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Quality Risk Management: A Review

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ABSTRACT

In the pharmaceutical industry today, there are some examples of the use of quality risk management but, they do not represent the full contributions that risk management has to offer. Quality risk assessment is a process of identification of hazards, analysis and evaluation of the risks associated with exposure to those hazards. Risk assessment is a main part of quality risk management process. The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the safety of the patient. For any pharmaceutical organization, quality risk management should aim at raising the level of protection for the patient, by reduction of the risk to which that patient is exposed at the time he/she receives a drug product. In the present seminar report all the aspects regarding quality, quality risk assessment and risk management are covered in great detail.

Keywords: quality, risk management, risk assessment, hazards, analysis, evaluation of risks

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INTRODUCTION

According to ISO8402-1986 standards **quality** is "the totality of features and characteristics of product or service that bears its ability to satisfy stated or implied needs". In manufacturing, a measure of excellence or state of being free defects, deficiencies and significant variations [1].

According to ISO 31000***, risk*** is the "effect of uncertainty on objectives" and an effect is a positive or negative deviation from what is expected [2].

A risk is ANYTHING that may affect the achievement of an organization's objectives. It is the UNCERTAINTY that surrounds future events and outcomes.

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of quality systems has been recognized in the pharmaceutical industry, and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. In addition, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater

assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk-based decisions, by both regulators and industry, regarding the quality of drug substances and drug products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators [3]. Quality and risk management are complementary and, together, are key components of healthcare governance. Effective risk management underpins healthcare quality management activity and can result in:

• Better patient care
• Improved public perception and confidence
• Reduction in errors
• Reduction in staff turnover
• Systematic identification of organizational weaknesses
• Improved communication with stakeholders
• Improved performance and effectiveness [9].

SCOPE

a) Quality risk management (QRM) principles can be applied to both MRAs and pharmaceutical manufacturers and MRAs

• MRAs: systematic and structured planning of reviews and inspections. The submission review and inspection programmes can also operate in a coordinated and synergistic manner.

• Manufacturers: development, manufacture, distribution of medicines. RM can be an integral element of organizational culture.

b) Science-based decision-making can be embedded into practice

• MRAs: company decisions easier to scrutinize. Acceptance of residual risks through understanding the RM decisions involved.

• Manufacturers: quality decisions and filing commitments can be based on science based process understanding and RM (quality by design). Process control focused on critical attributes. Uncertainty can be addressed explicitly.

c) Resources can be focused on risks to patients

• MRAs: RM can be used to determine best allocation of inspection resource, both in terms of product types and for specific areas of focus for a given inspection. This enables the most efficient and effective scrutiny of the most significant health risks.

Those manufacturers with poor histories of GMP compliance can also be more closely and frequently evaluated by on-site inspection than those manufacturers with better records.

• Manufacturers: evaluation of quality risk through science-based decisions can be linked ultimately to protection of the patient. Supports a corporate culture to focus on the patient as a primary stakeholder in all activities.

d) Restrictive and unnecessary practices can be avoided

• MRAs: regulatory scrutiny adjusted to level of process understanding. Improvement and innovation by manufacturers is encouraged.

• Manufacturers: instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company's quality management system. Real-time batch release is feasible. Innovation and the adoption of latest scientific advances in manufacturing and technology are supported.

e) Communication and transparency are facilitated

• MRAs: facilitated dialogue with pharmaceutical manufacturers and tailoring of the inspection programme. Improved clarity of a company's decision-making process and judgement on critical issues.

• Manufacturers: matrix team approach, stakeholders kept informed via science-based decisions. Culture of trust and "one-team" mindset with focus on product and patient.

QRM is the overall and continuing process of minimizing risks to product quality throughout its life-cycle in order to optimize its benefit/risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product.

It can be applied both proactively and retrospectively. QRM should ensure the evaluation of risk to quality based on scientific knowledge and experience that ultimately links to the protection of the patient.

This guideline will align with the general framework described within other current international papers on this subject [4].

PRINCIPLES OF QUALITY RISK MANAGEMENT

Four primary principles of QRM are:

- •The evaluation of the risk to quality should be based on scientific knowledge and 3 ultimately link to the protection of the patient;
- QRM should be dynamic, iterative and responsive to change;
- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk;
- The capability for continual improvement and enhancement should be embedded in the QRM process [3].

GENERAL QUALITY RISK MANAGEMENT PROCESS

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1). The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

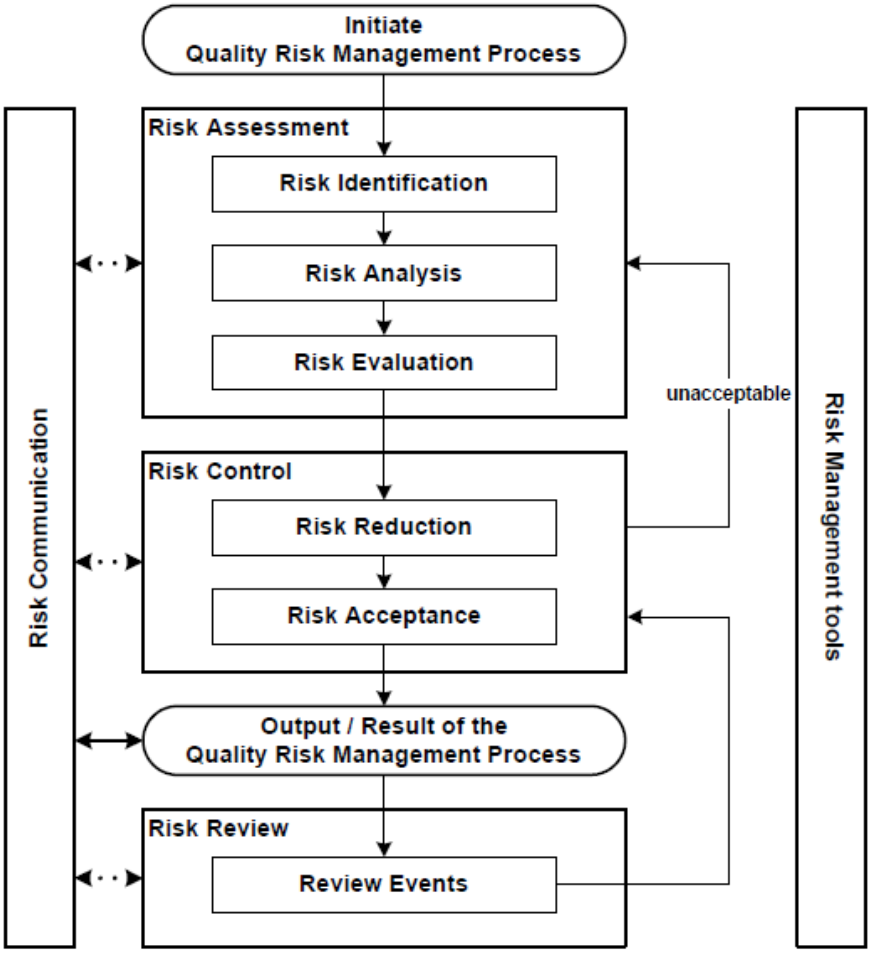


Figure 1: Overview of a typical quality risk management process

Decision points are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: "unacceptable" in the flowchart does not only refer to statutory, legislative, or regulatory requirements, but also to indicate that the risk assessment process should be revisited [4, 5, 6].

RESPONSIBILITIES

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams **(Assemble a QRM team)**. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics, and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Decision makers should

- Take responsibility for coordinating quality risk management across various functions and departments of their organization and
- Ensure that a quality risk management process is defined, deployed, and reviewed and that adequate resources are available [4]

INITIATING A QUALITY RISK MANAGEMENT

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk
- Assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment
- Identify a leader and critical resources
- Specify a timeline, deliverables, and appropriate level of decision making for the risk management process [4].

RISK ASSESSMENT

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information that will address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)? [5].

Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

1. Is the risk above an acceptable level?
2. What can be done to reduce or eliminate risks?

3. What is the appropriate balance among benefits, risks and resources?
4. Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk.

