Cd (µg/ serving)
Flaxseed oil	0.09	0.36	0.73	0.77	0.28
Microcrystalline Cellulose	0.15	0.60	1.20	0.23	0.14
Titanium Dioxide	0.06	0.24	0.48	0.40	0.10
Iron Oxide	0.09	0.36	0.72	0.30	0.11
Magnesium stearate	0.11	0.44	0.88	0.23	0.10
Total	0.50	2.00	4.00	1.93	0.73
Result					1.45 (µg/day)

Result = $\sum (C_i \times W_i) \times N$

C_i = elemental contaminant concentration in the individual component (µg/g)

W_i = weight of each individual component per serving of the FP (g/serving)

N = maximum daily intake of the FP recommended on the label (servings/day)

Residual Solvents – Overview

ICH Q3C (R4) adopted by TGA as an 'international scientific guideline' in 2014

S6, TGO 101 introduced in 2021 (tablets capsules and pills) specifies:

- Ph Eur 5.4

The EP general chapter incorporates the ICH guideline

Safe residual solvent levels derived from published literature using the NOEL/LOEL model

Residual solvent classification:

- Class 1 – *'To be avoided'*
- Class 2 – *'To be limited'*
- ***Class 3 – 'Low Toxic Potential' (PDE >50mg per day)***

Residual solvents:

- Organic volatile chemicals that have not been removed
- Can be found in drug product, substance or excipients

Residual Solvents – Assessment

'It is only necessary to test for solvents that are used or produced in the manufacture or purification of active substances, excipients, or medicinal product.' Ph Eur 5.4

1. Assessment of finished dosage form manufacturing processes for use of solvents
2. Engagement with suppliers of active substances and excipients on their use of solvents during production/purification steps
3. If no solvents are used = no testing required

*'If solvents of Class 2 or Class 3 are present at greater than their **Option 1** limits or 0.5 per cent, respectively, they should be identified and quantified.' Ph Eur 5.4*

However, if solvents are declared periodic testing required.

- Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5 per cent.
- Only Class 2 solvents X, Y, ... are likely to be present. All are below the Option 1 limit

  (Here the supplier would name the Class 2 solvents represented by X, Y, ...)
- Only Class 2 solvents X, Y, ... and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5 per cent.

Ph Eur 5.4

Residual Solvents – Assignment and quantification of limits

Limits

- Class 1 – avoided; Class 2 – individual PDE (Table 2); Class - 3 0.5%
- Class 3 Solvents – Can be analysed using non-specific test e.g., Loss on Drying if concentration levels less than 0.5%

Two main options (class 2 solvents):

- **Option 1** – Daily intake ≤10g, limits must meet concentration limits in table 2 based off the following calculation:

$$\text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}}$$

Acceptable for drug substances, excipients or products.

- **Option 2 – When a component is above the calculated concentration limits.**
  - Using the known daily dose and the corresponding mass of the ingredient calculate the quantity of residual solvents for each component.
  - Sum the quantities of the residual solvent in each ingredient of the finished dosage form.
  - Result should be less than PDE limits specified in Table 2.

Table 2. – *Class 2 solvents in pharmaceutical products*

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720

Table 2 - Ph Eur 5.4

Control of allergenic substances when manufacturing Listed Medicines

- A large number of permissible ingredients for listed medicines are allergens
- A large proportion of listed medicine facilities also manufacture food products.
- Label requirements and substances of concern are listed in Schedule 1 of TGO 92
- Chapter 5 of the PIC/S guide (PE-009) should be utilised for control strategies for storage, manufacture and handling of Schedule 1 substances (no toxicological evaluation required for listed medicine ingredients).

Listed medicine cleaning validation acceptance criteria:

- Visually clean
- Removal of detergents
- Microbiological limits met

None of the above methods can assure the absence of allergens!

Allergenic substances – when should you declare?

