syngenta

Residual Impurity Management

Crop Protection Quality Code of Practice

CPQ-CoP-005

Contents

Document Information

CPQ-CoP-005 Residual Impurity Management

Document history:

Version	Date	Nature of changes	Change Impact	Author
1	10-Dec-10	Original issue	N/A	Urs Stutz
2	23-Jun-14	Update of links	N/A	Christian Mueller
3	28-Nov-14	Update about new CropLife booklet, Standard Practice and RIRA 2.0	N/A	Christian Mueller
5	23-Feb-18	Extensive revision. Structure and requirements aligned with Standard Practice Assessment [6]	Major	Maike François CHBS
5	18-Feb-19	CP QMS, update of references (code changes only)	Minor	Maike Francois CHBS

Due to the extensive revision, the scope, and the potential impact to the business, the CoP implementation time is extended from one year to two years.

Residual Impurity Management
Crop Protection Quality Code of Practice
CPQ-CoP-005

1. Purpose

Contamination of Crop Protection Products with Residual Impurities (RI) has been identified as one of Syngenta's highest business risks. Contamination with residual impurities is an area of risk for any (multi-purpose) chemical synthesis, formulation and packaging unit, storage facility and (bulk-) transportation operation. Residual impurities may cause adverse effects on sensitive treated crops or non-target species as well as regulatory issues. An incident may severely damage the image and brand of Syngenta and the reputation of the agrochemical industry itself. This CoP defines the requirements for the RI Management System and the responsibilities for the implementation and maintenance of it.

2. Scope

This Code of Practice applies to all Syngenta functions / locations involved in the manufacture of Crop Protection products and their distribution (e.g. Syngenta Crop Protection sites, Tolling, Procurement and Bulk Distribution / Logistic Operations).

3. Definitions & Abbreviations

AI	Active Ingredient
Cleaning limit	The maximum concentration (in ppm) allowed of active ingredient(s), or any other extraneous substance(s), measured in the cleaning medium. **Cleaning limit** $\leq \frac{2}{3} RI\ limit\ (ppm)$
CropLife	CropLife International is an international trade association of agribusiness companies. Its members include the world's largest agricultural pesticide businesses.
Facility	A term used in RIRA 2.0 software; identical with a manufacturing unit/line and/or filling line
FPP	Finished Product Processing
Manufacturing Unit	Combination of technical equipment used for the manufacturing.
NOEL	No observed effect level
Residual Impurity (RI)	Cross contamination of active ingredients(s) from another product
RIRA 2.0	Residual Impurity Risk Assessment software
Residual Impurity Limit (RIL)	The maximum concentration in ppm of the previous active ingredient(s), or any other extraneous substance(s) below which it will not cause any adverse biological, toxicological, ecological effects or regulatory issues in the succeeding product. Calculated with RIRA 2.0 software

Shared manufacturing asset	Technical equipment (reactors, tanks, packaging lines, mills etc.) used for the manufacture and storage of different products (multi-purpose equipment).
Toller / Toll Manufacturer	A company synthesizing, formulating or packaging a product for Syngenta on a contractual basis. The term “toller / toll manufacturer” is synonymous with contract manufacturer or contractor.

4. Principles

A cross contamination (residual impurity) incident is a major risk to Syngenta’s crop protection business and may have far reaching consequences such as a breach of legal obligations, severely damaged value crops, environmental damage, loss of reputation, and material financial impact.

Syngenta will ensure that their products on the market do not contain residual impurities in the form of active ingredients not defined in the product specification, at levels which will prejudice safety and efficacy, or which do not meet regulatory requirements. Syngenta will set the limits for their products, following an appropriate written risk assessment. Legal requirements such as US EPA Pesticide Regulation (PR) Notice 96-8 as well as any local legislation must be followed [1, Appendix C].

The manufacture in any kind of shared assets requires proper management and discipline of all involved stakeholders to mitigate the risk of a cross contamination and deliver on the promises made on the label without any undesirable side effects.

Syngenta promotes and adheres to the commitments and requirements of CropLife which are defined in the CropLife booklet ‘Contamination Prevention in the Manufacture of Crop Protection Products’ [1].

Syngenta manufacturing sites, third party toll manufacturers, suppliers and distribution / logistic operations for bulk storage and transportation must implement an RI Management System as outlined in this document.

4.1 Management Responsibility

Management of the following functions is responsible for implementation, maintenance and resourcing of the RI Management System and must ensure compliance to the RI Management system requirements as defined in this document.

Function	Scope
Syngenta sites	AI synthesis and FPP
Tolling Management	All FPP tolling activities
Procurement	Tolling and purchasing of AI’s, intermediates, raw materials, formulation inerts, purchased finished goods (range enhancement)
Distribution / Logistic Operations	Bulk storage and bulk delivery

Herewith the management has further specific responsibilities:

Global Head P&S CP Quality, Management representative for RI Management:

- Act as the Syngenta contact to external stakeholders on all aspects of contamination (e.g. Authorities – Member of CropLife Product Integrity Team (PIT))
- Understand and develop approach to ensure compliance to legal and regulatory requirements
- Ensure appropriate NOEL determination and RIL together with Product Safety
- Communicate the requirements of this RI Management CoP to the relevant stakeholders in the functions and Regions
- Manage the implementation and verification of effectiveness of all key controls outlined in this CoP
- Design and offer continuous training to increase awareness to the relevant people and monitor the effectiveness

Ensure that exceptions to any of the **general requirements** have documented approval from appropriate management.

Site Managers, Tolling Management, Procurement, Distribution / Logistics:

- Monitor and review information on identified external and internal issues and define improvement plan or risk mitigation measures as appropriate
- Communicate the requirements of this CoP to the relevant personnel
- Ensure that local procedures, work instructions, checklists and other production documents include RI prevention measures, and are implemented in accordance with policies and CropLife requirements [1]
- Provide sufficient qualified resources for all aspects of contamination prevention

Line Managers

- Ensure actions to address risks and opportunities are carried out and evaluate the effectiveness
- Develop and implement an implementation plan of the key controls outlined in this document
- Verify the effectiveness of the key controls on a regular basis

Procurement Managers

- Ensure that any purchased active ingredient complies with this CoP and CropLife requirements

Regulatory:

- Any changes to product application or toxicological data have to be handled through via Product and Process Change Control (PPCC) [5] and communicated accordingly to the relevant stakeholders.

Head Global Quality Systems:

- Own and administer RIRA 2.0 (Residual Impurity Risk Assessment) Software
- Maintain and update, if necessary, the RIRA 2.0 software

4.1.1 Site and Toller assessments in existing collaborations

The potential impact of the externally provided processes, products and services on Syngenta's ability to consistently meet customer, statutory, and regulatory requirements must be considered as it forms an important pillar of Syngenta's business success. Besides the monitoring requirements for 3rd parties [3], management is responsible to ensure that regular site and toller assessments are in place and executed by competent personnel. Assessments must be documented and take into account at a minimum:

- A RI Management Assessment based on Syngenta Standard Practice (SP) maturity model [6] demonstrating compliance with the mandatory requirements therein.
- A compliance assessment of contamination prevention processes, technical and analytical equipment and the competency of staff against the CropLife Contamination Prevention criteria and "best practices" (CropLife self-assessment checklist) [1].
- An improvement plan to address any gap or nonconformity.
- Contractual agreement on RI Management requirements with toll manufacturers and suppliers based on CropLife requirements [1].

4.1.2 Qualification of new collaborations

Principal evaluation requirements for 3rd Parties are defined in CPQ-CoP-010 and apply [3]. For tollers in addition an RI Standard Practice assessment followed by a full RI audit must be performed at any new toller or third party supplier performing synthesis based on Syngenta IP (Intellectual Property) and formulation operations before first commercial supply [3]. Third parties limited to packaging operations must be audited if the assessment indicates an RI risk (see chapter 5).

A toller is not qualified to start commercial supply as long as product compliance cannot be guaranteed (i.e. if major nonconformities have been identified which indicate a serious risk of cross contamination).

4.1.3 Quality Incident management for Residual Impurities

In the event that an external RI incident occurs, speed is essential to mitigate the impact on the business. External Quality Incidents related to RI must be reported immediately to Emergency Management Syngenta if the RI incident is a serious business risk which might trigger regulatory action and product recall or attract media interest [4,8].