In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis [3, 4].

Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties (e.g., regulators and industry; industry and the patient; within a company, industry, or regulatory authority). The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances [3].

Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented. The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events

that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions [2, 3].

QUALITY RISK ASSESSMENT

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below).

When hazard identification and risk analysis is conducted safety concerns must be distinguished from quality concerns. An initial assessment should be performed based on an understanding of the business processes. Understanding can be derived from user requirements, design specifications, operating procedures, regulatory requirements and known functional areas [7].

The QRM team should list all the hazards that may be reasonably expected to occur at each step from production, testing and distribution up to the point of use. It should then conduct a hazard analysis to identify for the QRM plan which hazards are of such a nature that their elimination or reduction to acceptable levels is essential.

A thorough risk analysis is required to ensure an effective control point. A two-stage risk analysis is recommended. During the first stage, the team should review the materials, activities, equipment, storage, distribution and intended use of the product. A list of the hazards (biological, chemical and physical) which may be introduced, increased or controlled in each step should be drawn up.

The QRM team should then decide which potential hazards should be addressed in the QRM plan and what control measures, if any, exist that can be applied for each hazard. If a hazard has been identified at a step where control is necessary for safety, and no control measure exists at that step or any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure. More than one control measure may be required to control a specific hazard and more than one hazard may be controlled by a specified control measure.

This activity can be facilitated by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packing, reprocessing, storage or distribution. Potential hazards in relation to at least the following should be considered:

- Materials and ingredients;
- Physical characteristics and composition of the product;
- Processing procedures;

- Microbial limits, where applicable;
- Premises;
- Equipment;
- Packaging;
- Sanitation and hygiene;
- Personnel – human error; and
- Risk of explosions.

The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (e.g. high/medium/low) and may be related to a risk matrix .The scoring system and trigger points for mitigating action are subjective so the rationale for score categorization should be defined in as much detail as possible. If supported by factual evidence it should be more obvious what mitigating action is required – the mitigating action is as important as the score assigned. Professional judgment should be used in interpretation of factual evidence but must be subject to justification.

The expectation of QRM is to assess risks to the medicinal product and patient and then manage both to an acceptable level. It is appropriate for companies to assess their control systems to implement the optimum controls to ensure product quality and patient safety. If this can be achieved in a more cost-effective manner whilst maintaining or reducing risk to the product and patient then this is acceptable. Inappropriate risk assessment and mitigation in order to achieve cost savings but which could be to the detriment of the patient must be avoided [4].

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process .You will also need to consult a range of documentation held by your organization. For example:

- Risk registers
- Strategy and policy documents
- Previous assessment reports
- Internal audits, National Audit Office reports or other assurance reporting
- An Information Asset Register (IAR), or similar database, which your organization has used to map the relationships between its information assets, business use and technological environment [4, 14].

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms.

In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions. In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations.

Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge, gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems. The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high," "medium," or "low," which should be defined in as much detail as possible. Sometimes a *risk score* is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation [5].

How often should the assessment be reviewed?

Risk assessments must be reviewed regularly:

- Every two years as a minimum
- Immediately following a serious incident or where there is reason to suspect it is no longer valid.

What should be recorded in the written risk assessment?

All risk assessments should consider and record the following:

- Identification of the hazards
- Determination of who might be harmed and how
- Description of existing controls, and whether these adequately control the risk

- Description of additional steps to take (if necessary), in the form of an action plan
- Measures to be taken if things go wrong – an emergency action plan
- Date of the assessment
- Signatures of assessor(s) and workers involved [8, 13].

RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision making. It provides documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and, sometimes, detectability of the risk. Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/or internal procedures) based on, for example, compilation of observations, trends, and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations, and allocation of resources.

In addition, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/or internal procedures (e.g., standard operating procedures). Below is a no exhaustive list of some of these tools:

1. Basic risk management facilitation methods
2. (Flowcharts check sheets, etc.)
3. Failure Mode Effects Analysis (FMEA)
4. Failure Mode, Effects, and Criticality Analysis (FMECA)
5. Fault Tree Analysis (FTA)
6. Hazard Analysis and Critical Control Points (HACCP)
7. Hazard Operability Analysis (HAZOP)
8. Preliminary Hazard Analysis (PHA)
9. Risk ranking and filtering
10. Supporting statistical tools

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles. The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/or criticality of the issue to be addressed. It is important to note that no

one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

1. Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision making are:

• Flowcharts

• Check Sheets

• Process Mapping

• Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)

2. Failure Mode Effects Analysis (FMEA)

FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures, and the likely effects of these failures.

Potential Areas of Use(s)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

3. Failure Mode, Effects, and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode, Effects, and Criticality Analysis. In order for such an analysis to be performed, the product or process specifications should be established. FMECA can 2identify places where additional preventive actions might be appropriate to minimize risks.

Potential Areas of Use(s)

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk “score” for each failure mode, which is used to rank the modes on a relative risk basis.

4. Fault Tree Analysis (FTA)

The FTA tool is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or subsystem) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential Areas of Use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

5. Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety .It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products. HACCP consists of the following seven steps:

1. Conduct a hazard analysis and identify preventive measures for each step of the process
2. Determine the critical control points
3. Establish critical limits
4. Establish a system to monitor the critical control points
5. Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control
6. Establish system to verify that the HACCP system is working effectively
7. Establish a record-keeping system

Potential Areas of Use(s)

HACCP might be used to identify and manage risks associated with physical, chemical, and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that

facilitates monitoring of critical points not only in the manufacturing process but also in other lifecycle phases.

6. Hazard Operability Analysis (HAZOP)

HAZOP is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called guide words. Guide words (e.g., No, More, Other Than, Part of) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. HAZOP often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s)

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

7. Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product, or system. The tool consists of:

- The identification of the possibilities that the risk event happens,
- The qualitative evaluation of the extent of possible injury or damage to health that could result,
- A relative ranking of the hazard using a combination of severity and likelihood of occurrence, and
- The identification of possible remedial measures

Potential Areas of Use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures;

thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

8. Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful for management to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

9. Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

- Control charts, for example:
  - Acceptance control charts (see ISO 7966)
  - Control charts with arithmetic average and warning limits (see ISO 7873)
  - Cumulative sum charts (see ISO 7871)
  - Shewhart control charts (see ISO 8258)
  - Weighted moving average [9, 11, 12].
- Design of experiments (DOE)
- Histograms
- Pareto charts
- Process capability analysis [2, 3, 10].

Dissociating approach towards QRM

The implementation of Risk Management will be effective only if this requires a volume of resources compatible with the possibilities of the organization. Therefore, the approach developed consists in dissociating the constants from the variables in the policy of Quality Risk Management.

Constants encompass all areas, except products, which are implemented by the organization including processes, facilities, equipment, personnel; they are indicated in a generic way under name of "System";

Variables are given by the specific characteristics of the products manufactured, handled or even simply harvested by the System; these variables are indicated by "Product". According to the approach, Global Risk determination (Rg), as required by the regulatory framework, corresponds to the risk of manufacturing the considered product in the existing system. The Global Risk (Rg) is then obtained as a result of the multiplication of the System Risk (Rs) by a modulating factor called "Product factor" (P) ,then: $Rg = Rs \times P$

This dissociating approach thus proposes to the organization to initially evaluate its systemic risk (Rs) independently of the products, which are manufactured. The introduction of the product as a factor (P) avoids reworking all elementary steps for each different product. Moreover, the dissociating approach makes it possible to define the limits of acceptability of the system and authorizes the prospective and retrospective analyzes. These limits will be given in specific documents, called "rational techniques" which will support the decisions of acceptance of the risk by the Organization. It is interesting to stress that technical rationales could advantageously be established on recurring questions (such as the prevention of the airborne contaminations, the performances of cleanings, etc.) to avoid the repetition of specific studies. The integration of the diagram given with the principle of the dissociating approach led to the establishment of the complete diagram given below:

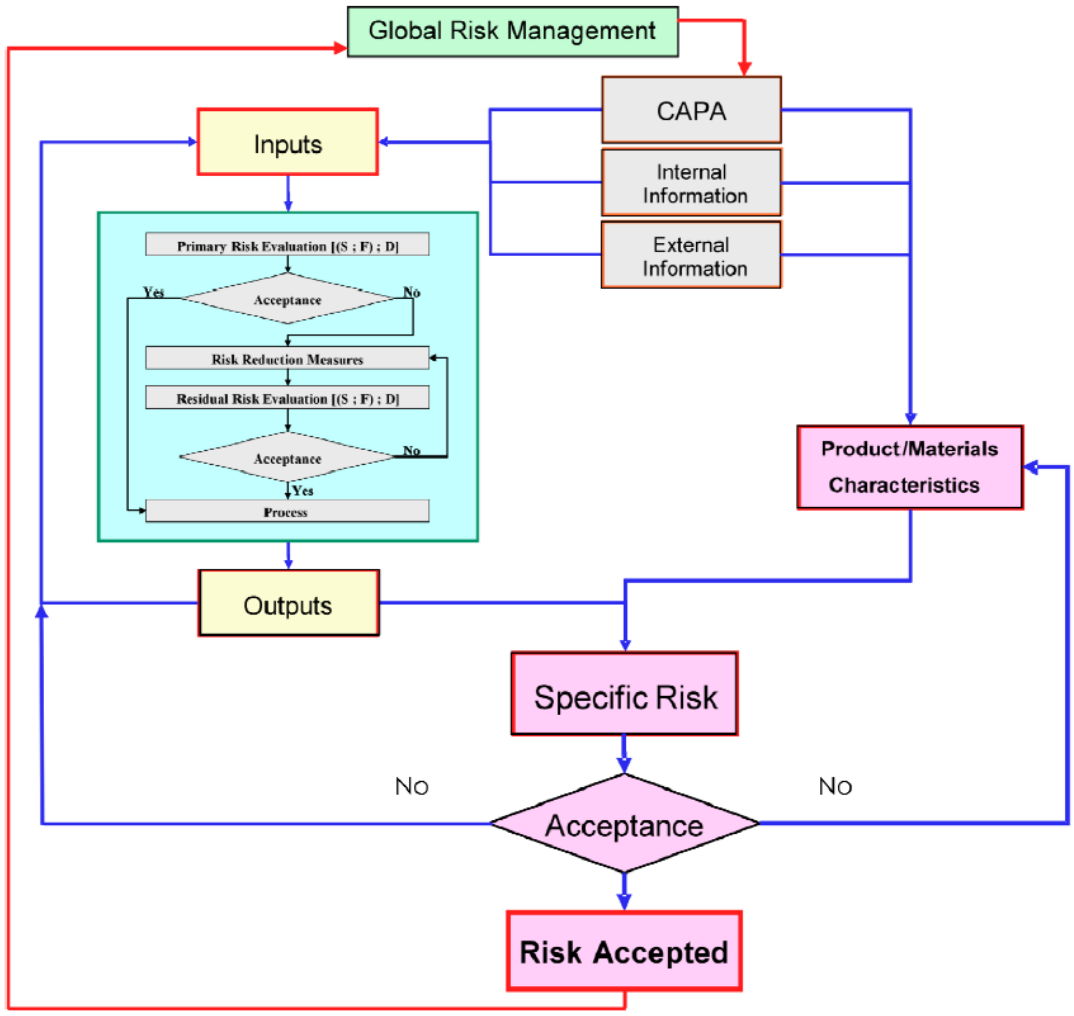


Figure 2: Global Risk Management Diagram [6]

Implementation of methodology

Quantification

For its implementation, the example of methodology requires to define the rules of quantification for the different parameters Severity (S), Frequency (F) and Detectability (D) entering calculation of the systemic risk (Rs):

- **Severity (S):**
  1. 0; Not addressed explicitly or implicitly by the applicable GMP
  2. 1; Addressed by applicable GMP, but without possible impact on the manufactured product
  3. 2; Possible impact on the manufactured product but without risk for the patient (end user)
  4. 3; Possible impact on the manufactured product and with possible hazard for the patient (end user)

- **Frequency (F):**

➢ 0; Event intervening with a frequency lower than 10e-6

➢ 1; Accidental event, occurrence exceptional

➢ 2; Frequent but non-systematic event

➢ 3; Event noted each time or almost

- **Detectability (D):**

➢ a; Undetectable

➢ b; Absence of system of detection but detection is still possible by chance

➢ c; Presence of a single system of detection which is not 100% reliable

➢ d; System of multiple and independent detection tools or a single system of detection which is 100% reliable [5,6].

Determination of the systemic risk

Each elementary step for each stage included in these processes is submitted to the system risk assessment according to a standardized mode as represented in the following form:

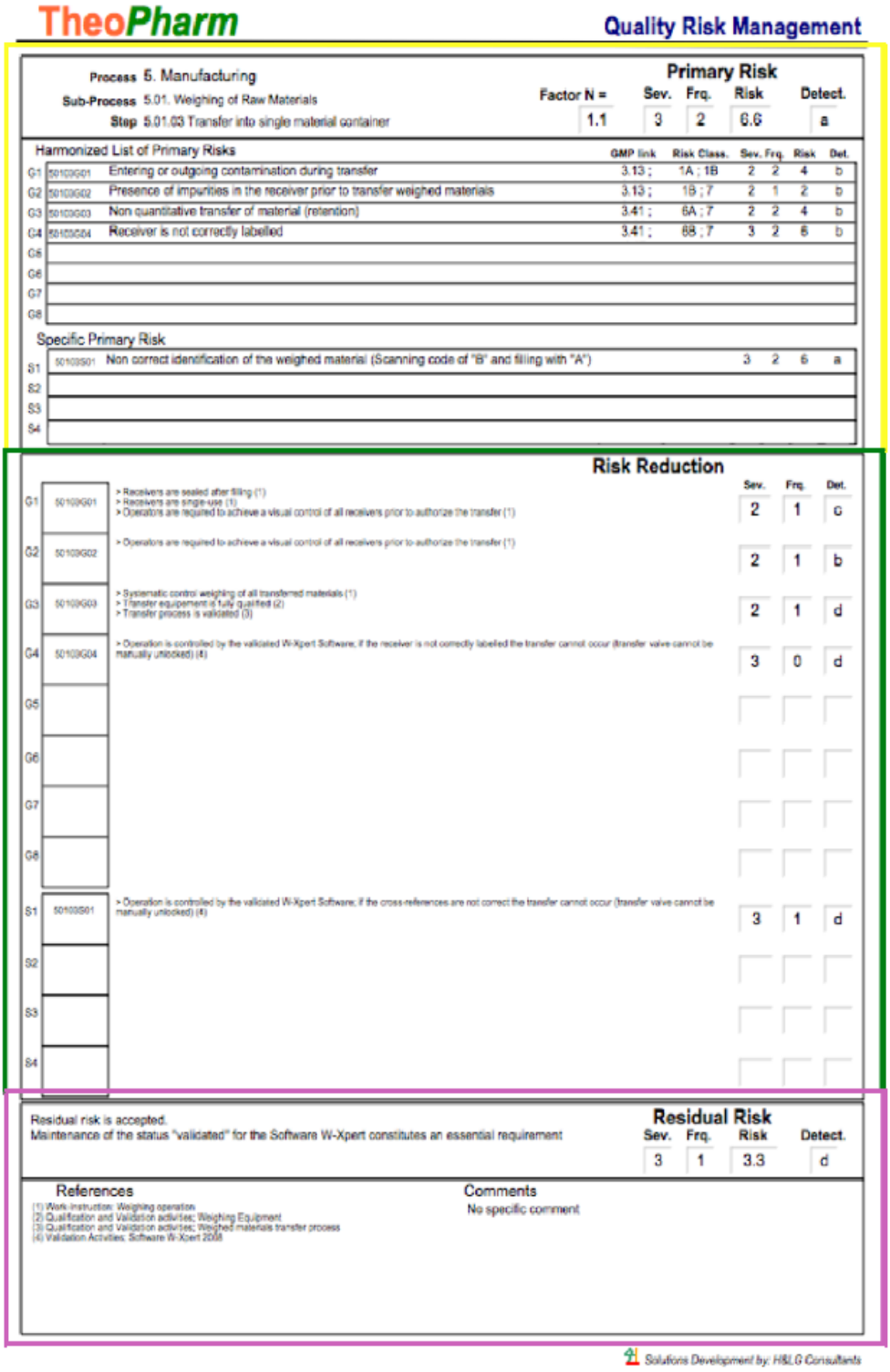


Figure 3: Standardized form for an elementary step

The document developed as a database where the selection of a single step loads all data (such as compiled primary risks) related to that step will facilitate the systematic review and risk assessment for every activities and every process of the Organization.

