Quality Risk Management

Implementation of ICH Q9 in the pharmaceutical field an example of methodology from PIC/S

Document

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Content

* Previously issued in a simplified version as PS/INF 20/2009

1. Introduction

Since a couple of years Quality Risk Management (or QRM) has become a mandatory regulatory requirement towards healthcare organizations either they are active in the sectors of Medical Devices* or in Pharmaceuticals†.

The ICH-Q9 guideline concerning Quality Risk Management in the pharmaceutical field (active substances and medicinal products) was adopted by the European Union and PIC/S‡ in Annex 20 of the EU and PIC/S GMP Guides. It is gradually being applied by drug manufacturers in particular as regards sections 1.5 and 1.6 of part I of the aforementioned§.

> *1.5 Quality risk management 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.*
>
> *1.6 The quality risk management system should ensure that:*
> *- the evaluation of the risk to quality is based on **scientific knowledge, experience with the process** and ultimately links to the **protection of the patient***

* See international standard ISO-14971
† See ICH-Q9
‡ PIC/S : Pharmaceutical Inspection Cooperation Scheme
§ Eudralex: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm and PIC/S GMP Guide: http://www.picscheme.org/publication.php?id=4

*- the **level of effort**, formality and documentation of the quality risk management process is **commensurate with the level of risk***

However, the practical methods for the implementation of these new requirements are still perceived as being singularly difficult to interpret and implement.

In this context, a small, informal Working Group within PIC/S has started to develop an objective and pragmatic example of methodology, directly usable by the widest audience. It is also able to meet the demands of both operators and inspectors and to comply with all regulatory requirements.

This example of methodology is not intended to be issued later by PIC/S as a recommendation or as a guideline for industry and / or for GMP inspectors but it could be used by PIC/S for training purposes. Whether this example is used by industry for other purposes is of no concern to PIC/S and will not influence the outcome of PIC/S inspections.

2. Description of the methodology

2.1. Objective of the Quality Risk Management

For any pharmaceutical organization, Quality Risk Management should aim at raising the level of protection for the patient, by the reduction of

the risk to which that patient is exposed at the time he receives a drug product.

This general objective can only be achieved if the implemented policy of Quality Risk Management exceeds the unique intend of GMP compliance by increasing the control of the Organization on developed (or under development) processes to improve:

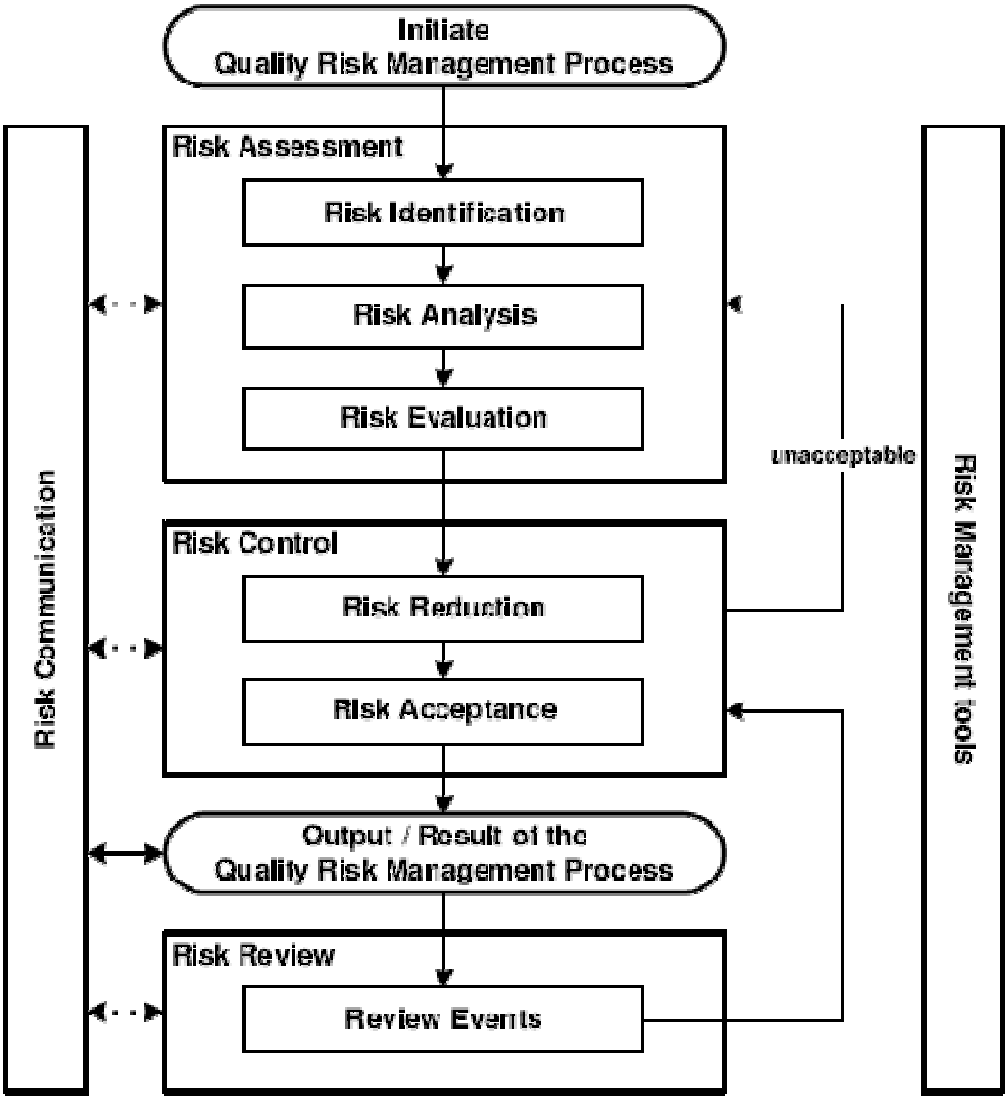
- Relevance of implemented processes;
- Knowledge within the Organization;
- Confidence in performed operations.

At the opposite, Quality Risk Management should not set for finality:

- Adjustment of controls to the currently available resources in the Organization;
- Provision of a wrongfully validated excuse not to comply with the regulatory requirements.

2.2. General approach

The scheme of a Quality Risk Management process as proposed by ICH-Q9 is reproduced below:



Scheme S1; ICH-Q9 Risk Management diagram

For a practical implementation of this process, the guidance draws up the list of the principal known methods of risk analysis and gives a description of their specificities.

Among those one will retain for example:

- FMEA (Failure Mode Effect Analysis)
- FTA (Fault Tree Analysis)
- HAZOP (Hazard Operability Analysis)
- HACCP (Hazard Analysis and Critical Control Points)

If these tools often proved to be efficient and reliable in risk assessment and/or risk control, they, by design, remain limited when they have to support a global policy of Risk Management. Moreover, it has been noticed that a systematic use of these tools to address all explicit and implicit issues of ICH-Q9 would generally be incompatible with available resources.

In this context, the example of methodology presented hereafter is aimed at providing training, help, inspiration or assistance to interested and volunteered stakeholders.

2.3. Description of QRM methodology

2.3.1. Preamble

A Risk (R) is a mathematical expression with two parameters: severity (S) and Frequency (F). The risk is then expressed as: R = S x F.

A risk evaluation is then nothing but addressing a quantified answer to the double question:

- What probability?
- Which consequences?

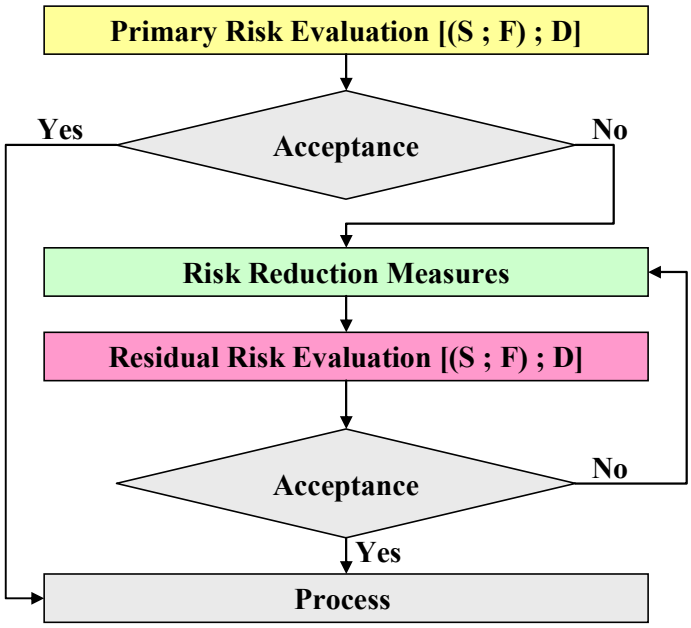
Quantification should follow a qualitative step of hazards inventory. A hazard is defined as an event, which has the potential to have a negative impact on the considered objective (i.e.: patient safety). To comply with the ICH-Q9 diagram provided in scheme S1; hazards and risks have then to be considered in a two consecutive stages process with:

- Risk Assessment *(stage of qualitative categorization and quantitative estimate of the identified hazards)*
- Risk Control *(stage of risk reduction and acceptance decision)*

Finally, Risk Management should integrate these stages of Risk Assessment and Risk Control in a policy established to maintain the relevance and the efficiency of the analytical work.

2.3.2. Design of methodology

To meet the requirement of exhaustiveness of hazards and risks reviewing, the methodology should initially proceed to the inventory of all the activities implemented in the processes covered by the quality system as applicable within the Organization. These activities should then be themselves divided into elementary steps, which are then individually introduced in the decisional diagram given below:



Scheme S2; "Risk Treatment Process" for elementary steps

Thus, for each elementary step, the method of Risk Management initially envisages an intrinsic evaluation of the primary risk, which, if it is not directly acceptable, will claim/require an iterative series of risk mitigation measures aiming at obtaining an acceptable residual risk.

In this diagram, S indicates severity, F the frequency and D the detectability.

In a traditional manner, the risk (R) is expressed as the multiplication of Severity (S) by the frequency (F) of occurrence of the hazard: R = S X F. The detectability is not integrated in the calculation of the risk value and would only be considered under specific condition to decide whether the risk could be accepted or not.

According to the diagram S2, there are two levels of risks, which are submitted/proposed to acceptation:

- primary Risks Rs_p
- residual Risks Rs_r

2.3.3. Input and output

The starting point of methodology thus consists in the inventory of all elementary steps entering the scope of Quality Risk Management. This inventory could be the result of the internal work of a multi-disciplinary team within the Organization or could be acquired from the "Shared Structure" platform according to the operating process described in paragraph 3 (or both).

Each elementary step treated according to the decision tree called "Risk Treatment Process" and depicted on Scheme 2 will allow to establish the risk assessment (relevant tools such as rationale, FMEA, FTA may be integrated here) through the implementation of reduction measures to primary risks related to elementary steps.

If as for the inventory stage, primary risks may be originated from the results of multi-disciplinary working team or acquired from the database maintained by "Shared Structure" platform, reduction measures proposal and actual implementation will lie with the user.

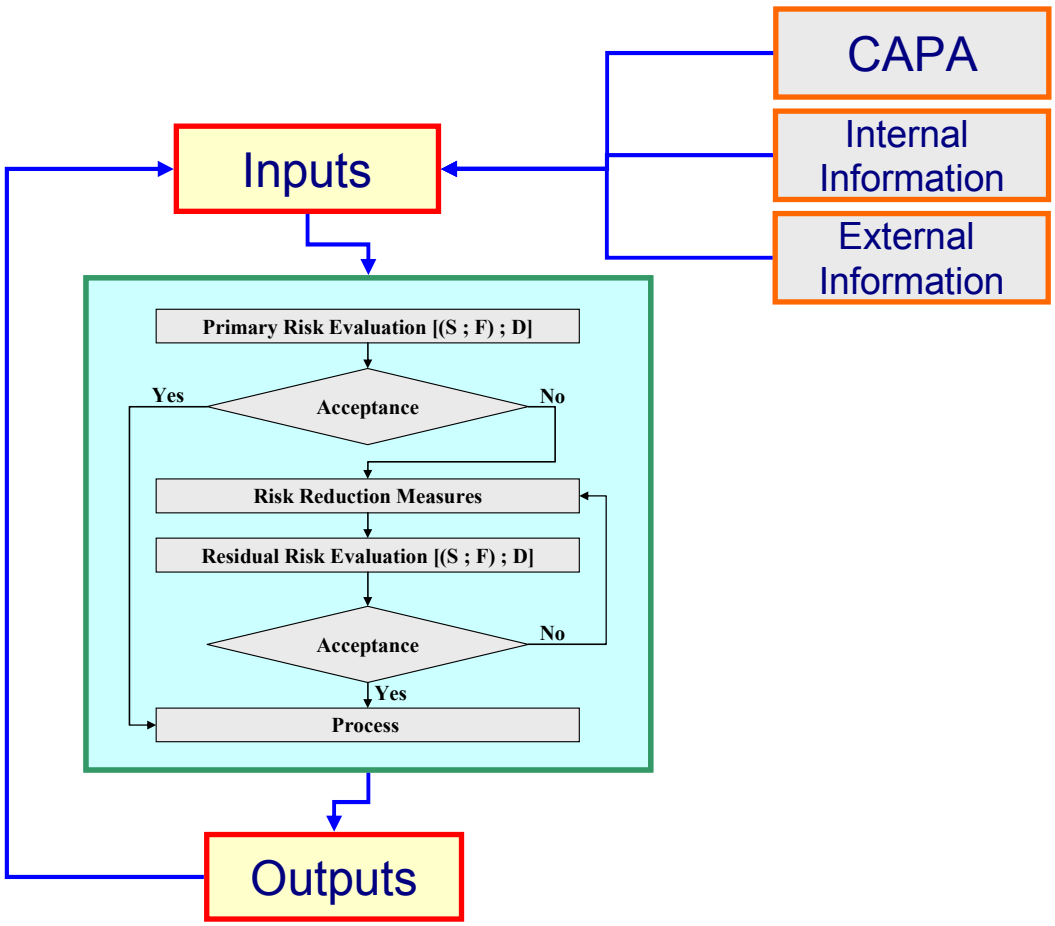
Risk assessment for a given elementary step is then documented as an output of the Risk Treatment Process.

The compilation of these outputs is permanently challenged for their capacity with being in adequacy with the evolutions of the regulatory framework applicable and periodically reviewed to take into consideration relevant new information coming generally from.

- CAPA: Corrective Action Preventive Action
- Internal Information: refers to relevant data coming from the Organization but not directly linked to the concerned manufacturing process
- External Information: refers to relevant data coming from the outside of the Organization and related subsidiary; e.g.: guidance and regulatory notes issued from national agencies

The result of an event or periodic revision (at least annual) is materialized by a new version of the document compiling the output data of Quality Risk Management of the Organization.

The permanent control of the outputs as described here constitutes the main difference between Risk Analysis and Risk Management and is essential to its efficiency.



Scheme S3; "Risk Management Process" for elementary steps

At this stage, it is important to note that the manufactured product has not been considered yet. The following paragraph will show the approach adopted for its integration in order to limit the volume of required resources.

2.3.4. Dissociating approach

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"

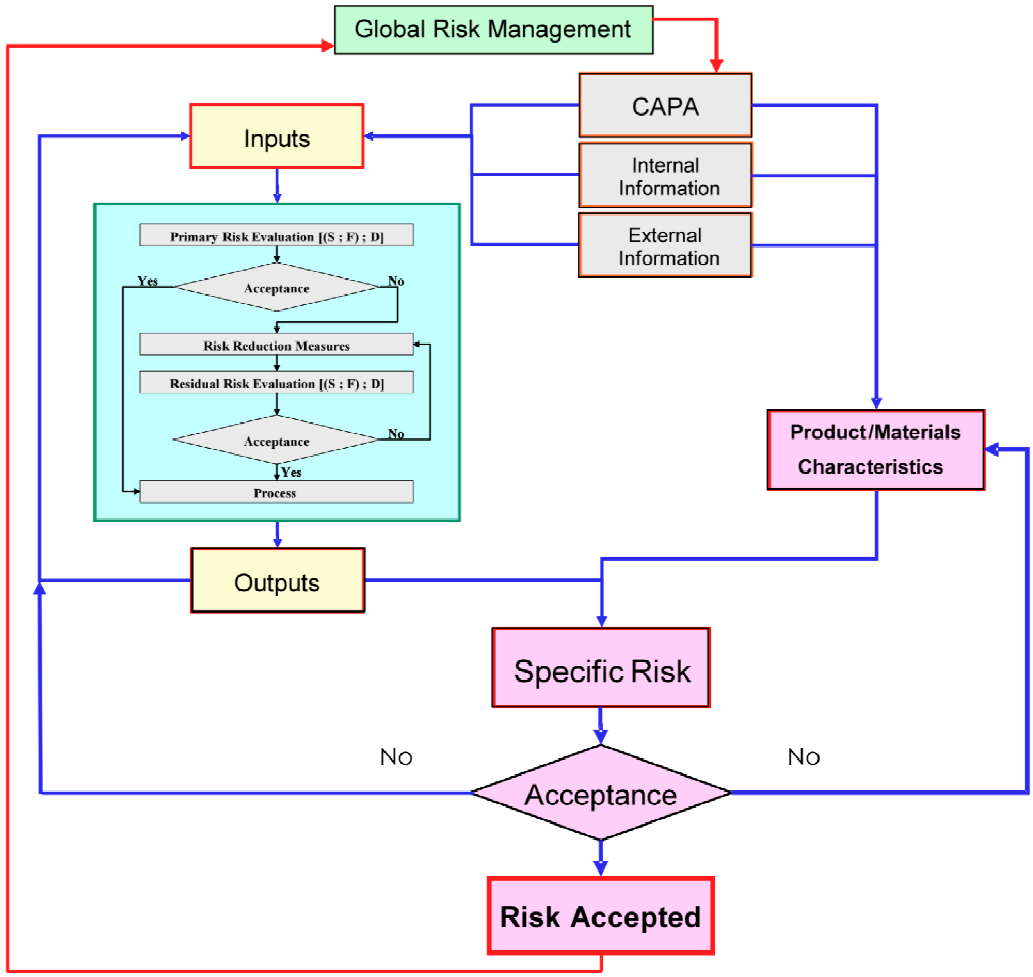
According to the approach, Global Risk determination (Rg), as required by the regulatory framework, corresponds to the risk of manufacturing the considered product in the existing system. The Global Risk (Rg) is then obtained as a result of the multiplication of the System Risk (Rs) (corresponding then to the description given in paragraph 2.3.3.) by a modulating factor called "Product factor" (P).

One has then: Rg = Rs x P

This dissociating approach thus proposes to the Organization to initially evaluate its systemic risk (Rs) independently of the products, which are manufactured. This approach is placed under permanent control according to the principle describes in section 2.3.3. 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 to section 2.3.3 with the principle of the dissociating approach led to the establishment of the complete diagram given below:



Scheme S4; Global Risk Management Diagram

This diagram thus combines the evaluation of the systemic risk, placed in a process of permanent control, and the Product factor produced for a total management of the risk.

2.3.5. 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):

- 0; Not addressed explicitly or implicitly by the applicable GMP
- 1; Addressed by applicable GMP, but without possible impact on the manufactured product
- 2; Possible impact on the manufactured product but without risk for the patient (end user)
- 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

Factor (N):

In complement of these parameters, the example of methodology envisages also the integration of a parameter (N) taking into account the experience gained by the Organization on its systemic environment. This factor (N) which modules the expression of the risk is defined in the following way:

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 non-addressed non-conformity.

Systemic risk (Rs):

The quantification of the systemic risk will be then based on the following expression:

$Rs = S \times F \times N$

According to whether it is of a primary risk or a residual risk one then obtains with the indices "p" and "r" the following expressions:

primary Risk: $Rs_p = S_p \times F_p \times N$

residual Risk: $Rs_r = S_r \times F_r \times N$

The parameter of detectability (D) is not directly included in the calculation of the risk. It intervenes as a conditional parameter for the decision of acceptance of the risk (Boolean operator). This aspect will be described in a more complete way in the following section of the document.