Regionally led RI Emergency Management training must be carried out with site relevant stakeholders in a planned manner, but at least once every two years to ensure the process is understood and can be executed without delay if needed.

All RI nonconformities/incidents must be escalated to the CP FPP Head within 24 hours.

4.2 Training and Awareness

RI training must be in place on a site level and conducted on a regular basis, at least annually. The training package must cover key risks and local procedures and must be based on CropLife guidelines and this CoP. All new employees (permanent and temporary) or contract workers must receive basic RI training within one month of their start date. It is prohibited for untrained personnel to carry out any production tasks without the supervision of a qualified operator.

4.3 Equipment Design and Segregation

4.3.1 Separation rules

Non-herbicides must not be produced in the same equipment as herbicides (highly active, low rate and normal rate herbicides), i.e. separation between manufacturing units must be guaranteed. This applies to all synthesis, formulation, filling and packaging operations (chapter 4.2 “Contamination Prevention in the Manufacture of Crop Protection Products – Guidelines and Best Practices”) [1].

An exception to this rule is only permitted with written approval from the Regional Production Head and Regional Quality Lead on the deviation [9]. The approval could be issued with regional validity [1]. Herbicide and insecticide/fungicide synthesis lines must at least be dedicated to AI class during the campaign. Existing physical connections to other lines must be blinded off. Stringent cleanliness of the equipment must be confirmed by achievement of the applied cleaning limit in the rinsate.

Seed treatment products must be separated from herbicides (highly active, low rate and normal rate herbicides) for all formulation and fill and pack procedures. Herbicide and Seed treatment active ingredient synthesis lines must always be separated. No exception to this rule is allowed as the multiplication of steps from relatively small volumes of product to large volumes of treated seeds and eventually hectares of crops, significantly increases the financial risk to Syngenta.

The use of any industrial chemical (non-agrochemical) must comply with the requirements of the CropLife Contamination Prevention guidelines [1]. Pesticides including active ingredients must not be manufactured and/or transported together with:

- Human and Veterinary pharmaceutical products
- Personal Care and other health care products
- Food and feed stuffs (including vitamins)

4.3.2 Planning rules

Production and packaging sequences must be scheduled to avoid high RI risk(s) whenever possible. Product changeovers with very high RI risks are not allowed. These are defined as:

- Changeover with RIL ≤ 10 ppm for liquids
- Changeover with RIL ≤ 50 ppm for solids

Exceptions to this rule must be justified and approved by the Regional Production Head and Regional CP Quality Lead.

4.3.3 Peripheral equipment

Flexible hoses, transfer lines and connections must be clearly labelled by product or product type. Transfer lines must be dedicated for highly active herbicides. Flexible hoses and connections must be dedicated for highly active, low rate and normal rate herbicides.

4.4 Cleaning Procedures

Cleaning of the production unit is essential for effective contamination prevention, the Residual Impurity limit (RIL) required for a product-changeover is the primary indication of the risk involved in the changeover [1]. Cleaning procedures must be available for each (shared) synthesis, formulation and packaging line, clearly describe the cleaning steps and processes to be executed ensuring repeatability (e.g. the type and amount of solvent, temperature, agitation speed, holding time) and must be validated for their purpose. Cleaning operations must take place as soon as possible after the production has

stopped. This applies when changing from one product to the next, and also if the equipment will be left idle. Cleaning of the equipment must be documented.

