ICH Q9: Quality Risk Management (QRM) & Risk based approach on impurity NDMA

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ICH Quality Guidelines – the second wave

- Q8 Pharmaceutical Development
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality Systems
- Q11 API Dev. & Manufacture
- Q12 Lifecycle Mgmt

Aspirational guidelines setting out a new vision for Product & Process Development

Adapted well defined concepts and tools

Not much prior experience

- **Encourages Industry & regulators to develop and adopt a "new quality paradigm"**
- **Recognises need for culture change in Industry & Regulators**

ICH Q9 Quality Risk Management – step 4, Nov. 2005 (approved)

"This guideline is not intended to create any new regulatory expectations; but rather

- provides an inventory of internationally acknowledged risk management methods and tools together with a list of potential applications at the discretion of manufacturers
- and should be considered as a resource document that can be used together with existing quality-related guidelines when a risk-based approach is appropriate."

Optional but can benefit from its use!

- Old: Informal approach
- New: Opportunity to use a structured process

Implementation in 2006 of a Legal position for ICH Q9

- US / FDA:
  - Guidance for Industry (June 2006)
  - By law, guidance documents are not enforceable or binding; FDA will use
  - the document internally in this spirit, as well
- Japan / MHLW:
  - Product GMP Guideline; “Annex”: ICH Guidelines
- EU / EMEA: EUDRALEX Volume 4 - Medicinal Products for Human & Veterinary Use : Good Manufacturing Practice;
  - The ICH Q9 guideline as such has been implemented with the new Annex 20 (March 2008)
  - The chapter I with the revisions highlighted and the new Annex 20 are enclosed
- PIC/S and EMEA training session for European Inspectors- Dec. 07:
  - working session “to define future role of inspectors when auditing Quality Risk Management – QRM comes into operation for Pharma Industry.

Principles of QRM – ICH Q9

- **The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient**

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

ICH
harmonisation for better health

Outline of Concept Paper

Revision of ICH Q9 - Quality Risk Management

Dated 12 September 2019

Endorsed by the Assembly on 19 November 2019

There are four areas of particular concern with the current application of QRM:

a) **High levels of subjectivity in risk assessments and in QRM outputs** – differences in how risks are assessed and how hazards are perceived lead to widely differing approaches and decision-making for to the management of risks, with varying levels of effectiveness.

b) **Failures to adequately manage supply and product availability risks** – ICH Q9 is not a supply chain guideline, but the management of risks in the supply chain to ensure product quality and availability is important for patients. ICH Q9 already addresses product availability issues - its definition of harm includes damage 'from a loss of product availability' - but an increased emphasis on this would be beneficial, where the need for risk-based drug shortage prevention and response plans could be highlighted.

c) **Lack of understanding as to what constitutes formality in QRM work** - this area is under-developed and poorly understood, leading to ineffective QRM activiites. There has been significant confusion and uncertainty in the industry (and among regulators) as to what constitutes formality in QRM work, and how to generally interpret this principle.

d) **Lack of clarity on risk-based decision-making** - while there are references in ICH Q9 to decision-making and how QRM may improve decision making, there is a lack of clarity on what good risk-based decision making actually means, or how it might be achieved. There is a breadth of peer-reviewed research in this area, but the level of visibility (and uptake) of that research within the pharmaceutical industry appears to be low.

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b) Definition of harm includes damage 'from a loss of product availability'

c) Significant confusion and uncertainty in the industry as to what constitutes formality in QRM work, and how to generally interpret the principle

d) Lack of clarity on what good risk-based decision making actually means.