Product factor (P):

The Product factor (P) balances the systemic risk Rs to give the global risk Rg according to:

$$Rg = P \times Rs$$

The values taken by the factor (P) are increasing and monotonous; they take their origin with P = 1.000.

This means that for product having a value of (P) equal to 1.000 one will have:

$$Rg = Rs$$

The factor (P) is defined as being the addition of a component (E) and a component (C) increased by 1.000.

$$P = E + C + 1.000$$

The component (E) represents the experience gained by the Organization with the product considered; it takes into account parameters such as:

- Development or clinical phase of the product;
- Number of occurrence for successful manufacturing of the product within the organization;

- Origin of the product;
- …

The component (C) translated the intrinsic characteristics of the product; it takes into account parameters such as:

- Pharmacological and toxicological data
  - NOEL ; NOAEL
  - Physiologically active dosage
  - Bioavailability
  - …
- Physicochemical data
  - Solubility
  - Granulometry (particle size distribution)
  - Density
  - …
- API manufacturing process
  - Chemical synthesis
  - Animal origins
  - …
- Miscellaneous
  - Class of therapeutic indication
  - …

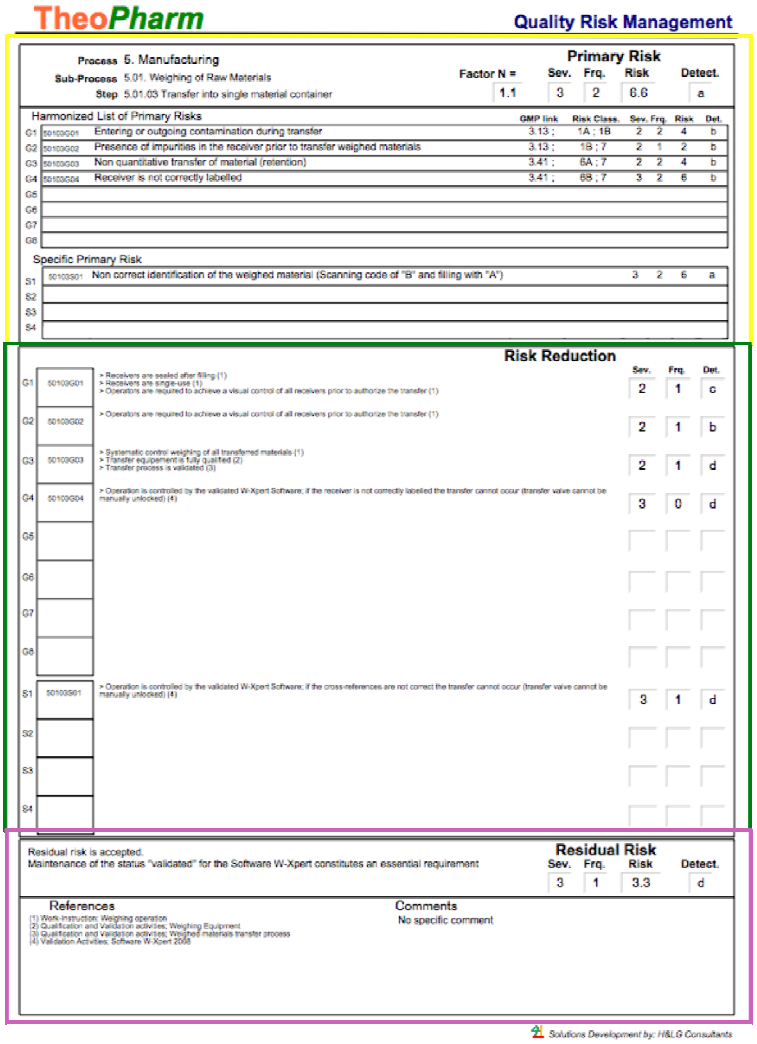
Each parameter included in calculations of components (E) and (C) for the determination of factor (P) has been worked out considering scientific literature and published results.
This approach allows an objective determination of the factor (P).

In order to rationalize the capture of information using the calculation of the factor (P), a table of acquisition of entering parameters was established (cf paragraph 3.2) allowing automatic calculations of the values of (E) and (C) and by consequence of (P).

3. Implementation of methodology

3.1. 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:



TheoPharm — Quality Risk Management

Process 5. Manufacturing
Sub-Process 5.01. Weighing of Raw Materials
Step 5.01.03 Transfer into single material container

Primary Risk — Factor N = 1.1 — Sev. 3 — Frq. 2 — Risk 6.6 — Detect. a

Harmonized List of Primary Risks

			GMP link	Risk Class.	Sev.	Frq.	Risk	Det.
G1	50103G01	Entering or outgoing contamination during transfer	3.13 ;	1A ; 1B	2	2	4	b
G2	50103G02	Presence of impurities in the receiver prior to transfer weighed materials	3.13 ;	1B ; 7	2	1	2	b
G3	50103G03	Non quantitative transfer of material (retention)	3.41 ;	6A ; 7	2	2	4	b
G4	50103G04	Receiver is not correctly labelled	3.41 ;	6B ; 7	3	2	6	b
G5								
G6								
G7								
G8								

Specific Primary Risk

S1	50103S01	Non correct identification of the weighed material (Scanning code of "B" and filling with "A")	3	2	6	a
S2						
S3						
S4						

Risk Reduction

			Sev.	Frq.	Det.
G1	50103G01	> Receivers are sealed after filling (1) > Receivers are single-use (1) > Operators are required to achieve a visual control of all receivers prior to authorize the transfer (1)	2	1	c
G2	50103G02	> Operators are required to achieve a visual control of all receivers prior to authorize the transfer (1)	2	1	b
G3	50103G03	> Systematic control weighing of all transferred materials (1) > Transfer equipement is fully qualified (2) > Transfer process is validated (3)	2	1	d
G4	50103G04	> Operation is controlled by the validated W-Xpert Software; if the receiver is not correctly labelled the transfer cannot occur (transfer valve cannot be manually unlocked) (4)	3	0	d
G5					
G6					
G7					
G8					
S1	50103S01	> Operation is controlled by the validated W-Xpert Software; if the cross-references are not correct the transfer cannot occur (transfer valve cannot be manually unlocked) (4)	3	1	d
S2					
S3					
S4					

Residual risk is accepted.
Maintenance of the status "validated" for the Software W-Xpert constitutes an essential requirement

Residual Risk — Sev. 3 — Frq. 1 — Risk 3.3 — Detect. d

References
(1) Work-Instruction: Weighing operation
(2) Qualification and Validation activities; Weighing Equipment
(3) Qualification and Validation activities; Weighed materials transfer process
(4) Validation Activities; Software W-Xpert 2008