Medicine labels: Guidance on TGO 91 and TGO 92 states the following:

> *'When there is no cut-off specified in the Schedule 1 entry, sponsors should declare the substance if:*
> *- it has been added during any of the manufacturing processes (even as a manufacturing aid) and there is any likelihood that it remains in the finished goods*
> *-it is a known component, or likely to be a component, of one of the ingredients in the medicine.'*

Excerpt from Schedule 1 - Therapeutic Goods Order 92:

Column 1 Substance name or Group of substances name	Column 2 Circumstances (if any) and additional requirements (if any)	Column 3 Route of administration	Column 4 Name to be included on the label
fish and fish products (see Note 2), including: cod cod – liver oil halibut tuna		All	fish; or fish products
galactose		Oral	galactose
gluten or ingredient derived from gluten-containing grain (see Note 3)	**Circumstance:** Where gluten is present in a concentration of 20 parts per million or more.	All, other than skin and mucous membrane applications	gluten

Scenario 1: Example for compliant labelling:

- Contract manufacturer produces various medicine and food products
- Receives food grade ingredients for medicine manufacture

Is evidence available from suppliers that food grade materials are free from schedule 1 substances and no schedule 1 substances used in the raw material manufacture?

YES → Label declaration not required

NO → Label declaration may be required

Example Deficiency – Allergen Controls

Scenario 2: Example for compliant manufacturing:

- Contract manufacturer makes both food and medicine products, some of which contain Schedule 1 substances

Deficiency:

'Medicinal products were produced on common manufacturing equipment, however evidence was not available to demonstrate that the manufacturer had assessed the risk of cross contamination with allergenic substances and justify why additional controls had not been implemented.'*

**Controls = Specific analytical methods, potentially dedicated sampling/dispensing tools, dedicated product contact manufacturing equipment and/or dedicated rooms*.

Manufacturing with Schedule 1 substances: Assessing Risk

Materials

- Consideration of materials held onsite

Cleaning validation

- Have Schedule 1 substances been incorporated into the worst case assessment for the cleaning validations?
- What are the analytical capabilities versus the prescribed limits for Schedule 1 substances?

Manufacturing Processes

- Cross contamination risks
  - Dust/aerosols
  - Cross over points
  - Ineffective cleaning
  - Reused cleaning solutions
- Shared equipment?
- Shared rooms?

Procedures

- Adequate detail?
- Spills?
- Labels?

Manufacturing with Schedule 1 substances: Controlling Risk

Materials

- Assessment of entire material inventory (e.g., therapeutic, food and cosmetics) for Schedule 1 substances.
- Assessment of Schedule 1 substances handled at the raw material supplier (e.g., questionnaire)

Cleaning validation

- Use of Schedule 1 substances as worst case material.
- Use of specific allergen test kits
- Remember column 2 of Schedule 1

Manufacturing Processes

- Localised extraction
- Dedicated rooms/tools and equipment
- Separate gowning

Procedures

- Cleaning: pictures/diagrams, assembly/disassembly of equipment.
- Specific requirements for spillages of Schedule 1 materials
- Appropriate checks for master product labels
- New product introduction

Common deficiency: Heavy metals, Residual Solvents, Allergens

The requirements of Clause 1.9 (v) that the finished products contain active ingredients complying with the **qualitative** and quantitative composition of the **Marketing Authorisation** or Clinical Trial Authorisation, are of the **purity** required, and are enclosed within their proper containers and **correctly labelled**, had not been met, for example:

- The manufacturer performed secondary packaging and release for supply of soft capsule products, however no evidence of elemental impurity testing relating to batches undergoing release were available from the site performing RFS or from the bulk product manufacturer.
- The system of evaluating raw materials did not have provision for assessing the potential presence of residual solvents. It could therefore not be determined if products manufactured onsite contained acceptable levels of residual solvents at the time of batch release.
- The system for approving master finished product labels did not include provision for verifying if labels complied with relevant regulations (i.e. TGO 92), noting that a number of Schedule 1 materials were held onsite.
- The training programs for the Authorised Person and his/her delegates did not include awareness of regulatory requirements applicable to the dosage forms undergoing release (e.g., TGOs 92, 100, 101).

Questions?

www.tga.gov.au

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration