Australian Government
Department of Health
Therapeutic Goods Administration

How to improve your GMP Compliance for Listed Medicines and GMP implementation of TGOs 92 and 101

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TGA Health Safety Regulation

Therapeutic Goods Order 92

- **What is TGO 92?**
- TGO 92 Standard for labels of non-prescription medicines replaced TGO 69 in 2016
  - Outlines the general requirements for the labels of non-prescription medicines
  - Describes what information is required about the medicine such as identity, potency, content, storage, expiry date, directions for use etc.
- TGO 92 Commenced in August of 2016 and the transition period of 4 years ended on September 2020
- Full effect since September 2020
- Consequences affect both the consumer and the manufacturers – Recalls and Adverse Events

TGO 92 Schedule 1

Schedule 1

If | and | and | then

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
aspartame		Oral	aspartame
antibiotics	When the antibiotics is not an active ingredient and is present only as a residual impurity	All	Contains residual 'antibiotic name'
benzoates, including: benzoic acid sodium benzoate		All	benzoates
crustacea and crustacean products (see Note 1), including:		All	crustacea; or crustacean products

- Within TGO92, Paragraph 8(1)(j) lists the information to be included in the medicine label with reference to Schedule 1

(j) where:
(i) a substance or substance within the group of substances referred to in Column 1 of Schedule 1 to this Order is present in the medicine;
(ii) the circumstances as set out in Column 2 of Schedule 1 exist in relation to such a substance or no circumstances are set out in Column 2; and
(iii) the medicine is intended to be administered via any one or more of the route(s) of administration referred to in Column 3 of Schedule 1, then:
(iv) a statement:
(A) indicating that the medicine contains the substance expressed using the Name stated in Column 4 of Schedule 1; and
(B) where any of the circumstances and requirements set out in Column 2 of Schedule 1 exist in relation to the substance – a statement of the kind referred to as a 'requirement' in that Column (if any); and
TGO 92 - Section 8 J

Schedule 1

"...the presence of the substance or group of substances is required to be declared on the label irrespective of any circumstance, concentration or amount of the substance or group of substances present in the medicine."
TGO 92 - Schedule 1

Understand the Risk ➡ Mitigate/Eliminate ➡ Control

Understanding the Risk

- **Assessment of raw materials**
  - Schedule 1 substances handled on site
  - Schedule 1 substances handled at the raw material supplier

- **Assessment of current cleaning validation strategy**
  - Have Schedule 1 substances been incorporated into the worst case assessment for the cleaning validations?
  - Is the manufacturing equipment free from Schedule 1 substances?

- **Assessment of the risks in your manufacturing processes**
  - Cross contamination
  - Shared Equipment
  - Shared Rooms

- **Assessment of the current procedural controls in place for cross contamination**
  - Procedural controls
  - Cleaning strategies

Mitigate or Eliminate the Risk

- **Schedule 1 substances used in manufacturing**
  - Common material sampling equipment
  - Raw material processing areas
  - Questionnaires for the raw material suppliers

- **Facilities and equipment**
  - Dedicated manufacturing equipment
    - Common tools for manufacturing
    - Common manufacturing equipment
  - Appropriate environmental containment controls

- **Cleaning Validation Strategy**
  - Risk based approach to the use of allergenic substances:
    - Incorporate allergens into the assessment of worst case for cleaning
    - Allergen testing could add to the data set used to justify the manufacturer's position on the risk of manufacturing with allergens

- **Procedural controls**
  - Ensure there are procedures in place to describe the correct handling of Schedule 1 materials

Control

- **Training**
  - Training for correct handling procedures and processes awareness of different handling requirements

- **Change Controls/New Product Introductions controls and considerations for allergens**
  - Ensure there are control strategies in place for new product introductions that are incorporated into the quality system

- Labels must comply within the existing labelling requirements of TGO 92

Deficiencies Cited at Inspection

Deficiency 1

The system to ensure labels were correct was inadequate, for example, the label for Product X capsules contained whey powder and did not include a declaration of "Milk Derivatives" on the product label, as mandated in TGO 92. The supplier agreement with the Marketing Authorisation Holder did mandate that supplied labels must be compliant to TGO 92, however there was no documented evidence that this requirement had been verified upon receipt of labels and/or during batch certification, (see also Clause 1.8iii).