Comments
No specific comment

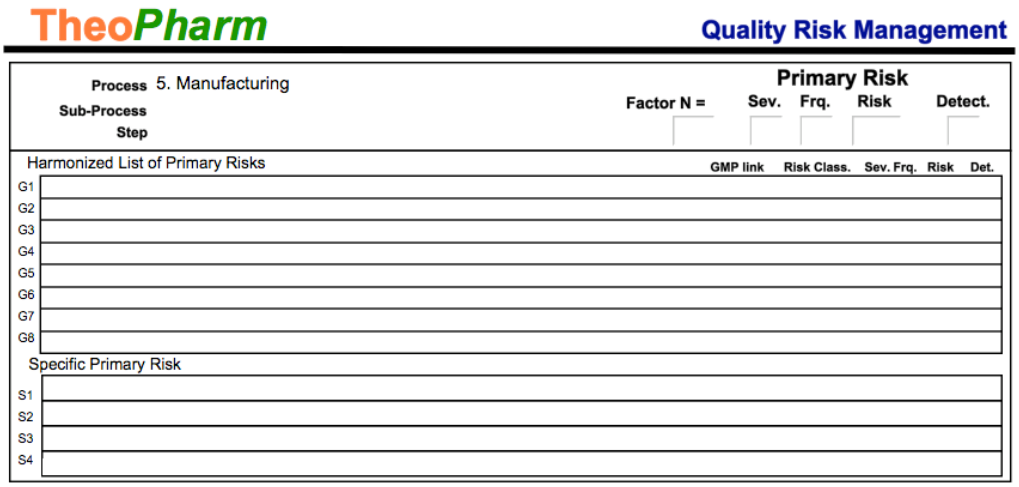
Solutions Development by: H&LG Consultants

Scheme S5; 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.

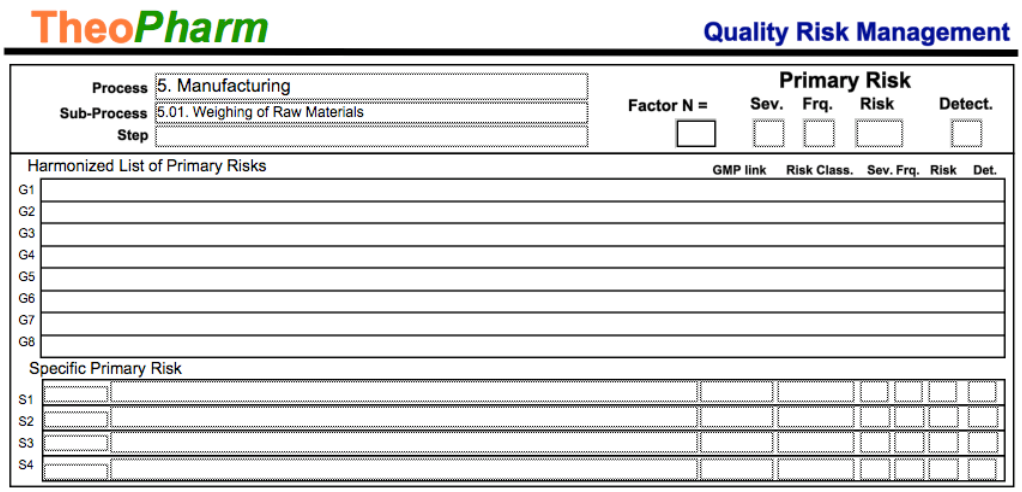
Basically, a working group will select the step and recorded data will be loaded.