4.4.1 Mandatory content of cleaning procedures

Written cleaning procedures must be in place and take into account:

- The individual Residual Impurity Limit (RIL) calculated by RIRA, product mix and sequence of products
- Type of operation (synthesis, formulation or packaging of liquids or solids)
- Physical/chemical properties of products
- Design of the production unit

Cleaning procedures must clearly describe:

- The calculated Cleaning Limit
- The cleaning medium used (e.g. water, soap, organic solvent)
- The sequence in which the individual parts of the manufacturing line(s) are cleaned
- The addition of the cleaning medium into the equipment, e.g. by use of a rotating spray head or high pressure cleaner
- The number of flushes (liquid or solid) applied and the minimum quantity of the cleaning medium per flush
- The (partial) dismantling of the equipment and the manual cleaning of the individual parts with the cleaning medium (if needed)
- Visual inspection to be performed and steps to be taken if residual material is visible in the equipment (at a minimum the cleaning step must be repeated)
- The description of sampling locations for flush samples
- The process of drying inner surfaces (if necessary) by either heating or purging the equipment with nitrogen or compressed air
- The parts to be cleaned have to be identifiable (e.g. labelled with a number) and referenced in the cleaning documentation
- The disposal / recycling procedure for the used cleaning medium

Operators must be informed about the adjacent steps / cleaning processes done to ensure complete cleaning of the entire equipment. Cleaning operation steps and results must be recorded by those performing them and signed by a supervisor.

4.4.2 Reworking, Blending and Recycling

All out of specification material must be clearly marked as such. Materials containing active ingredients being stored for rework must be quarantined or segregated from other packaged materials containing different active ingredients. No rework (including blending) of out of specification or expired batches from previous production runs is allowed without a written procedure. Rework of Syngenta products by a contract manufacturer can only take place with Syngenta's written approval.

Rinsates and flushes must not be recycled for use in production except where appropriate controls are in place to avoid mix-ups and full traceability allows quantitative and qualitative identification of all

residuals. Recycling of samples is prohibited (i.e. retain and QC samples may not be reintroduced into production).

4.5 Material Identification

Appropriate material identification is essential to avoid mix-ups in production and ensure full traceability. All materials including recycled / retained material and rinsate must have printed labels with product name, product code (unique), batch no., production date, quantity, delivery identification (if applicable). Production areas must be cleared of all products, raw materials, labels and packaging material from the previous production run. All materials (e.g. AI, raw materials, labels) required for the current production order must be confirmed against the relevant bill of material by a second person (4 eyes principle) prior to start of production.

4.6 Analytical Strategy

A testing plan must be defined for all materials.

4.6.1 Raw material release

All materials used in production must be adequately controlled to ensure they meet the requirements to manufacture product to a consistent quality level. It is prohibited to release a chemical raw material on the basis of a certificate of analysis without any additional analytical qualifiers which ensure the material is fit for purpose. This includes but is not limited to:

- Identity check (e.g. FTIR, Raman)
- Purity check (e.g. by refractive index, Melting Point)

Analytical results must be documented. Samples must be taken and retained until the raw material has been consumed and the resulting products have been released in specification. Samples must be kept in a dark, dry and cool place.

Exceptions must be justified and approved by the Regional Production Head and Regional CP Quality Lead.

4.6.2 Residual Impurity limits

All shared manufacturing and/or packaging assets used in the manufacture or packaging of active ingredients, intermediates and/or formulations must have RI limits defined. These are calculated with the *Residual Impurity Risk Assessment (RIRA)* software [7] and are output in the form of a matrix. Each Syngenta material and external active ingredient on shared lines must be covered in these matrices. Tollers are obliged to provide information about non-Syngenta active ingredients sharing the lines with Syngenta products [1]. The RI limits provided in the matrix must be applied at all times.

A RI matrix must be created, updated or recalculated at a minimum in following cases:

- New production / packaging line (facility)
- Product mix change of existing facility (additional product or residual impurity, relocation of existing product to another facility)
- After 3 years for registration information (application rates, crops, region, seed treatment) of all facility products
- After major update of the RIRA database (admin version change to next integer number, e.g. from 2.14 to 3.0)

In case of introduction of a new active ingredient on a line or major regulatory change in the registration of active ingredients, relevant information and data must be provided to the Regional CP Quality Lead by the Product Safety team, this point must be covered through Product and Process Change Control (PPCC) [5] as these changes may have an major impact to the risk assessment, these changes include for example:

- Newly approved application scenarios (e.g. addition of seed treatment applications for an AI which did not have that registration before)
- NOEL Data coming from CP Biology Research
- Initial registration of an AI in the US and Canada (EPA requirements)

The relevant data and information must be communicated accordingly to the right stakeholders to update the data in RIRA.