Remediation Considerations

- Product awareness in relation to TGO 92 Schedule 1
- Ensure existing labels are reviewed to contain the correct information
- Establish a system to ensure that products containing Schedule 1 substances are specifically checked to contain the required declarations when received and reviewed on site
- Establish procedures for new product introductions to contain these checks

Deficiencies Cited at Inspection

Deficiency 2

The requirements of Clause 5.18 that the risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other materials (starting or in-process), and products in process, from residues on equipment, and from operators' clothing should be assessed were not met. Specifically, there were a number of manufactured products that contain substances that must be declared on the product label (see TGO92), however, there was no assessment conducted to determine if all relevant product labels had been updated to reflect the presence of these substances. For example, the effectiveness of equipment cleaning validation studies had not been reviewed to confirm that products manufactured in the same equipment were not contaminated with these substances.

Remediation Considerations

- Ensure evidence is available to support that cleaning validations consider Schedule 1 Substances when justifying your “worst case” cleaning conditions
- Assess and record, then validate the cleaning strategies for common areas and shared equipment
- Ensure that the considerations and processes considered are justified to support the assertions made and ensure documentation of the choices made

Deficiencies Cited at Inspection

Deficiency 3

The requirements of Clause 5.21 that specific technical and organisational measures should be used to control risks for cross-contamination were not fully implemented and controlled, as evidenced by the following:

a. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems were designated for some products; however, these technical measures to minimise cross contamination were poorly implemented and controlled [Clauses 5.21 (Technical Measures)]

Remediation Considerations

- Avail evidence that cleaning validations consider Schedule 1 Substances in the assessment of worst case cleaning conditions
- Incorporate this consideration into the cleaning validations and record the justifications and evidence to support the assertions made

Deficiencies Cited at Inspection

Deficiency 3 continued

Dedicated production/packaging rooms were in use for some allergenic products such as probiotics, bee pollen and royal jelly; however, the use of dedicated equipment did not extend to all manufacturing activities. For example;

i. Dispensing was conducted in the main dispensary area. No additional cleaning validations had been conducted to support the use of these areas for both allergenic and non-allergenic materials. Further, dedicated dispensing tools, used for dispensing potentially allergenic raw materials, were not uniquely identified.

ii. Stainless steel transfer vessels, used throughout the facility, were non-dedicated and could not be uniquely identified.

Remediation Considerations

- Ensure there are measures in place to keep dedicated equipment separated and traceable to support the claim of dedicated equipment
- Assess and record the cleaning strategies for common areas and shared equipment

Key Points to Remember

- Identify the Schedule 1 Substances handled
- Identify the risks of cross contamination of product
- Mitigate the risks or eliminate the risks
- Control the ongoing risks
- Update the product labels that require updating