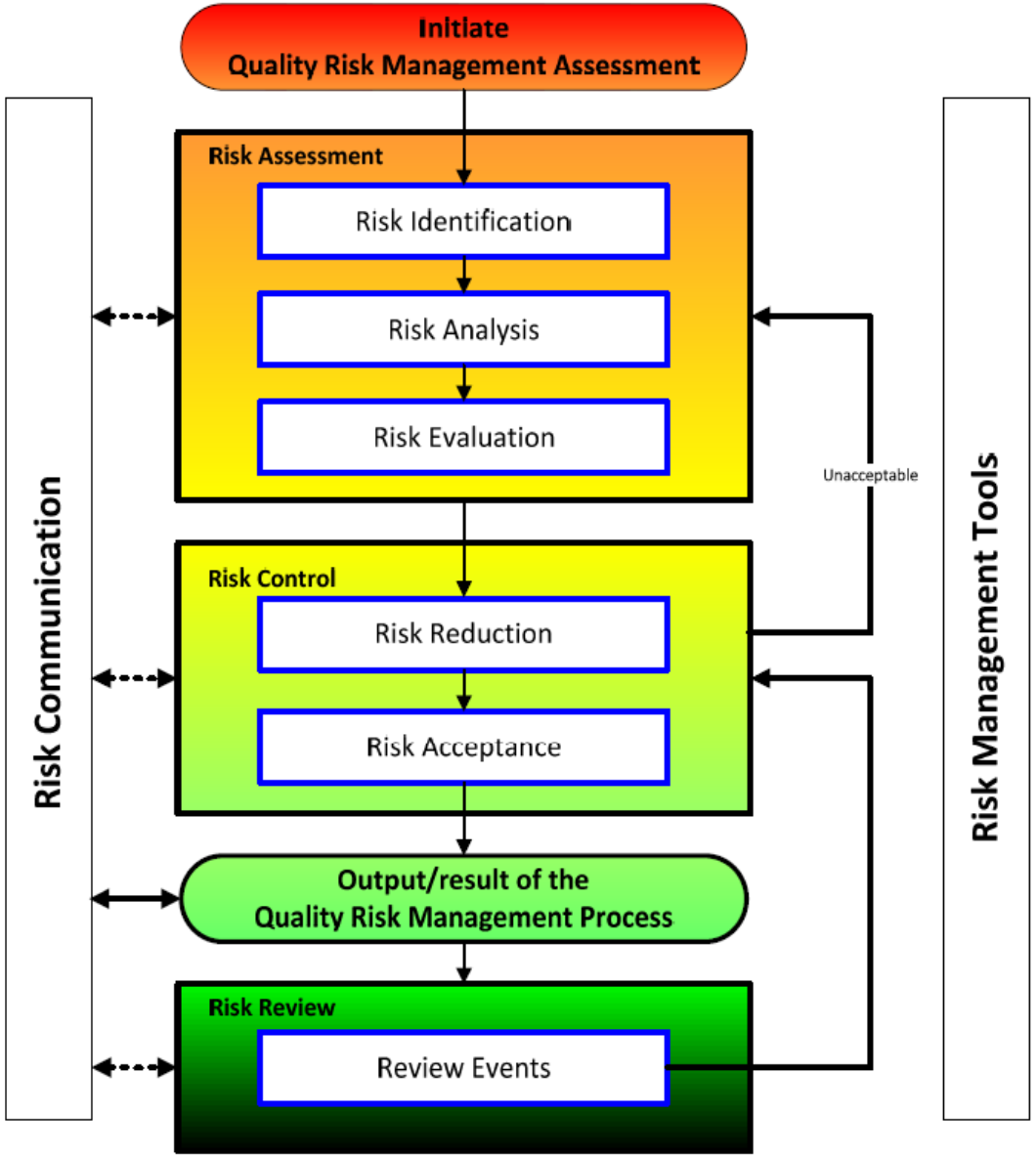
Process

Risk Identification
What might go wrong?

Risk Analysis & Evaluation
What is the likelihood (probability) it will go wrong?
What are the consequences (severity)?