1) Select Process



Scheme S6; Process is selected

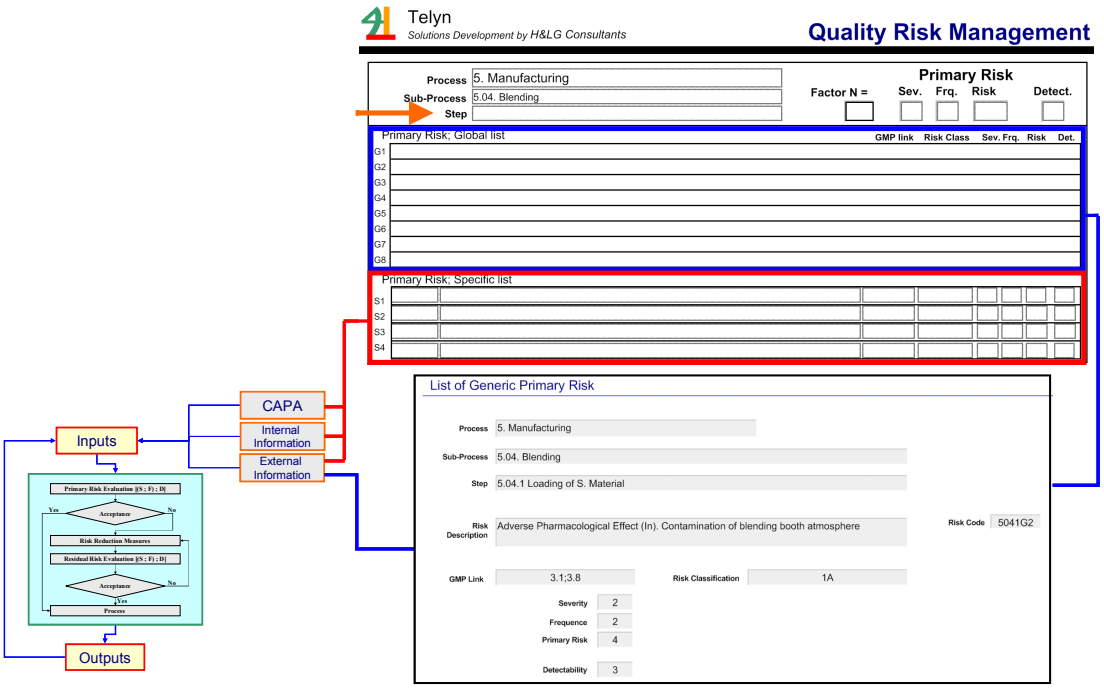
2) Select Sub-Process



Scheme S7; Sub-process is selected

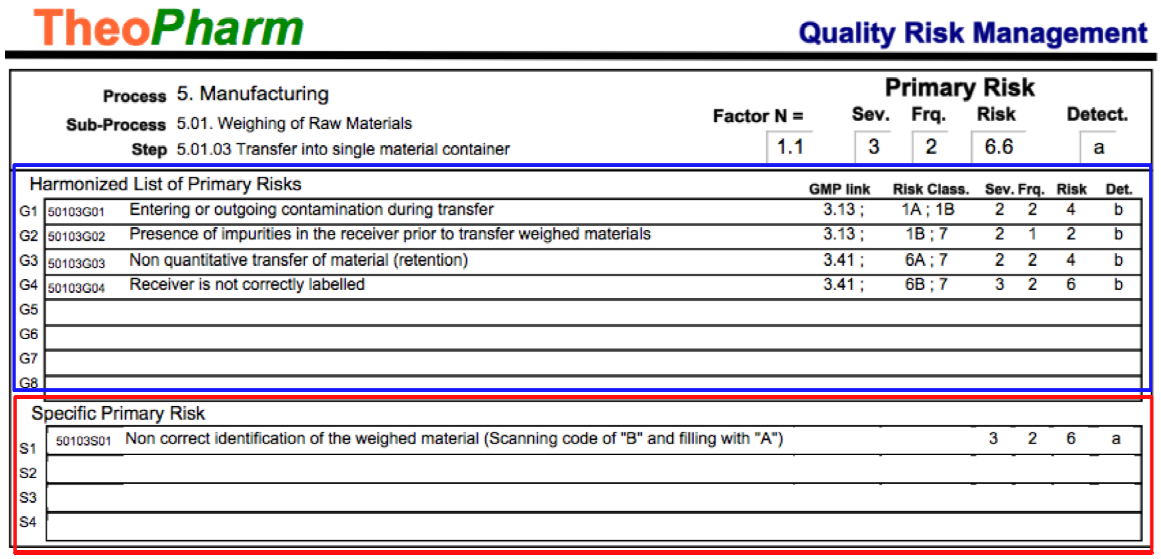
Selection of the elementary stage:

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:



Scheme S8; 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.



TheoPharm — Quality Risk Management

			Primary Risk			
Process	5. Manufacturing	Factor N =	Sev.	Frq.	Risk	Detect.
Sub-Process	5.01. Weighing of Raw Materials					
Step	5.01.03 Transfer into single material container	1.1	3	2	6.6	a

Harmonized List of Primary Risks			GMP link	Risk Class.	Sev.	Frq.	Risk	Det.
G1	50103G01	Entering or outgoing contamination during transfer	3.13 ;	1A ; 1B	2	2	4	b
G2	50103G02	Presence of impurities in the receiver prior to transfer weighed materials	3.13 ;	1B ; 7	2	1	2	b
G3	50103G03	Non quantitative transfer of material (retention)	3.41 ;	6A ; 7	2	2	4	b
G4	50103G04	Receiver is not correctly labelled	3.41 ;	6B ; 7	3	2	6	b
G5								
G6								
G7								
G8								

Specific Primary Risk							
S1	50103S01	Non correct identification of the weighed material (Scanning code of "B" and filling with "A")	3	2	6	a
S2						
S3						
S4						

Scheme S9; 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 x F x N

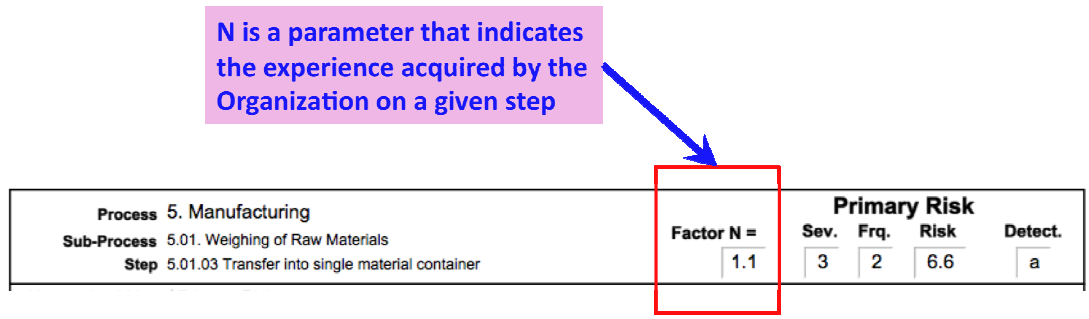
The values of the risk are discrete values belonging to the explicit series: [0.0; 1.0; 1.1; 1.2; 2.0; 2.2; 2.4; 3.0; 3.3; 3.6; 4.0; 4.4; 4.8; 6.0; 6.6; 7.2; 9.0; 9.9; 10.8]. These values define the zones of acceptance according to the rules given above with:

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

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

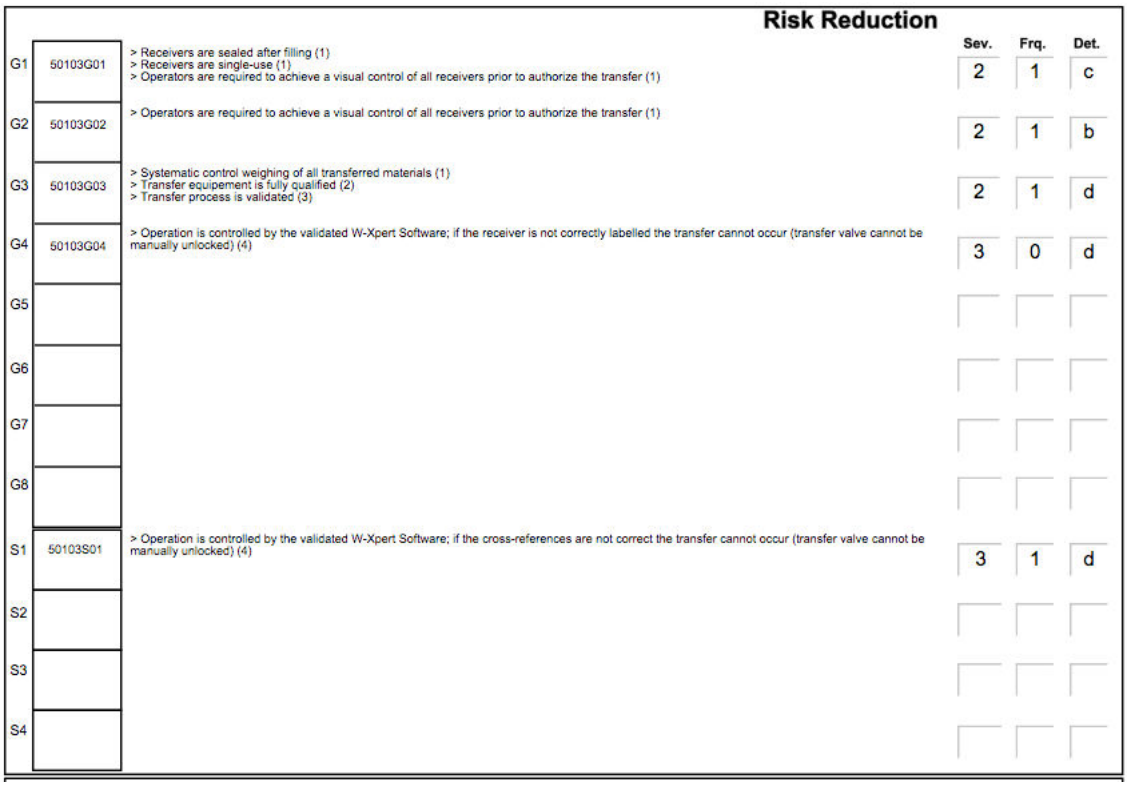
Scheme S10; Acceptance diagram

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



Scheme S11; Primary Risk

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.