4.6.3 Product release

Products manufactured must not be released before it is demonstrated that the concentration of residual impurities is below the Residual Impurity Limit (RIL). RI limits must be achieved in the product they have been calculated for.

The RI limit is used for the First Fill Analysis to release the product.

The Cleaning Limit is used for the rinsate analysis to release the equipment, this analysis must always be performed for equipment release for all changeovers regardless of the cleaning limit. For product release the analysis must be performed according to the rules defined below:

- First Fill Analysis (product in product) for changeover limits < 250 ppm
- For changeover limits ≥ 250 ppm, best practice is First Fill Analysis, on a risk based approach a rinsate analysis can be performed

Analysis of a rinsate instead of a product represents a risk of obtaining a false positive (release) result.

A release based on rinsate analysis can only be granted if the result fulfils the following requirement:

$$\boldsymbol{Analytical\ Result}\ [\boldsymbol{ppm}] \leq \boldsymbol{Cleaning\ Limit}\ (=\frac{2}{3}\boldsymbol{RI\ limit})\ [\boldsymbol{ppm}]$$

RI limits, the analytical result achieved and the method used must be part of the release documentation.

4.6.4 Validation of Methods

All methods used for the analysis of residual impurities must be validated, i.e. methods must fulfill the below requirements [1]:

- Specificity of the method – the ability to separate the signal of the AI from other components
- Recovery – the ability to accurately quantify the amount of the AI (e.g. by spiking)
- Repeatability – the ability to gain the same result when analyzing the same sample multiple times, different weights and different analysts
- Linearity – the ability to reliably quantify a component over a range of contents.

4.6.5 Calibration

Measurement traceability and confidence in the analytical results is essential, all equipment used in the process of final product release must be:

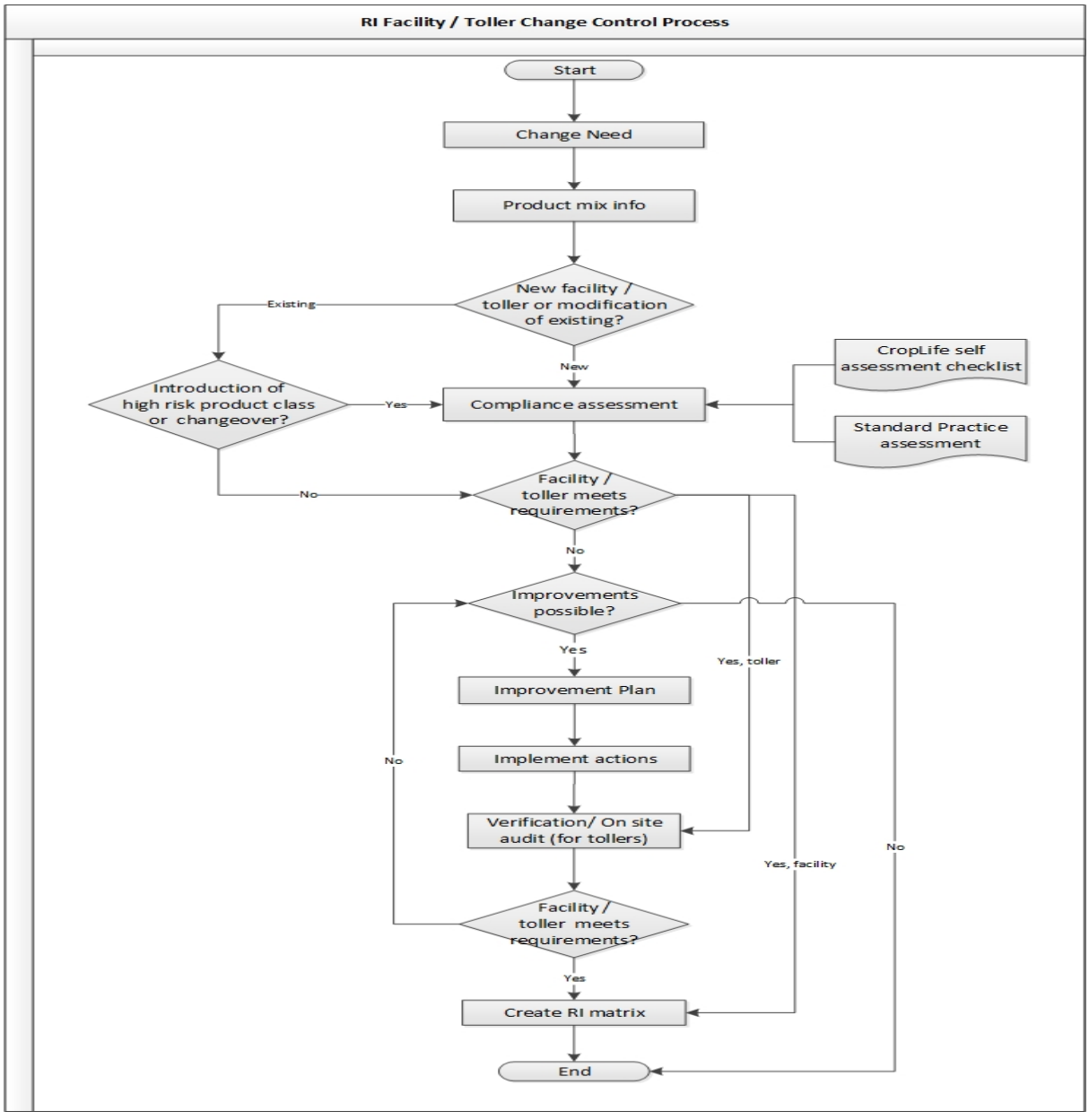
- Uniquely identified and documented in an inclusive list of equipment