Risk Level
- Severity, Probability/Occurrence

Risk Evaluation
- Safety Risk Level, Detectability

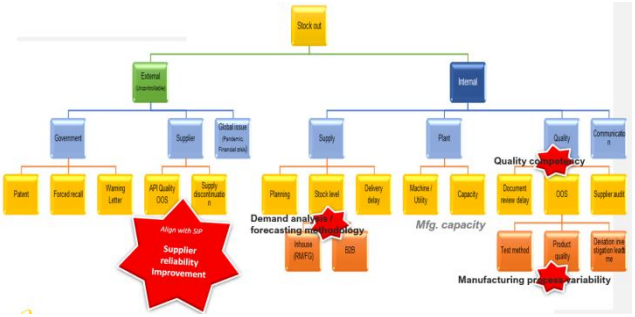


Overview: Some tools and their key words

- **Failure Mode Effects Analysis (FMEA)**
  - Break down large complex processes into manageable steps

항목 Item	실제 요소 Failure mode	위험 Hazard	위해요소 Harm	심각성 Severity	발생가능성 Probability	검출가능성 Detectability	RPN	영향 Impact	대처방안/관리 Mitigating Actions/Controls	비고 Comments
1	*EDI failure*	*No water supply*	*Possible PW shortage*	*5*	*4*	*5*	*100*	*Production stoppage*	*Install failure detection alarm system. Qualify system Routine Daily checks PPMs*	

- **Failure Mode, Effects and Criticality Analysis (FMECA)**
  - FMEA & links severity, probability & detectability to criticality
- **Fault Tree Analysis (FTA)**
  - Tree of failure modes combinations with logical operators
- **Hazard Analysis and Critical Control Points (HACCP)**
  - Systematic, proactive, and preventive method on criticality
- **Hazard Operability Analysis (HAZOP)**
  - Brainstorming technique
- **Preliminary Hazard Analysis (PHA)**
  - Possibilities that the risk event happens
- **Risk ranking and filtering**
  - Compare and prioritize risks with factors for each risk



NDMA Before Risk Based Approach

- **Cost comparison**

  - Expected cost for only one product in 2020 ~ 2023Y

Cost		
Analytical Equipments	480,000USD	N/A
Method Verification	13,000USD (1analyst/4years)	4,200 USD
Finished Products		5,000 USD (3batches)
Accelerated Stability test (0,1,3,6M)		15,000 USD (1product*3batches*3times)
Long-Term Stability test (0,3,6,9,12,18,24,36M)		35,000 USD (1product*3batches*7times)
Based on 1 product	610,000USD	60,000 USD
Total 27 products		**1,620,000 USD**

Risk Identification

1. 평가대상에 대한 상세 정보
Details of Subject to be Assessed

NDMA 등 니트로소아민류 발생가능성 평가보고서(완제의약품)

Nitrosoamine(NDMA, etc). Occurrence Possibility Evaluation Report(Finished Products)

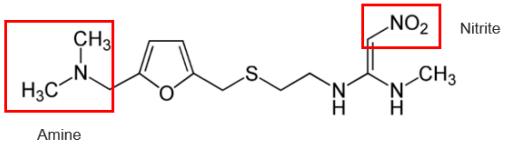
완제의약품(Finished Products)	
제품명 (Name)	제조원 (Manufacturer)
AAA 정	BBB

주성분 원료의약품(Active Pharmaceutical Ingredients)	
원료명 (Name)	제조원 (Manufacturer)
탈니플루메이트	CCC

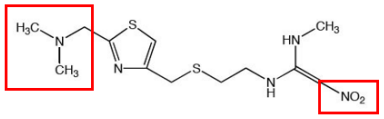
원료명	Solubility	구조식 상 Nitrate 함유여부	Nitrosamine 함유여부
탈니플루메이트	Insoluble in water	O	X
	Miscible with water	X	X
	Practically insoluble in water	X	X
	Insoluble in water	X	X
	Insoluble in water	X	X
	Insoluble in water	X	X
	Practically insoluble in water	X	X
	Soluble in cold water practically insoluble in hot water	X	X
	Miscible with water	X	X
	Practically insoluble in water	X	X
	N/A	X	X