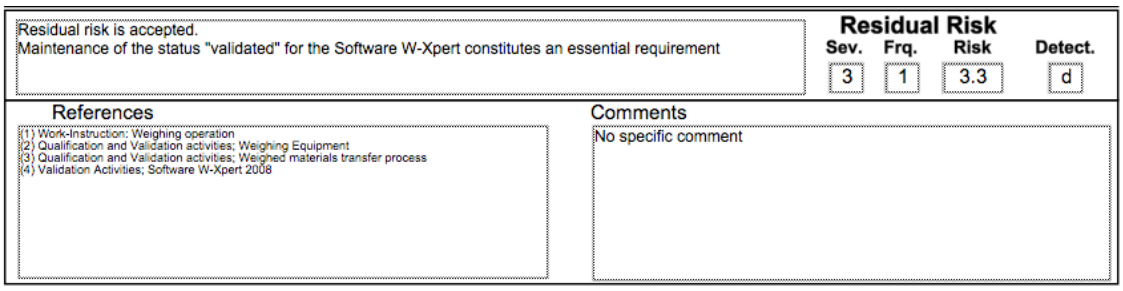


Risk Reduction			Sev.	Frq.	Det.
G1	50103G01	> Receivers are sealed after filling (1) > Receivers are single-use (1) > Operators are required to achieve a visual control of all receivers prior to authorize the transfer (1)	2	1	c
G2	50103G02	> Operators are required to achieve a visual control of all receivers prior to authorize the transfer (1)	2	1	b
G3	50103G03	> Systematic control weighing of all transferred materials (1) > Transfer equipement is fully qualified (2) > Transfer process is validated (3)	2	1	d
G4	50103G04	> Operation is controlled by the validated W-Xpert Software; if the receiver is not correctly labelled the transfer cannot occur (transfer valve cannot be manually unlocked) (4)	3	0	d
G5					
G6					
G7					
G8					
S1	50103S01	> Operation is controlled by the validated W-Xpert Software; if the cross-references are not correct the transfer cannot occur (transfer valve cannot be manually unlocked) (4)	3	1	d
S2					
S3					
S4					

Scheme S12; 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".



Scheme S13; Residual Risk and final statements

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:

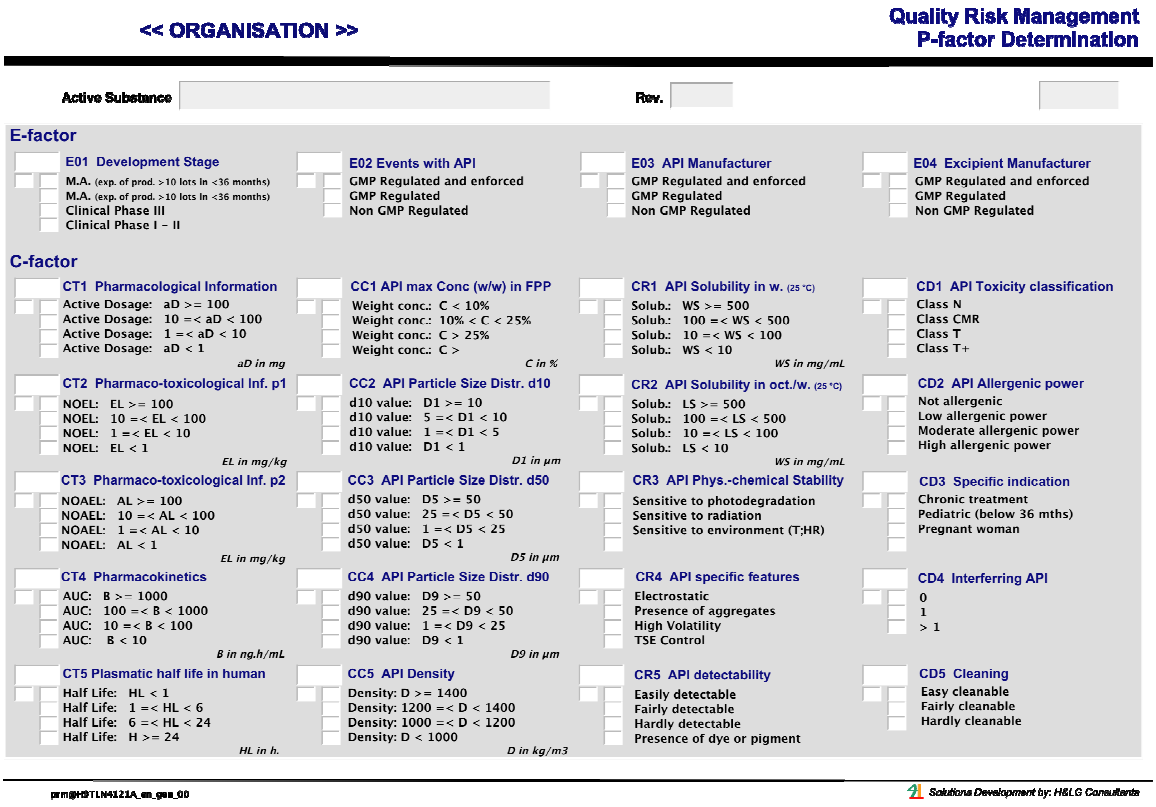
Step	Description	Severity * frequence	Experience	System Risk	Detection	System Acceptability
		S * F	N	Rs	D	As
4	Manufacturing Upstream					
4.1	Purchasing	3	1.0	**3.00**	d	Y
4.2	Admission	3	1.0	**3.00**	d	Y
4.3	Sampling	2	1.0	**2.00**	c	Y
5	Manufacturing In-Process					
5.01	Weighing					
5.01.01	Supply 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; Cristallization	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

Scheme S14; Compilation of elementary steps with values of systemic residual risks

This table gives synoptic systemic risk (Rs).

3.2. Product factor

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



<< ORGANISATION >>

Quality Risk Management
P-factor Determination

Active Substance | Rev.