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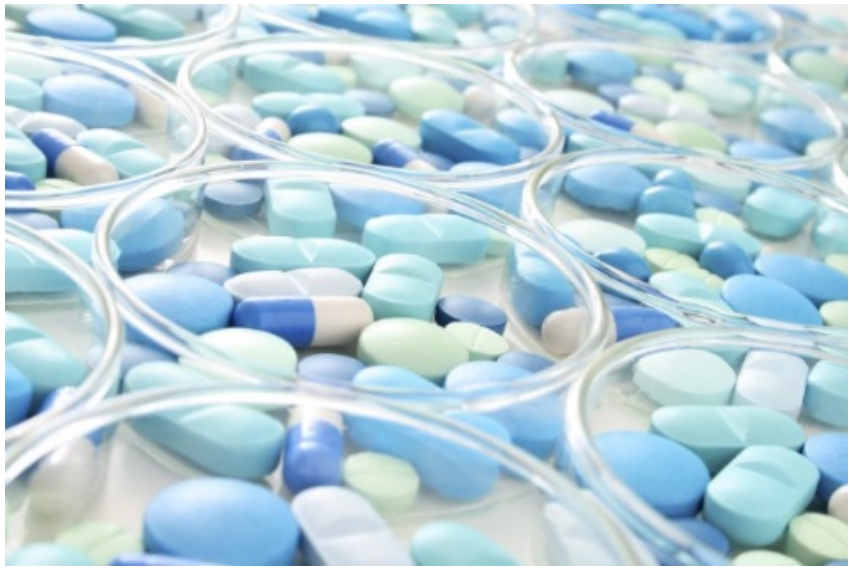
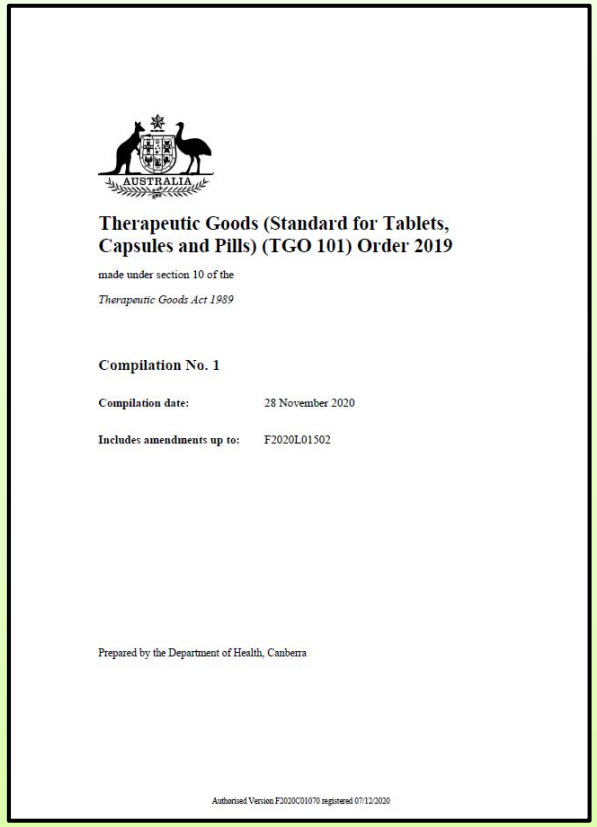
GMP Implementation of TGO 101 (Section 16)

- Overview and scope of Therapeutic Good Order
- Brief overview and comparison of Standards
- Achieving and maintaining GMP compliance
- Potential Issues



Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019



AUSTRALIA

Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019

made under section 10 of the

Therapeutic Goods Act 1989

Compilation No. 1

Compilation date: 28 November 2020

Includes amendments up to: F2020L01502

Prepared by the Department of Health, Canberra

Authorised Version F2020C01070 registered 07/12/2020

- Standard for tablets, capsules and Pills Aust (L) & Aust (R) **Finished Dosage Form**
- Replaces previous standard for tablets and capsules (TGO 78)
- Section 16 commences **30 June 2021**
- Schedule 3, Part 6 – Elemental Impurity concentrations in Pills commences **31 March 2021**

TGO 101 – Section 16, Subsections (1) and (2)

16 Elemental impurities and residual solvents

(1) The requirements for elemental impurities are those specified in either one of the following:

(a) chapter <2232> *Elemental Contaminants in Dietary Supplements* of the United States Pharmacopeia-National Formulary; or

(b) the ICH Q3D Guideline.

(2) The limits for residual solvents are those specified in European Pharmacopoeia (5.4) for solvent impurities.

Elemental Impurities (EI) – Overview of standards

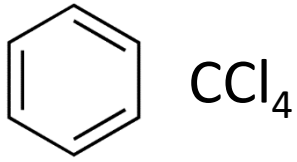
USP 2232	ICH Q3D (R1)
Dietary Supplements (Complementary Medicines)	"New finished drug products" (ICH Q6A and Q6B) New drug products containing existing drug substances
Oral administration (Inc. liquids and powders)	Oral, parenteral and inhalation administration
Arsenic, cadmium, lead, total mercury and methyl mercury	**Class 1, (As Cd; Pb; Hg); Class 2A, (Co, Ni and V);** Class 2B, (Class 3)
Scope and extent of testing based on risk	Scope and extent of testing based on risk
Limits based on PDE established for each element	Limits based on PDE established for each element
Ingredient analysis (µg/g)	Ingredient analysis (µg/g)
Drug Product analysis, (µg/day): • Summation of individual ingredient EI levels • Analysis of finished product	Finished Product Analysis, (µg/day): • Summation of individual ingredient EI levels • Analysis of finished product

Not for herbal products!