Caused by the structure

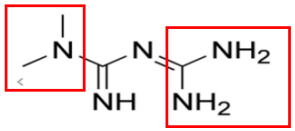
- **Ranitidine**

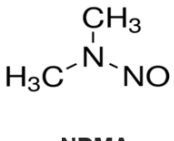


- **Nizatidine**



- **Metformin**





NDMA

Risk Identification

2. 잠재 위험성 기술
Potential Risk Description

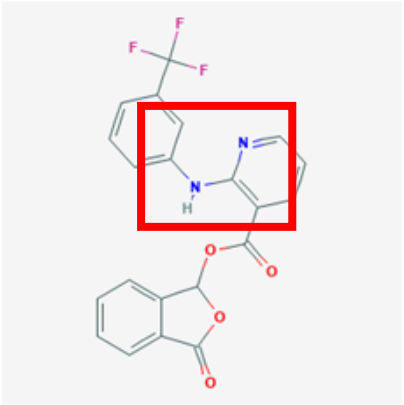
1.	2 차, 3 차 아민이나 4 차 암모늄 존재 하에서 아질산나트륨($NaNO_2$) 혹은 다른 아질산염을 사용하는가? (같은 공정 혹은 다른 공정에서) Do you use sodium nitrite($NaNO_2$) or other nitrites in the presence of secondary, tertiary amines or quarternary ammonium? (Same process or Different process)
	■ 아질산 관련 시약 사용하지 않음.
2.	원료의약품 제조공정에서 오염된 원료(용매, 시약, 촉매 등)을 사용하는가? → 회수된 물질(용매, 시약, 촉매 등) 사용에 따른 오염 가능성 Do you use contaminated raw mat substance manufacturing process' → Possibility of contamination by catalysts, etc.)
	■ 회수된 물질 사용하지 않음.
3	원료의 회수를 외부업체에 위탁하 방법으로 관리되고 있는가? If you are entrusting the recovery possibility of contamination during
	■ 외부업체에 위탁하지 않음.
4	NDMA 생성가능성이 있는 공정이 혹은 중간체를 사용하고 있는가? Are you using starting materials or processes or raw materials that ma
	■ 출발물질에 2 차, 3 차 아민 의 없음.
5	원료의약품 제조공정의 마지막 단 있는가? Is it possible that impurities are no substances manufacturing process
	■ N/A
6	기타 생성가능성이 있는가? → 생산라인 공유에 따른 교차오 Is there any other possibility of cre → Cross contamination due to sha
	■ N/A

1.	완제의약품의 포장과정에서 오염 가능성이 있는가? → 포장재질에 니트로셀룰로오스 또는 포장에 사용하는 잉크에 존재하는 아민류와의 결합에 따른 생성 가능성 Is there potential for contamination in the packaging of Finished Products? → Probability of formation due to binding to nitrocellulose in packaging materials or amines present in packaging inks.
	■ 포장자재 공급업체(DDD) 회신결과, 아민 및 니트로셀룰로오스 미함유 및 1 차 포장구역에서 제품 충전 ~ 캡 씰링공정 진행에 따른 포장공정에서 오염 및 생성가능성 없음. ■ 첨부문서 1. supplier nitrosamines declaration(DDD) 참조
2.	아질산염 또는 아민을 함유하는 의약품 성분이 용액 또는 현탁액(예: 과립공정)으로 존재하거나 고온에서 유지되는 작업(예: 건조공정)이 이뤄지고 있는가? Are pharmaceutical ingredients containing nitrites or amines present in solution or suspension (ex. Granulation) or are they maintained at elevated temperature(ex. Drying)?
	■ AAA 정 제조 시 결합액(Corn Starch + 정제수) 사용함에 따라 전성분(주원료 + 부원료)의 구조식 조사결과, 아질산염 또는 아민을 함유하고 있지 않으며 Solubility 평가결과, 부원료 중 포도당 및 프로필렌글리콜이 정제수에 용해되어 주원료 및 타 부원료와 결합할 가능성이 있지만 Nitrate 를 함유하고 있지 않음에 따라 NDMA 발생가능성은 없을 것으로 판단됨. (2.1.3 참조) ■ AAA 정 제조 시 건조공정(건조온도 : 60 ℃) 진행하지만 식약처의 "발사르탄 관련 중간조사결과발표 (2018.08.06_식약처)" 중 NDMA 는 130 ℃ 정도의 온도에서 생성되는 것으로 판단됨에 따라 NDMA 발생 가능성은 낮을 것으로 판단됨. ■ 첨부문서 2. AAA 정 제조공정흐름도 참조
3	아질산염 또는 아민을 함유하는 부형제가 있다면 주원료와 반응하여 NDMA 발생가능성이 있는가? If there are excipients containing nitrite or amine, is there a possibility of NDMA occurring by reacting with the API?
	■ AAA 정의 제조에 사용되는 전성분(주원료 + 부원료) 구조식 확인결과, Nitrate, 아질산염 및 아민을 함유하고 있지 않으므로 NDMA 발생가능성은 없을 것으로 판단됨.