- Calibrated or verified, or both, maintained at specified intervals, against measurement standards traceable to international or national measurement standards
- Safeguarded from adjustments, damage or deterioration that would invalidate the calibration status and subsequent measurement results

Calibration and maintenance must be documented allowing full traceability of the operations (i.e. including identification, frequency, dates, results and tolerances, operator performing the activity).

5 Change Control

Changes must be controlled to maintain compliance with regulatory and statutory requirements for products and processes and to ensure meeting the customer expectations, following CoP-8.1 [5], and managed through Product and Process Change Control (PPCC) [5] The implementation of new CP tollers and changes to existing facilities (internal and external) e.g. introduce new AI's will follow the below process for RI management purposes:



Summary sheet	
Title	CPQ-CoP-005 Residual Impurity Management
Purpose	Contamination of Crop Protection Products with Residual Impurities (RI) has been identified as one of Syngenta's highest business risks. Contamination with residual impurities is an area of risk for any (multi-purpose) chemical synthesis, formulation and packaging unit, storage facility and (bulk-) transportation operation. Residual impurities may cause adverse effects on sensitive treated crops or non-target species as well as regulatory issues. An incident may severely damage the image and brand of Syngenta and the reputation of the agrochemical industry itself. This CoP defines the requirements for the RI Management System and the responsibilities for the implementation and maintenance of it.
Scope	This Code of Practice applies to all Syngenta functions / locations involved in the manufacture of Crop Protection products and their distribution (e.g. Syngenta Crop Protection sites, Tolling, Procurement and Bulk Distribution / Logistic Operations).
Personal Scope	[X] General Policy / CoP [__] Functional Policy / CoP
Geographic Scope	[X] Group Policy / CoP [__] Country Policy / CoP
Target audience	All Syngenta functions / locations involved in the manufacture of Crop Protection products and their distribution
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Approved by	Gray Tom CHBS; French Richard CHBS
Issued by	Crop Protection Quality
Originator	Maike Francois CHBS
Process Owner	Maike Francois CHBS

Further References	[1] Contamination Prevention in the Manufacture of Crop Protection Products - Guidelines and Best Practices" [2] ISO 9001:2015 [3] CPQ-CoP-010 Third Party Management [4] CPQ-CoP-011 Product Recall [5] CPQ-CoP-008 Change Control [6] CPQ-FR-005-04 Standard Practice Assessment [7] CPQ-PR-005-01 RI Matrix Creation [8] CPQ-CoP-002 Nonconformity Management [9] CPQ-FR-005-08 Residual Impurity Management Deviation Record
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