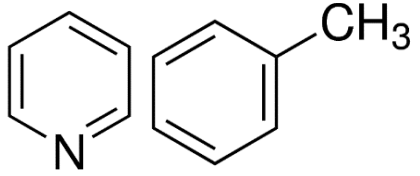
Ph Eur 5.4 Residual Solvent (RS) Classification

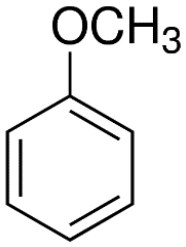
"Residual solvents in active substances, excipients, and in medicinal products are within the scope of this guideline. Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents"
Ph Eur 5.4

Class 1	Class 2	Class 3
"To be avoided"	***"To Be Limited"***	***"Low Toxic Potential"***
Known Human carcinogens	Neurotoxins/ teratogens	PDE >50mg per day
Environmental hazards	Specified conc. limits	Non-specific tests permitted



CCl_4





CH_3CH_2OH

Residual Solvents - Limits and Tests

Class 2 Solvents – Option 1

Drug product/substance/excipient tested meets concentration limits in Table 2.

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

(Dose = 10g)

Class 2 Solvents – Option 2

- **Sum the quantities of residual solvent(s) in each ingredient in the finished dosage form**
- **Result should be less than PDE limits specified in Table 2.**

Finished product testing is permitted, but only if option 1 and 2 tests do not pass

Can be analysed using Loss on Drying if concentration levels less than 0.5%

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

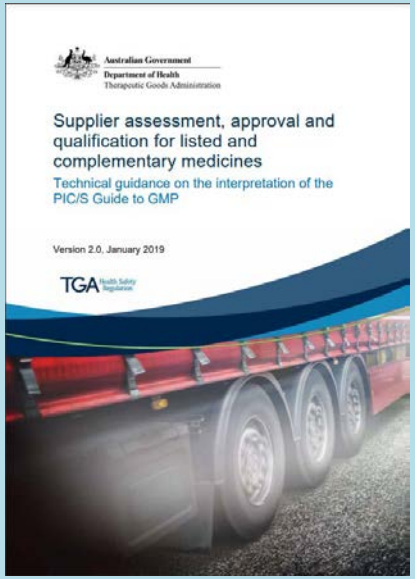
Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	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

Achieving and maintaining GMP Compliance

How do I know if I need to test for Elemental Impurities and/or Residual Solvents or not?

If I do need to test, to what extent, and how frequently?

Whether you have tested or not, the finished dosage form must comply to required limits for impurities!



Do I Need to Test for Residual Solvents?

"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

"Manufacturers of pharmaceutical products need certain information about the content of residual solvents in excipients or active substances in order to meet the criteria of this guideline….."
Ph Eur 5.4

- 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

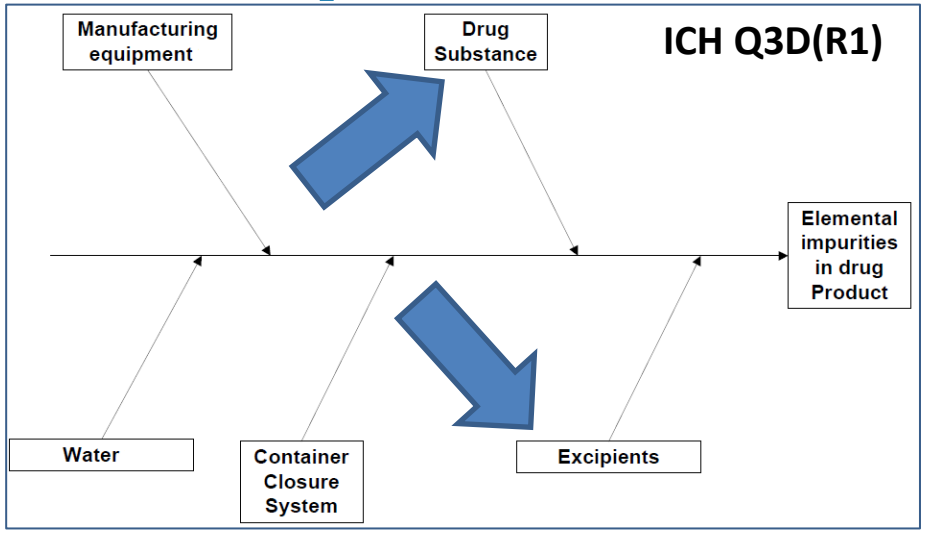
  (Here the supplier would name the Class 2 solvents represented by X, Y, ...)
- Only Class 2 solvents X, Y, ... and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5 per cent.