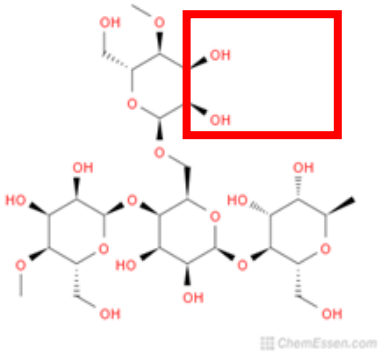
Risk Identification

2. 잠재 위험성 기술
Potential Risk Description

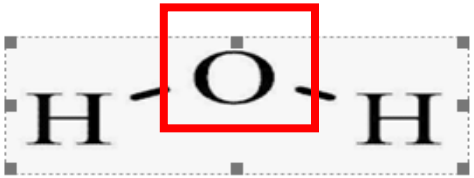
2.1.1. API(탈니플루메이트) 및 결합액(Corn Starch + 정제수) 구조식



(탈니플루메이트)



(Corn Starch)



(정제수)

Drying conditions :
50-60°C & 4-5Hrs

CH_3-CH_2-OH

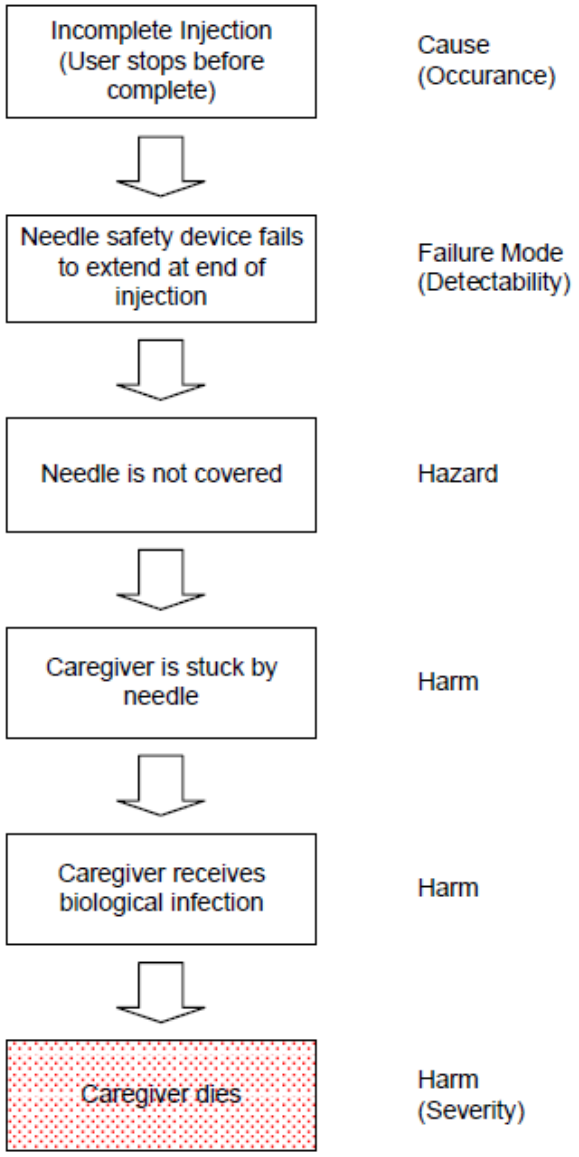
(Ethyl Alcohol)