Basically, a working group will select the step and recorded data will be loaded.

Select Process

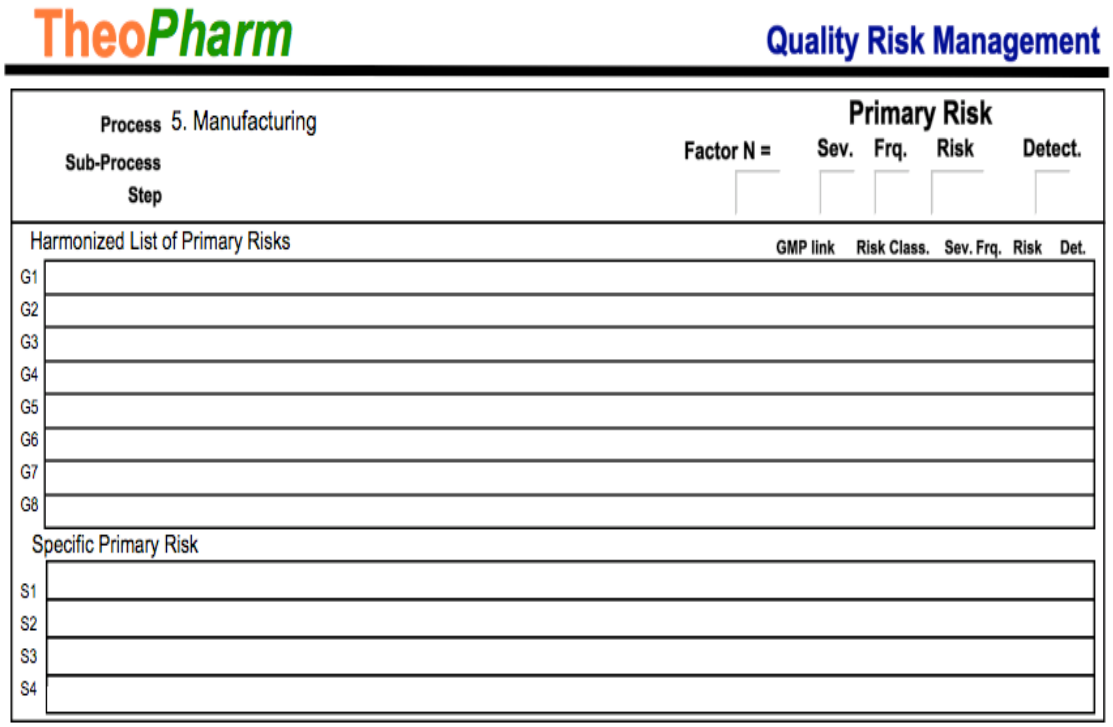


Figure 4: Process is selected

Select Sub-Process

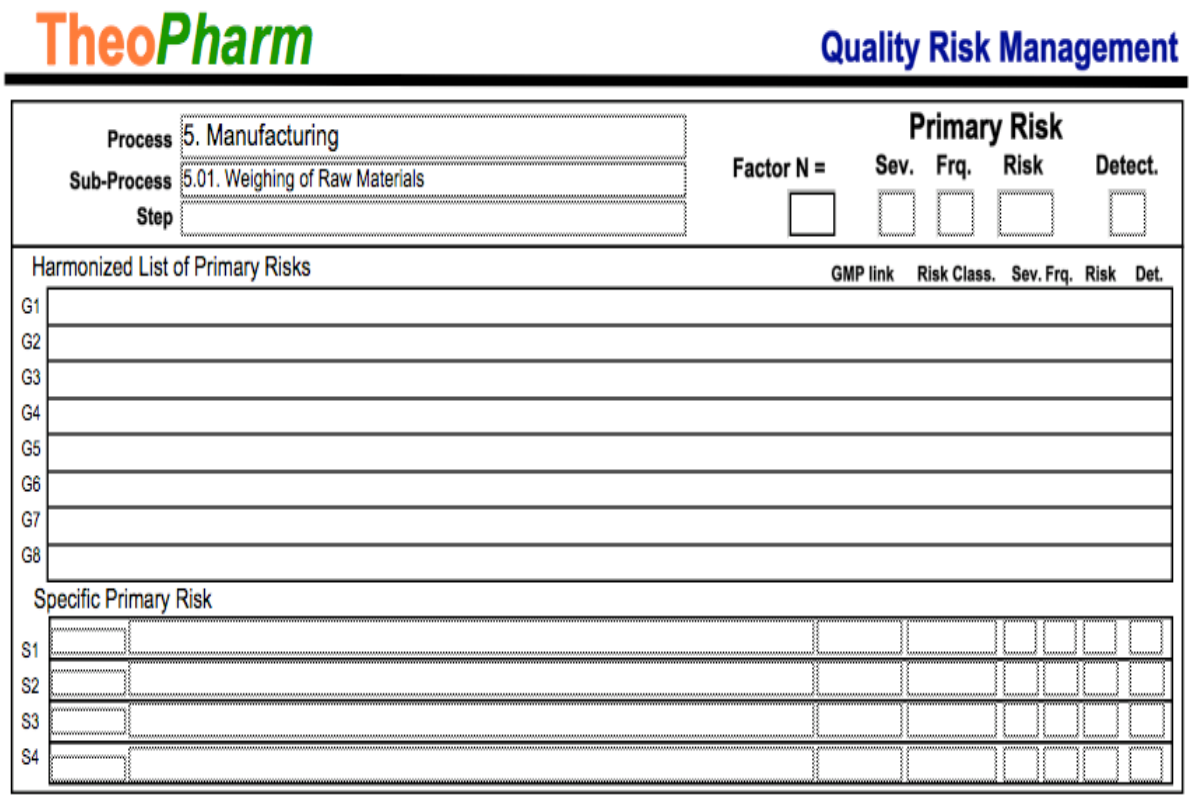


Figure 5: Sub-process is selected

Selection of the elementary stage:

The selection of an elementary step will cause the automatic loading of the harmonized primary risks to which the Organization will add, if necessary, risks specific to its environment:

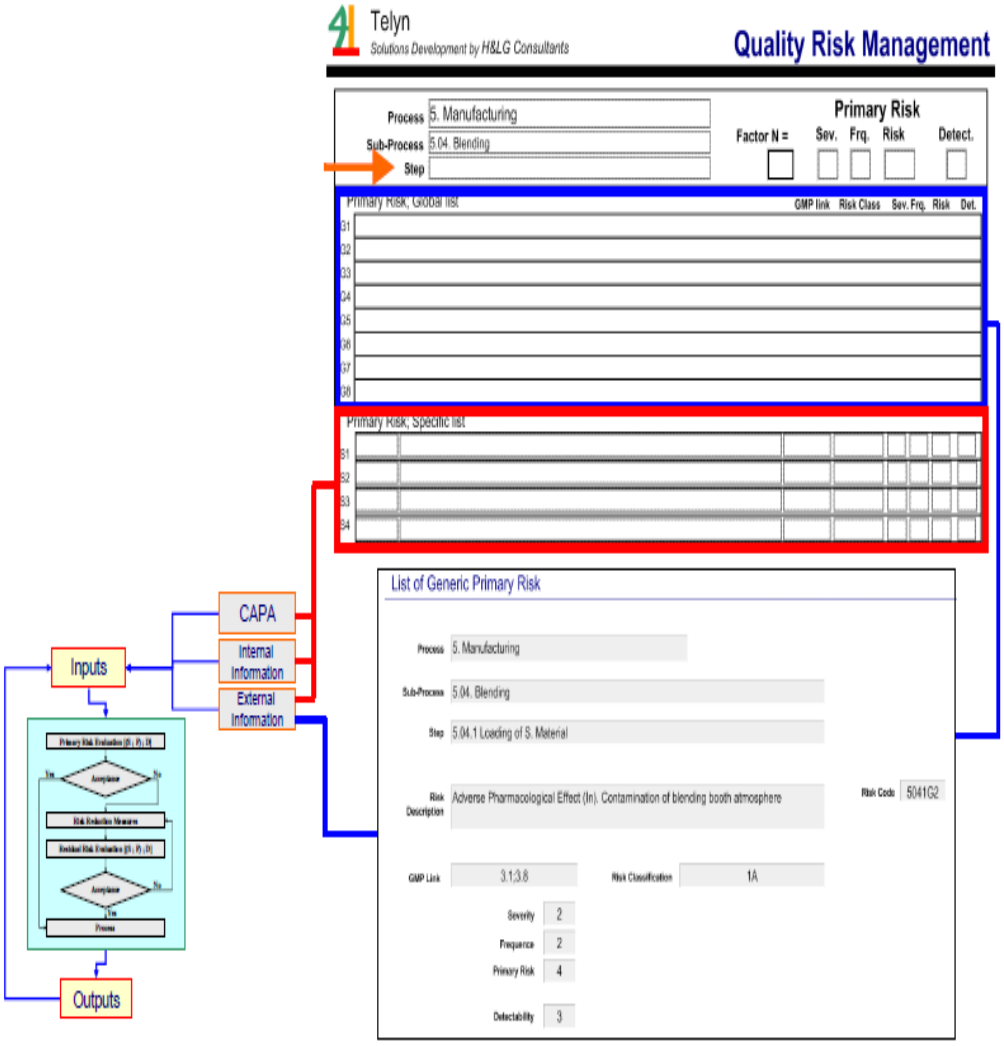


Figure 6: Elementary step is selected

The blue square is automatically filled out from the database with the harmonized risks; the red square is dedicated to the specific risks.

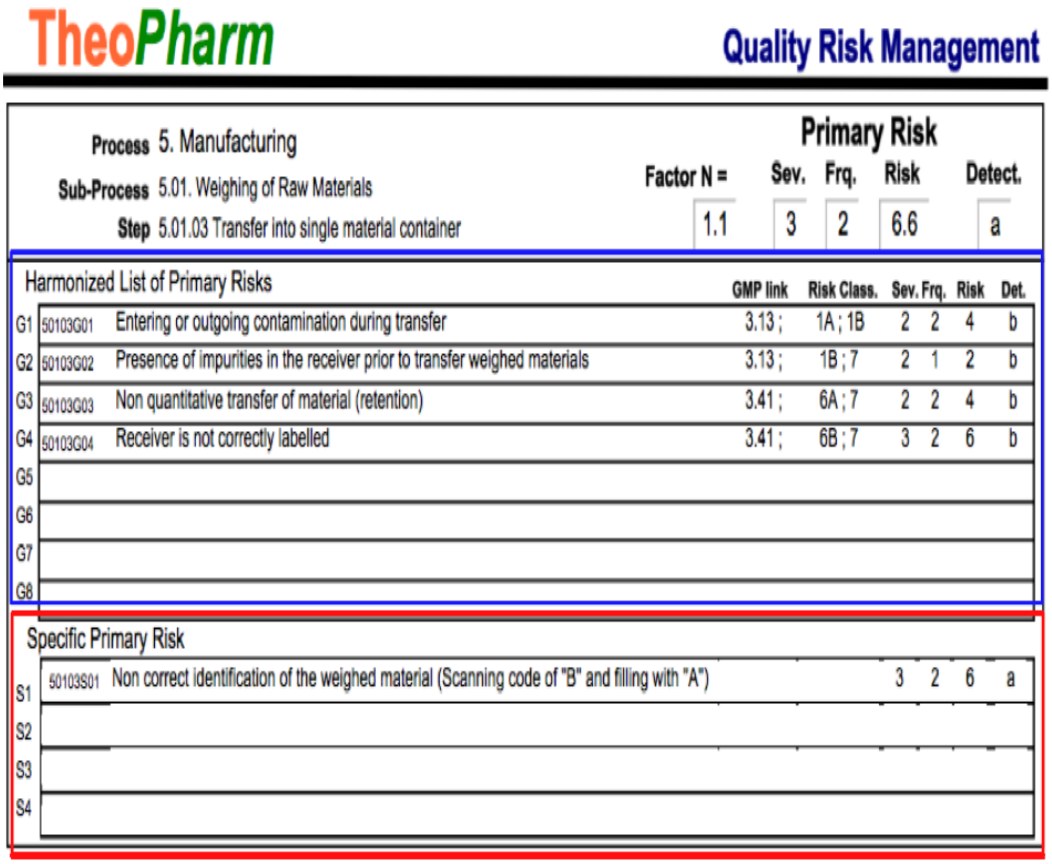


Figure 7: Primary risks are filled out

Each primary risk is referenced and can be evaluated in an independent way, by definition, it is agreed that a level of risk R is:

- Low if: 0 =< R < 3
- Moderate if: 3 =< R < 5
- High if: R >= 5

It is also agreed that:

A risk is **acceptable** if it is **low**

A risk is also **acceptable** if it is **moderate** and detection is certain (D = d)

A risk which is **not acceptable** is **unacceptable**.

For a given elementary step, the value of risk associated with this step is the highest S x F value of the identified/indexed primary risks combined with the value of the factor of experience (N) according to the definition:

$$Rs = S \times F \times N$$

The values of the risk are discrete values belonging to the explicit series:

[0.0; 1.0; 1.1; 1.2; 2.0; 2.2; 2.4; 3.0; 3.3; 3.6; 4.0; 4.4; 4.8; 6.0; 6.6; 7.2; 9.0; 9.9;10.8].

These values define the zones of acceptance according to the rules given above with:

- In green; the zone of direct acceptance
- In red; the non acceptable zone
- In yellow; the zone subject to condition of detection

Table 1: Acceptance diagram

S X F	NR: +00%	NR: +10%	NR: +20%
0	0	0	0
1	1	1.1	1.2
2	2	2.2	2.4
3	3	3.3	3.6
4	4	4.4	4.8
6	6	6.6	7.2
9	9	9.9	10.8

The highest calculated value of the primary risk for an elementary step is indicated in the upper part of the form:

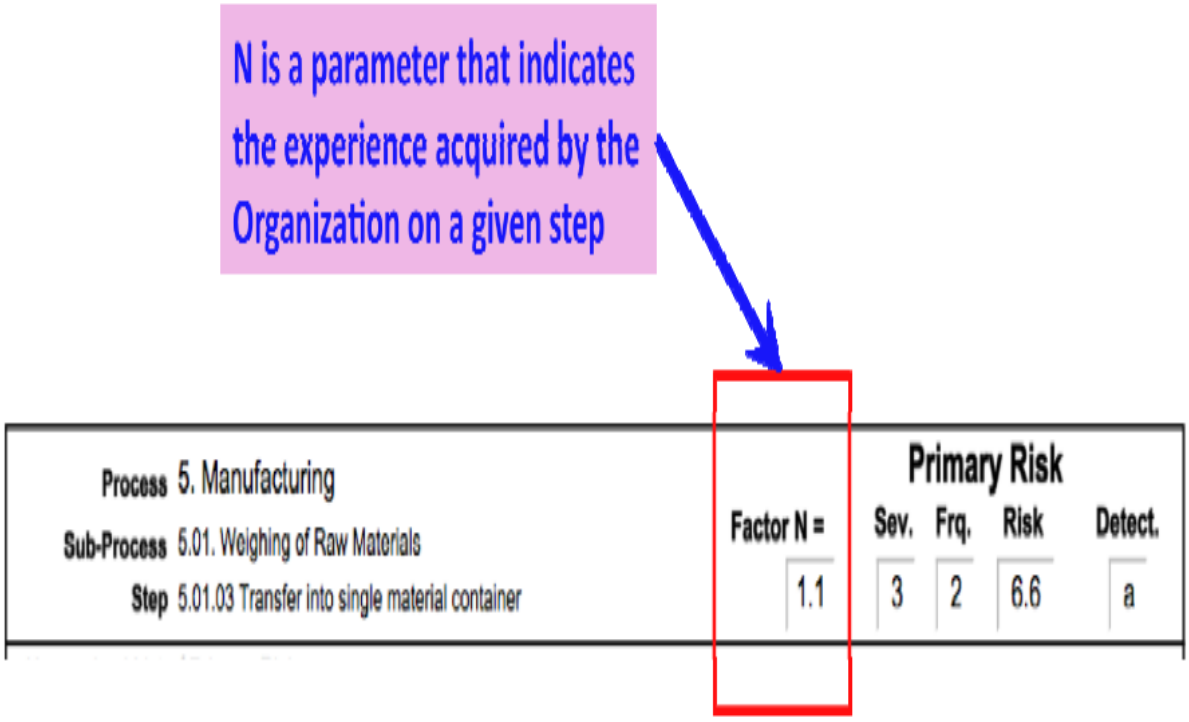


Figure 8: Primary Risk [6, 13].

N	Description
1.0	Existence of documented evidence, established by an independent entity, proving the ongoing compliance to regulatory requirements during more than 36 months.
1.1	Existence of documented evidence, established by an independent entity, proving the ongoing compliance to regulatory requirements since less than 36 months.
1.2	Absence of documented evidence, established by an independent entity, proving the compliance to regulatory requirements or existence of a no addressed non-conformity.

As soon as the section of the primary risks is completed in the form, methodology invites the users to introduce the implemented measures of risk reduction.

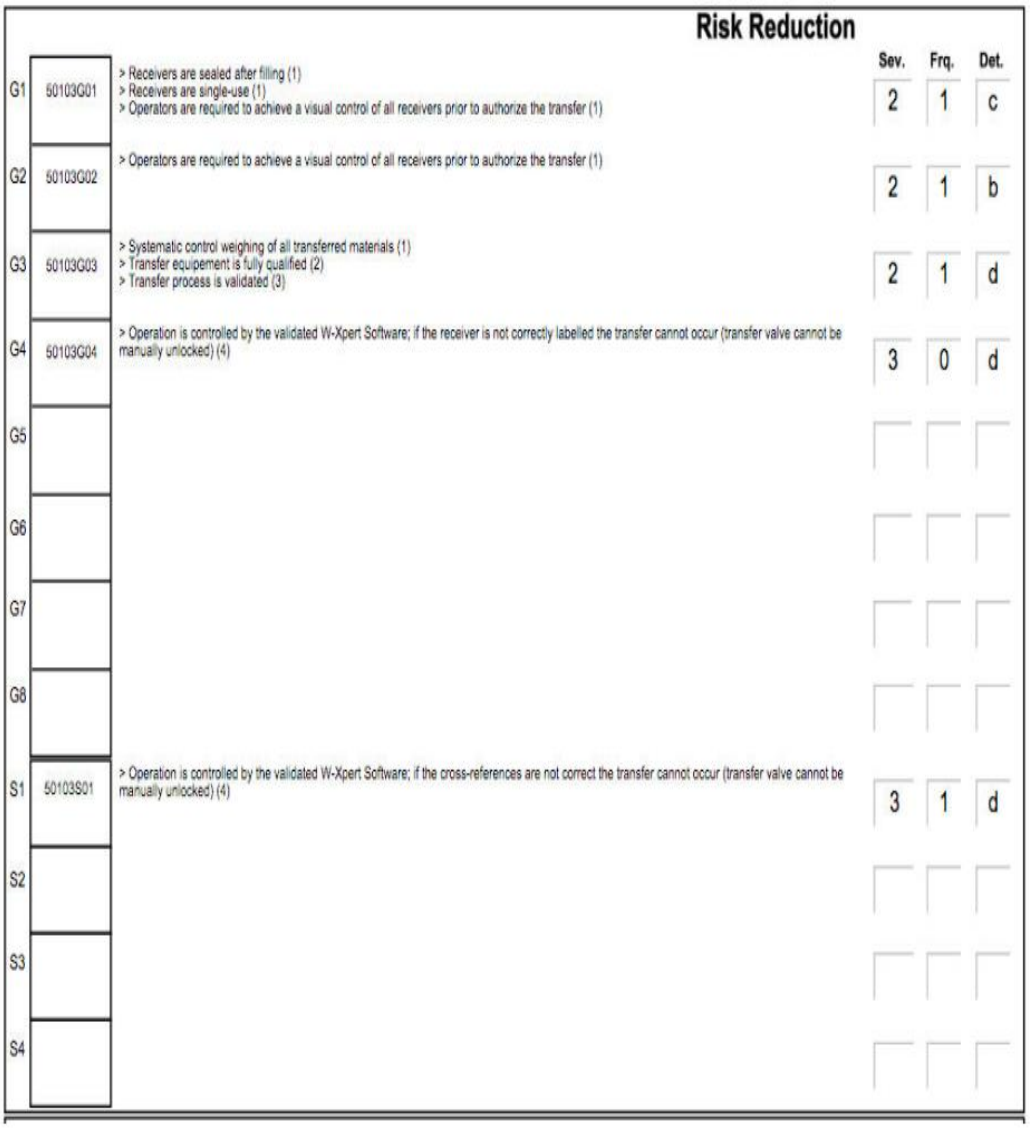


Figure 9: Risk Reduction

Implemented measures of risk reduction are brought for each primary risk. These measures of risk reduction make it possible to calculate a new value for the parameters S, F, D associated with this risk and thus establish the value of the residual risk. Ideally, it is expected that measures of risk reduction is supported by documented evidence quoted within the section "Related references".

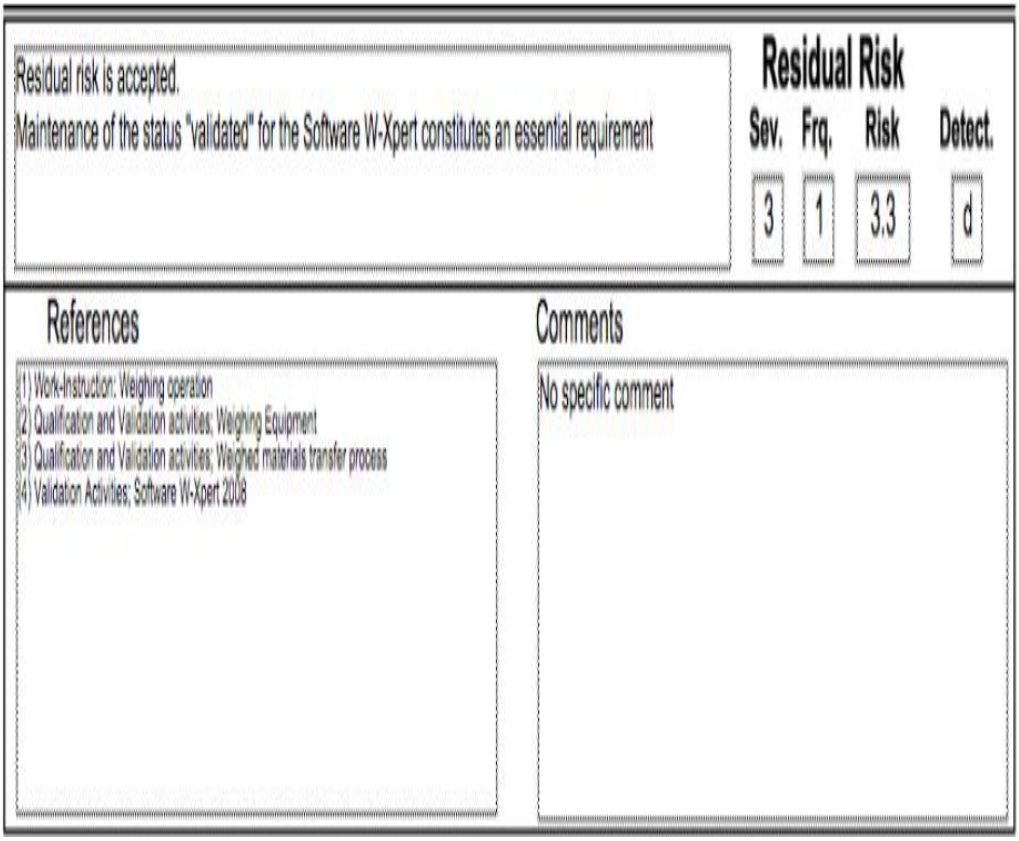


Figure 10: Residual Risk and Final statement

The residual risk consists of e.g.