E-factor

E01 Development Stage
- M.A. (exp. of prod. >10 lots in <36 months)
- M.A. (exp. of prod. >10 lots in <36 months)
- Clinical Phase III
- Clinical Phase I - II

E02 Events with API
- GMP Regulated and enforced
- GMP Regulated
- Non GMP Regulated

E03 API Manufacturer
- GMP Regulated and enforced
- GMP Regulated
- Non GMP Regulated

E04 Excipient Manufacturer
- GMP Regulated and enforced
- GMP Regulated
- Non GMP Regulated

C-factor

CT1 Pharmacological Information
- Active Dosage: aD >= 100
- Active Dosage: 10 =< aD < 100
- Active Dosage: 1 =< aD < 10
- Active Dosage: aD < 1

aD in mg

CC1 API max Conc (w/w) in FPP
- Weight conc.: C < 10%
- Weight conc.: 10% < C < 25%
- Weight conc.: C > 25%
- Weight conc.: C >

C in %

CR1 API Solubility in w. (25 °C)
- Solub.: WS >= 500
- Solub.: 100 =< WS < 500
- Solub.: 10 =< WS < 100
- Solub.: WS < 10

WS in mg/mL

CD1 API Toxicity classification
- Class N
- Class CMR
- Class T
- Class T+

CT2 Pharmaco-toxicological Inf. p1
- NOEL: EL >= 100
- NOEL: 10 =< EL < 100
- NOEL: 1 =< EL < 10
- NOEL: EL < 1

EL in mg/kg

CC2 API Particle Size Distr. d10
- d10 value: D1 >= 10
- d10 value: 5 =< D1 < 10
- d10 value: 1 =< D1 < 5
- d10 value: D1 < 1

D1 in µm

CR2 API Solubility in oct./w. (25 °C)
- Solub.: LS >= 500
- Solub.: 100 =< LS < 500
- Solub.: 10 =< LS < 100
- Solub.: LS < 10

WS in mg/mL

CD2 API Allergenic power
- Not allergenic
- Low allergenic power
- Moderate allergenic power
- High allergenic power

CT3 Pharmaco-toxicological Inf. p2
- NOAEL: AL >= 100
- NOAEL: 10 =< AL < 100
- NOAEL: 1 =< AL < 10
- NOAEL: AL < 1

EL in mg/kg

CC3 API Particle Size Distr. d50
- d50 value: D5 >= 50
- d50 value: 25 =< D5 < 50
- d50 value: 1 =< D5 < 25
- d50 value: D5 < 1

D5 in µm

CR3 API Phys.-chemical Stability
- Sensitive to photodegradation
- Sensitive to radiation
- Sensitive to environment (T;HR)

CD3 Specific indication
- Chronic treatment
- Pediatric (below 36 mths)
- Pregnant woman

CT4 Pharmacokinetics
- AUC: B >= 1000
- AUC: 100 =< B < 1000
- AUC: 10 =< B < 100
- AUC: B < 10

B in ng.h/mL

CC4 API Particle Size Distr. d90
- d90 value: D9 >= 50
- d90 value: 25 =< D9 < 50
- d90 value: 1 =< D9 < 25
- d90 value: D9 < 1

D9 in µm

CR4 API specific features
- Electrostatic
- Presence of aggregates
- High Volatility
- TSE Control

CD4 Interferring API
- 0
- 1
- > 1

CT5 Plasmatic half life in human
- Half Life: HL < 1
- Half Life: 1 =< HL < 6
- Half Life: 6 =< HL < 24
- Half Life: H >= 24

HL in h.

CC5 API Density
- Density: D >= 1400
- Density: 1200 =< D < 1400
- Density: 1000 =< D < 1200
- Density: D < 1000

D in kg/m3

CR5 API detectability
- Easily detectable
- Fairly detectable
- Hardly detectable
- Presence of dye or pigment

CD5 Cleaning
- Easy cleanable
- Fairly cleanable
- Hardly cleanable

prm@H5TLN4122A_en_gen_00

Solutions Development by: H&LG Consultants

Scheme S15; Table of data acquisition for 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.

3.3. 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	Experience	System Risk	Detection	System Acceptability	Experience with Product	Product Characteristics	P Factor	Global Risk	Global Acceptability
		S * F	N	Rs	D	As	m	C	P	Rg	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) ; Siefting	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

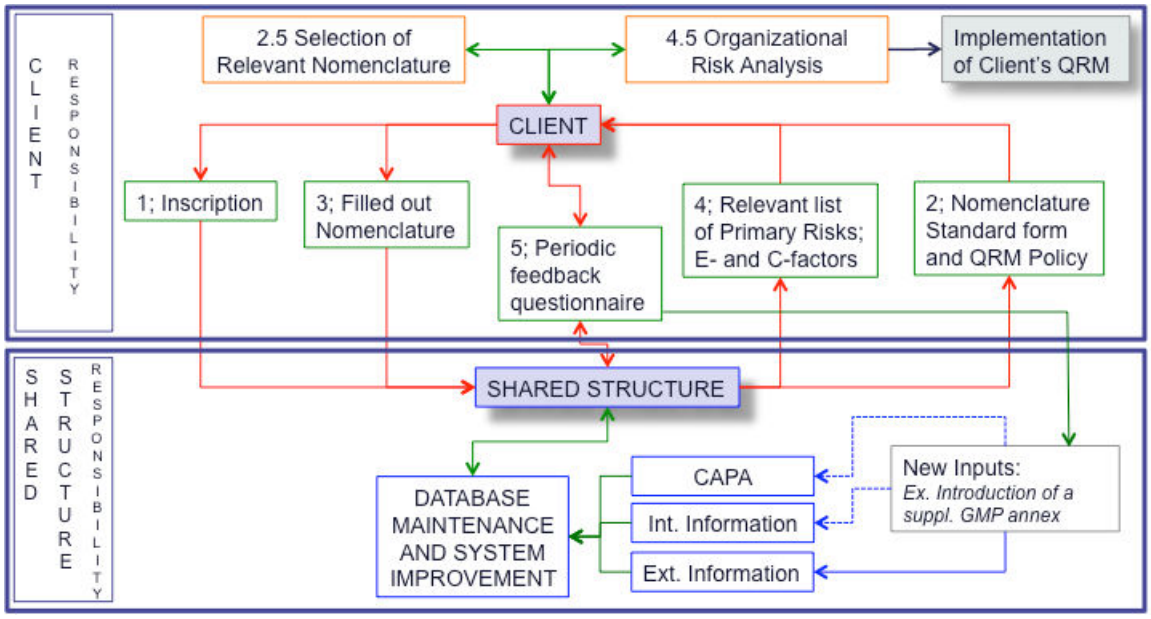
Scheme S16; Compilation of elementary steps with values of systemic residual risks and global risks

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

4. Deployment of methodology

The developed example of methodology provides for the means of its implementation by making training tools available as well as a starting kit with all the primary risks harmonized for the activity developed by the Company. The methodology relies on an interactive database, which is accessible to the users. This service, expected to be soon available, should then be developed, hosted and maintained on an independent

platform bringing together the different partners such as industry, professional associations, etc. The Company will then integrate the system on a voluntary "Customer - Supplier" basis. The operation of the service is demonstrated in the diagram below:



Scheme S17: Deployment diagram

The platform will make available the assistance necessary to implement the method, guarantee confidentiality and use the information supplied exclusively for implementing the Risk Management methodology and nothing else. The platform will not interfere with free choice or the responsibility of the Company itself as regards its Risk Management by providing dedicated sections intended to include primary risks specific to her environment.

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