Do I Need to Test for Elemental Impurities?

"The extent of testing can be determined using a risk-based approach that takes into account the likelihood of contamination"

"Manufacturers should consider the presence of unexpected elemental contaminants to determine compliance."

USP <2232>



- Significant amount of ingredients used in listed/comp medicines come from natural origin
- Materials that come from natural origin are subject to contamination from the environment via pollution and agricultural practices.
- Highly likely that ingredients from natural origin will need to be tested for Elemental Impurities

Suppler Vendor Questionnaire items

- Information about how the material is produced and what impurities could be present.
- The site of manufacture of the material and (any) alternative sites used.
- The harvesting location, time of harvest, identification of raw herbs and method of preparation, (e.g. extraction).

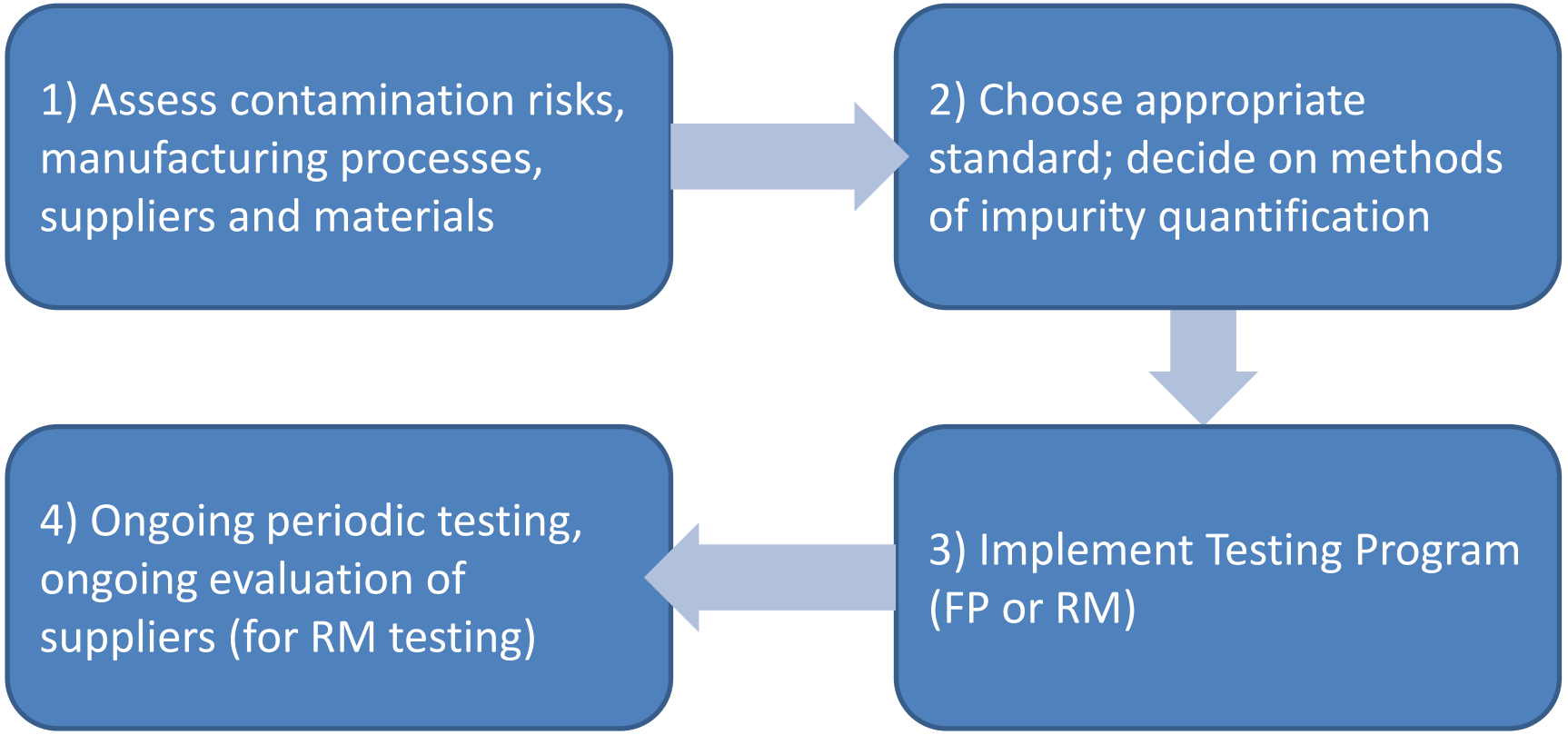
EI/RS Impurity Testing Frequency

For finished product analysis:
Periodicity of ongoing testing based on results/trends/risk

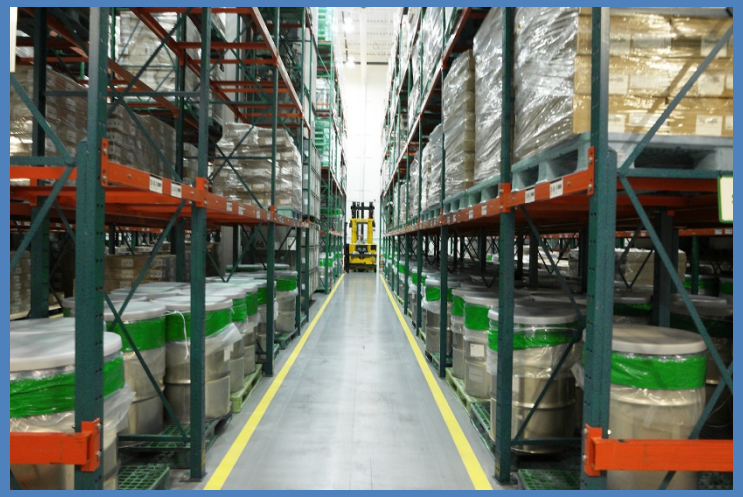
For component analysis

- Initially perform applicable impurity testing on **three** different specific manufacturer's lots of starting material.
- Review the results and compare with specified impurity limits and supplier CoA
- Upon successful testing of three batches, **rotational** impurity testing can then be utilised for that material from the qualified supplier.

Summary


1) Assess contamination risks, manufacturing processes, suppliers and materials
2) Choose appropriate standard; decide on methods of impurity quantification
3) Implement Testing Program (FP or RM)
4) Ongoing periodic testing, ongoing evaluation of suppliers (for RM testing)

Potential Issues – Supplier Assessment



- Lack of scrutiny over vendor questionnaire responses
- No detail in corresponding procedure on minimum vendor requirements for raw materials
- No ongoing/periodic review of existing suppliers

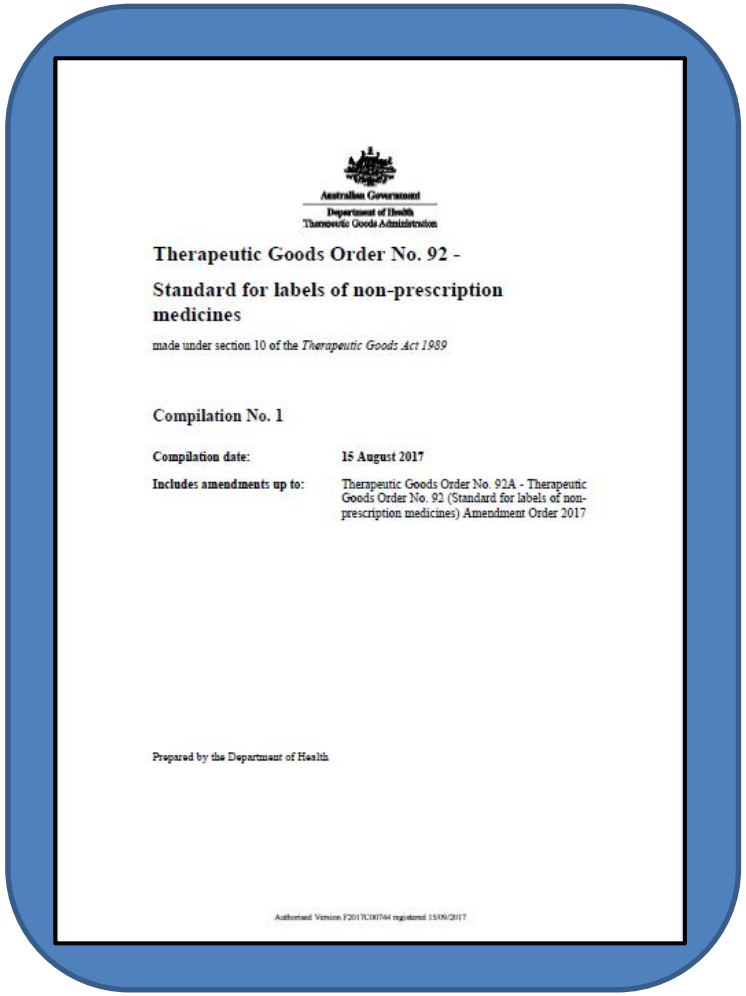
Potential Issues – Quality Risk Assessment