Definition

- Severity: Each harm shall be assigned a severity rating based upon the harm resulting from a single occurrence of that harm. When assessing severity, the worst-case harm shall be assumed

- Probability: The assessment of the likelihood of a failure mode arising shall be calculated from the worst-case probability of occurrence of those contributing conditions (including human intervention) that are needed to cause a failure mode unless

- Detectability: An assessment of the likelihood that the potential failure mode can be detected shall be made by considering existing process controls, historical data for process performance, procedure operating procedures, and/or product usage. In this respect, FMEAs may incorporate detectability in the estimation and evaluation of process risk by calculating a Risk Priority number (RPN).



Risk Level

❖ Risk level = Severity of the impact x Likelihood of Occurrence

➢ Severity(심각성) of the impact

Rating	Classification	Description
1	경미함 minor	허가나 GMP 규정 준수 부작용을 유발하지 않는 결함 Complaints 위험성 증가
2	중대함 Major	허가나 GMP 규정 미 준수 제품 품질(안전성, 유효성)에 영향 제품 회수 (recall)를 유발할 가능성이 있는 결함 일시적 부작용을 유발할 수 있는 경우
3	심각함 Severe	허가나 GMP 규정 미 준수 제품 품질(안전성, 유효성)에 치명적 영향 환자에게 치명적 위험(심각한 부작용, 사망 등)을 유발할 수 있는 결함

Risk Level

➢ Occurrence(발생가능성)

Rating	Occurrence	Description
1	희박 Very unlikely	처음 확인된 위험성 재발 가능성이 없거나 희박함
2	매우 낮음 Rare	재발 가능성은 희박하나 배제할 수는 없음
3	낮음 Occasional	재발 가능성 있음
4	높음 Likely	재발 가능성이 거의 확실함
5	거의 확실 Almost certain	영구적으로 빈번히 발생

		Likelihood					Rank	
Classification	Description	Chronological	DPO	PPM	Sigma Level	CpK	Quantitative	Qualitative
Very High	Failure is almost inevitable	More than one occurrence per day	≥1 in 2	500,000	1.5	< 0.33	10	High
High	Repeated failures	One occurrence per week	1 in 8	125,000	2.7	≥ 0.51	8	
Moderate	Occasional failures	One occurrence every six months to one year	1 in 400	2,500	4.3	≥ 1.00	5	Medium
Low	Relatively few failures	One occurrence every one to three years	1 in 15000	67	5.3	≥ 1.33	3	Low
Remote	Failure is unlikely	One occurrence in greater than five years	≤1 in 1500000	0.7	6.3	≥ 1.67	1	