- Hazards that have been assessed and risks that have been accepted
- Hazards which have been identified but the risks have not been correctly assessed
- Hazards that have not yet been identified
- Hazards which are not yet linked to the patient risk

The global value of the residual risk is calculated according to a principle identical to that used for the globalized value of the primary risk. It should be noted that the value of the factor of experience (N) remains the same one for the calculation of the primary and residual risks. The results obtained for the whole of the elementary steps are then compiled in a synoptic table according to the model given below:

Step	Description	Severity * Frequence S*F	Experience N	System Risk Rs	Detection D	System Acceptability As
4	Manufacturing Upstream					
4.1	Purchasing	3	1.0	**3.00**	d	Y
4.2	Admission	3	1.0	**3.00**	d	Y
4.3	Sampling	2	1.0	**2.00**	c	Y
5	Manufacturing In-Process					
5.01	Weighing					
5.01.01	Supply of raw materials	3	1.1	**3.30**	d	Y
5.01.02	Weighing	3	1.1	**3.30**	d	Y
5.01.03	Transfer into single material container	3	1.1	**3.30**	d	Y
5.02	Management of weighed materials					
5.02.1	Distribution of weighed materials	1	1.0	**1.00**	b	Y
5.02.2	Handling of excess materials	1	1.0	**1.00**	b	Y
5.03	Manufacturing ; Preparation					
5.03.01	Preparation; Materials loading	2	1.0	**2.00**	b	Y
5.03.02	Preparation; Stirring phase 1	3	1.0	**3.00**	d	Y
5.03.03	Preparation; Material addition	2	1.0	**2.00**	b	Y
5.03.04	Preparation; Stirring phase 2	3	1.0	**3.00**	d	Y
5.03.05	Preparation; Evaporation	3	1.0	**3.00**	d	Y
5.03.06	Preparation; Cristalization	2	1.0	**2.00**	b	Y
5.03.07	Preparation; Drain	3	1.0	**3.00**	d	Y
5.03.08	Preparation; Filtration	3	1.0	**3.00**	d	Y
5.03.09	Preparation; Drying	3	1.0	**3.00**	d	Y
5.03.10	Preparation; Filter opening and collect of the product	3	1.0	**3.00**	d	Y
5.03.11	Preparation; Cleaning of facilities and equipment	2	1.0	**1.50**	c	Y
5.04	Finishing					
5.04.01	Finishing (Recipe A) ; Siefting	2	1.2	**2.40**	c	Y
5.04.02	Finishing (Recipe A) ; Homogeneization and packaging	2	1.2	**2.40**	b	Y
5.04.03	Finishing (Recipe A) ; Cleaning of facilities and equipment	2	1.0	**2.00**	b	Y

Figure 11: Compilation of elementary step with values of systemic residual risks

This table gives synoptic systemic risk (Rs) [6].

Product factor

Product factor is then assessed for the considered product. Results are presented in a standardized table as shown below:

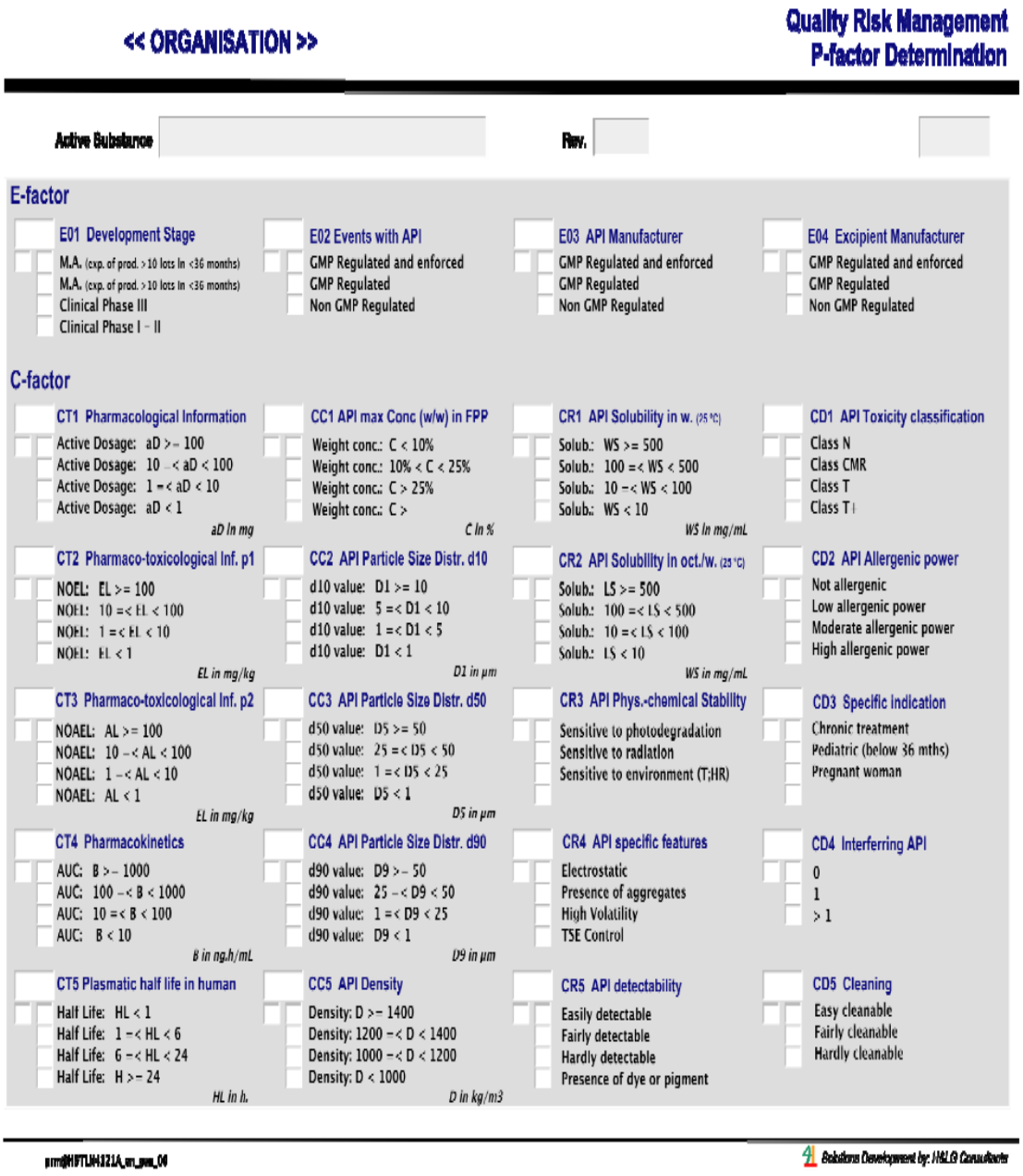


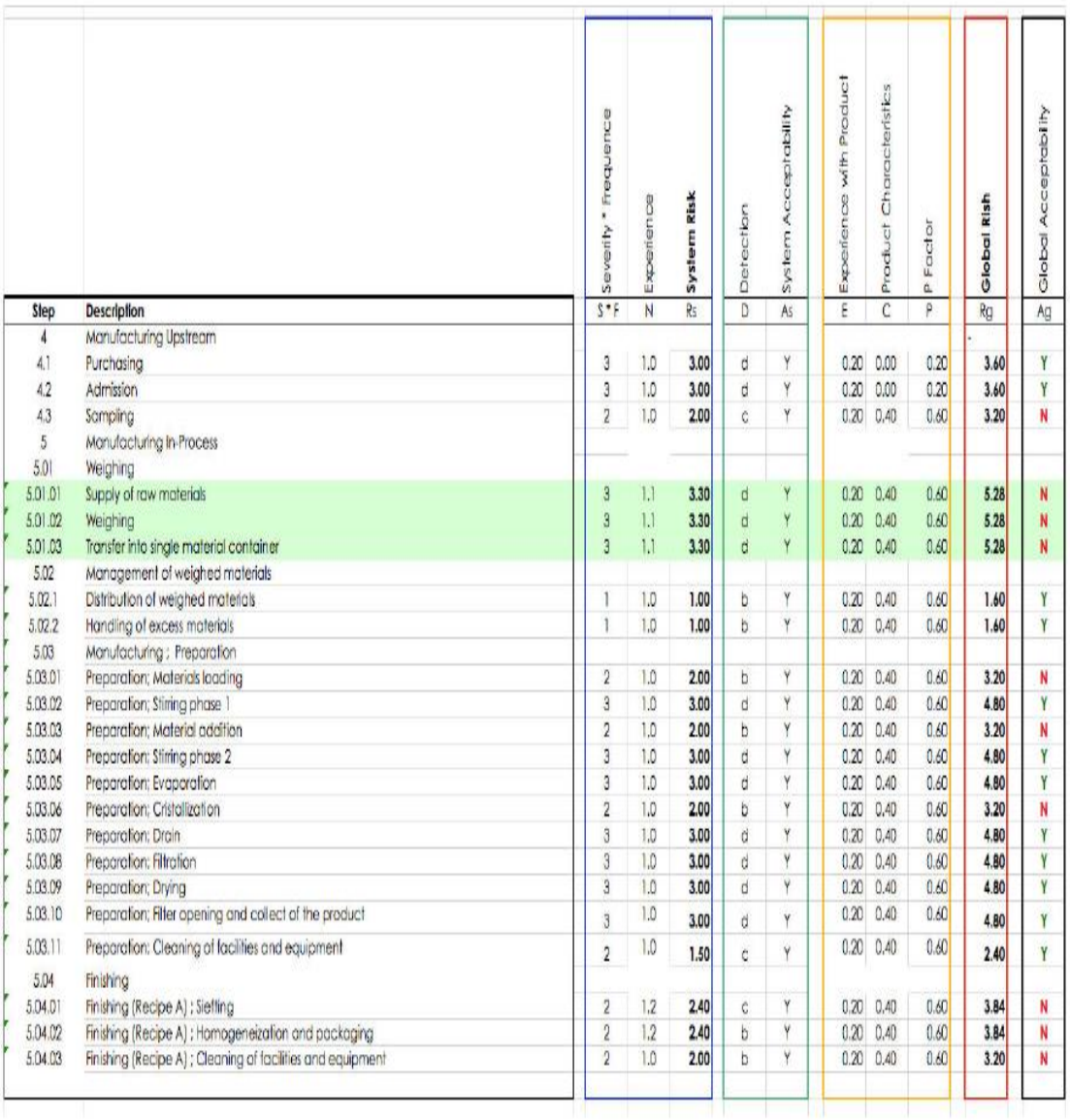
Figure 12: Determination of Product factor

The fact of ticking off the boxes corresponding to specificities of the product generates in a transparent way for the operator a value of Product factor (P).As for the evaluation of the systemic risk, the computation charts of the factor (P) are organized in databases from which the parameters of calculation are accessible to the database administrators [6].

Determination of the total risk

The determination of the total risk is obtained by the multiplication of the systemic risk (Rs) by weighting produced (P).

A synoptic table of the risk total for a particular product is then produced with the following format:



Step	Description	Severity * Frequence S*F	Experience N	System Risk Rs	Detection D	System Acceptability As	Experience with Product E	Product Characteristics C	P Factor P	Global Risk Rg	Global Acceptability Ag
4	Manufacturing Upstream										
4.1	Purchasing	3	1.0	3.00	d	Y	0.20	0.00	0.20	3.60	Y
4.2	Admission	3	1.0	3.00	d	Y	0.20	0.00	0.20	3.60	Y
4.3	Sampling	2	1.0	2.00	c	Y	0.20	0.40	0.60	3.20	N
5	Manufacturing In-Process										
5.01	Weighing										
5.01.01	Supply of raw materials	3	1.1	3.30	d	Y	0.20	0.40	0.60	5.28	N
5.01.02	Weighing	3	1.1	3.30	d	Y	0.20	0.40	0.60	5.28	N
5.01.03	Transfer into single material container	3	1.1	3.30	d	Y	0.20	0.40	0.60	5.28	N
5.02	Management of weighed materials										
5.02.1	Distribution of weighed materials	1	1.0	1.00	b	Y	0.20	0.40	0.60	1.60	Y
5.02.2	Handling of excess materials	1	1.0	1.00	b	Y	0.20	0.40	0.60	1.60	Y
5.03	Manufacturing : Preparation										
5.03.01	Preparation: Materials loading	2	1.0	2.00	b	Y	0.20	0.40	0.60	3.20	N
5.03.02	Preparation: Stirring phase 1	3	1.0	3.00	d	Y	0.20	0.40	0.60	4.80	Y
5.03.03	Preparation: Material addition	2	1.0	2.00	b	Y	0.20	0.40	0.60	3.20	N
5.03.04	Preparation: Stirring phase 2	3	1.0	3.00	d	Y	0.20	0.40	0.60	4.80	Y
5.03.05	Preparation: Evaporation	3	1.0	3.00	d	Y	0.20	0.40	0.60	4.80	Y
5.03.06	Preparation: Cristallization	2	1.0	2.00	b	Y	0.20	0.40	0.60	3.20	N
5.03.07	Preparation: Drain	3	1.0	3.00	d	Y	0.20	0.40	0.60	4.80	Y
5.03.08	Preparation: Filtration	3	1.0	3.00	d	Y	0.20	0.40	0.60	4.80	Y
5.03.09	Preparation: Drying	3	1.0	3.00	d	Y	0.20	0.40	0.60	4.80	Y
5.03.10	Preparation: Filter opening and collect of the product	3	1.0	3.00	d	Y	0.20	0.40	0.60	4.80	Y
5.03.11	Preparation: Cleaning of facilities and equipment	2	1.0	1.50	c	Y	0.20	0.40	0.60	2.40	Y
5.04	Finishing										
5.04.01	Finishing (Recipe A) ; Sieffing	2	1.2	2.40	c	Y	0.20	0.40	0.60	3.84	N
5.04.02	Finishing (Recipe A) ; Homogeneization and packaging	2	1.2	2.40	b	Y	0.20	0.40	0.60	3.84	N
5.04.03	Finishing (Recipe A) ; Cleaning of facilities and equipment	2	1.0	2.00	b	Y	0.20	0.40	0.60	3.20	N

Figure 13: Compilation of elementary steps with values of systemic residual risks and global risks

This table gives the decisional tool for the acceptability of the global risk [6].

CONCLUSION

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance and by agencies regulating these industries. Although there are some examples of the use of quality risk management (QRM) in the pharmaceutical industry today, they are limited and do not represent

the full contributions that risk management has to offer. In addition, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance. The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. In addition, use of quality risk management can improve the decision making if a quality problem arises.

The purpose of this document is to offer a systematic approach to QRM. It serves as a foundation or resource document that is independent of, yet supports other ICH quality documents and complements existing quality practices, requirements, standards and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of QRM that can enable more effective and consistent risk-based decisions, by both regulators and industry, regarding the quality of drug substances and drug products across the product lifecycle.

Lastly it is concluded that an effective QRM can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight.

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