- Scientific approach not taken/assessment not supported with evidence
- Focus of risk assessment not based on product quality or patient safety
- Any additional measures/controls identified in the RA do not get actioned.

Potential Issues – Sampling & Testing

- Qualification of supplier/material not performed - vendor's CoA relied upon instead
- Rotational testing plan not adhered to
- Non-compliance to standards, calculation errors relating to impurity concentration levels

Questions?



Australian Government
Department of Health
Therapeutic Goods Administration

Therapeutic Goods Order No. 92 -

Standard for labels of non-prescription medicines

made under section 10 of the *Therapeutic Goods Act 1989*

Compilation No. 1

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Includes amendments up to: Therapeutic Goods Order No. 92A - Therapeutic Goods Order No. 92 (Standard for labels of non-prescription medicines) Amendment Order 2017

Prepared by the Department of Health

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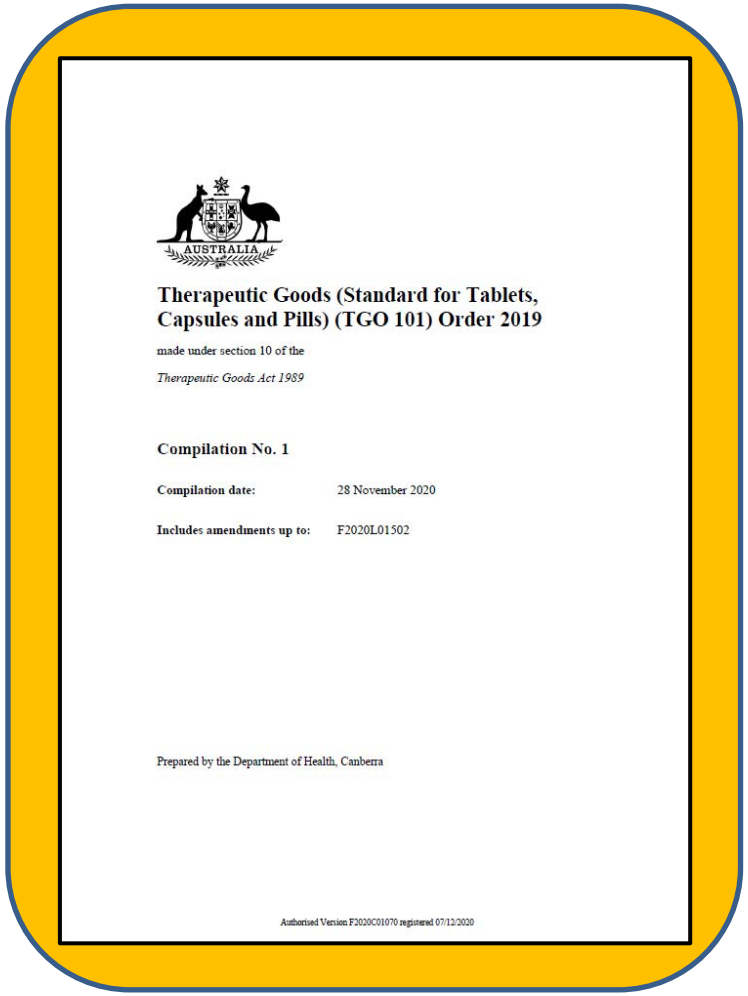

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