Case Study Example

Illustration from the Case Study – Risk Assessment for PSD Control

What is the **Impact** that ---------- will have on purity? 1) minimal 5) moderate 9) significant						
What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely						
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely						
Unit Operation	**Parameter**	IMPACT	PROB.	Detect	RPN	**Comments**
Crystallization	Feed Temperature	1	5	1	5	
Crystallization	Water content of Feed	1	5	5	25	
Crystallization	Addition Time (Feed Rate)	9	5	9	405	Change in addition time is easy to detect, but rated high since there is no possible corrective action
Crystallization	Seed wt percentage	9	5	5	225	
Crystallization	Antisolvent percentage	1	1	1	1	Yield loss to crystallization already low (< 5%), so reasonable variations in antisolvent percentage (+/- 10%) will not affect the percent of batch crystallized, and will not affect PSD
Crystallization	Temperature	9	5	9	405	Change in crystallization temperature is easily detected, but rated high since no possible corrective action (such as, if seed has been dissolved)
Crystallization	Agitation (tip speed)	9	5	5	225	Prior knowledge indicates that final PSD highly sensitive to Agitation, thus requiring further study.
Crystallization	Seed particle size distribution	9	1	1	9	Seed PSD controlled by release assay performed after pin milling.
Crystallization	Feed Concentration	1	1	1	1	Same logic as for antisolvent percentage

To be investigated in DOE

Detailed working documents like this would likely not be included in the submission

High Priority **10 Products**

Products	API	API supplier	Manufacturing Plan	Lot.No	Test result
					3 lots test result, below quanti tative limit(QL)
					3 lots test result, below QL
					3 lots test result, below QL
					3 lots test result, below QL
					API test schedule: June, 2021
					API test schedule: start test in Sep, 2020 & complete it in Ju ne, 2021
					FFF : will be tested (schedule: not fixed) → provide test res ult in 2020
					EEE Limited :3 lots test result, below QL FFF : will be tested(schedule: n ot fixed)→ provide test result in 2020
					1, 2 : No possibility 3. GGG: testing result in Nov
					API test result: Nov

Risk Evaluation

❖ Risk Evaluation = Risk Level (= Severity x Probability) x Capability to detect

➢ Detection(발견가능성)

Rating	Detection	Description
1	높음 High	결함을 감지하고 제거할 가능성이 매우 높음 100%에 근접한 관리
2	중간 Moderate	IPC나 통계적 관리에 의해 발견 가능 유통 중 혹은 환자 (냄새, 색상, 외관 등)에 의해 발견 가능성이 높음
3	낮음 Low	검출 가능성이 매우 낮아 우연한 경우에 발견 사용 전 검출될 가능성이 거의 없음

Risk Control

- Decision-making activity
  - Is the risk above an acceptable level?
  - What can be done to reduce or eliminate risks?
  - What is the appropriate balance between benefits, risks and resources?
  - Are new risks introduced as a result of the identified risks being controlled?
- Risk acceptance is a formal decision to accept the risk

Risk Control

- Decision making process with related dept
  - Risk reduction
    - Site action plans for all (or Major, etc.) risks identified
    - High level tracking of residual Critical risks (RM database);
    - Coordination with Operations, Regulatory Affairs, Industrial Development, …
    - QRM approach allow to define priorities
    - (Detectability increase)
  - Risk acceptance
    - Site level (e.g. batches not release, defect corrected)
    - Within Quality, with Operations, Affiliate, as appropriate
      - Ad hoc quality meetings
      - Quality Alert steering committees

Risk Control with timeline/DRI (Directly Responsible Person)

- Ways to minimize the risk
  1) Change the supplier
  2) Change the manufacturing process
  3) Ask supplier to control
  4) Forced Degradation Study - FGs & APIs

- Way to increase detectability
  1) Test of incoming materials (APIs)
  2) Test of finished products
  3) Stability

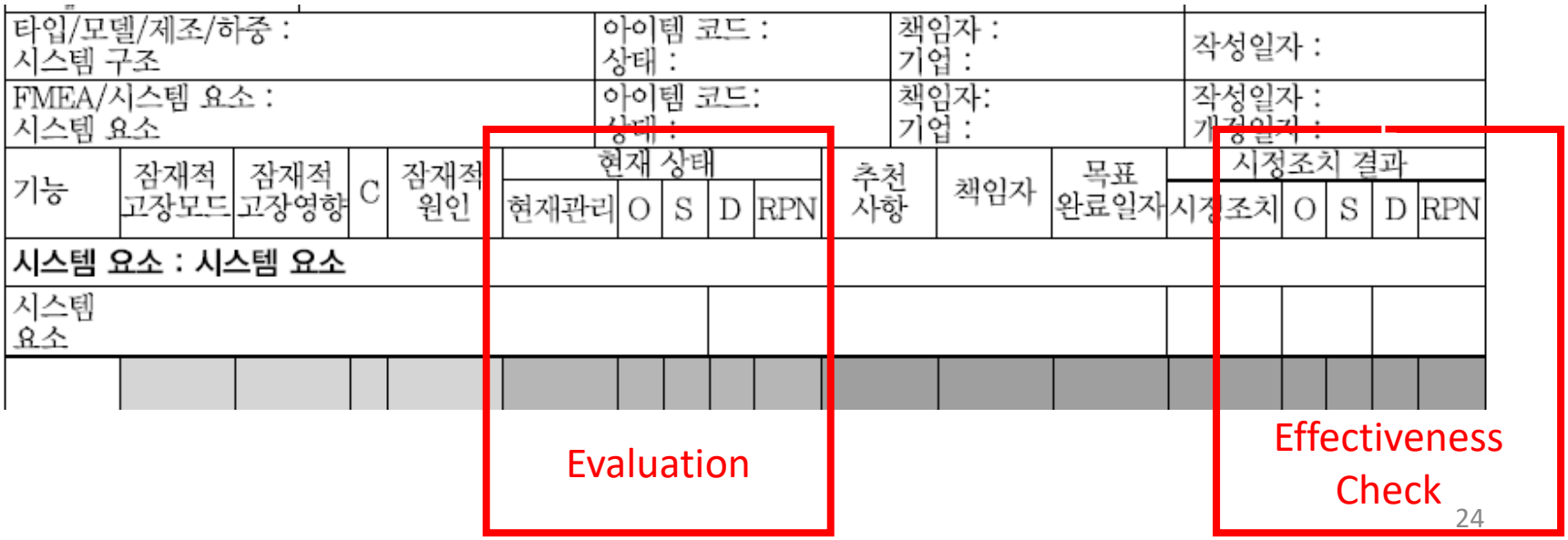
Risk Acceptability

RPN	Severity				
	Negligible	Minimal	Marginal	Critical	Catastrophic
501-1000	Cannot achieve this rating	Cannot achieve this rating	Intolerable	Intolerable	Intolerable
101-500	Cannot achieve this rating	ALAP	ALAP	Intolerable	Intolerable
51-100	Broadly Acceptable	ALAP	ALAP	ALAP	ALAP
26-50	Broadly Acceptable	Broadly Acceptable	Broadly Acceptable	ALAP	ALAP
1-25	Broadly Acceptable	Broadly Acceptable	Broadly Acceptable	Broadly Acceptable	ALAP

Risk Level	Risk Acceptability
High/Intolerable	Unacceptable if no further risk reduction measures are feasible. (Individual risks may be accepted on a case-by- case basis by proving that the quality risk/benefit ratio is favorable, once all reasonable risk reduction measures have been taken.)
Medium/ALAP	This level of risk is considered tolerable only if further reduction is not possible and the benefits outweigh the residual risk.
Low/Broadly Acceptable	These are acceptable risks. No further risk control measures needed if product safety cannot be improved.

* ALAP : As Low As Possible

Effectiveness Check



타입/모델/제조/하중 : 시스템 구조					아이템 코드 : 상태 :					책임자 : 기업 :			작성일자 :					
FMEA/시스템 요소 : 시스템 요소					아이템 코드: 상태 :					책임자: 기업 :			작성일자 : 개정일자 :					
기능	잠재적 고장모드	잠재적 고장영향	C	잠재적 원인	현재 상태					추천 사항	책임자	목표 완료일자	시정조치 결과					
					현재관리	O	S	D	RPN				시정조치	O	S	D	RPN	
시스템 요소 : 시스템 요소																		
시스템 요소																		

Evaluation

Effectiveness Check

Thank You