

藥品儲存之品質風險概況

Date: 5/29/2015 Speaker: Pichiang Hsu (許弼強) Email: <u>pichiang.hsu@gmail.com</u> PichiangHsu@impaxlabs.com.tw

CONFIDENTIAL. DO NOT DETAIL, COPY, OR DISSEMINATE

4. Risk Assessment in GDP 優良運銷規範 的風險評估

- Risk to assess, control, and review
 - What are the risk sources?

Preface

It is of key importance that medicinal products are not only made to a high quality in accordance with Good Manufacturing Practice, but that the quality and integrity of these products are maintained through the entire supply chain to the patient. This is where Good Distribution Practice (GDP) comes into play.



• Risk Sources – Equipment 設備



1. Product packaging



4. Transport vehicle



2.Storage



5. Monitoring system



3. Shipping container



6. Data- and communication system

Equipment and its components must be qualified/validated to eliminate and to reduce the risk of failures.

• Risk Sources – Processes 流程

- 1. Pre-shipment
 - Planning
 - Procedures / SOPs / Process flows
 - Risk assessments
 - Contingency plans
 - Equipment qualification/validation
 - Packout assembly
 - Export documentation
- 2. In-transit
 - Loading/unloading transport vehicle
 - Transit nodes
 - Cargo handling processes
 - Communication processes
 - Custom inspection/clearance
- 3. Post-shipment
 - Roles and responsibilities towards temperature excursions
 - Storage of the goods
 - Inventory management



Application of Lean Six Sigma drives continuous improvement of processes and reduces failures

- Risk Sources People 人員
 - 1. Skilled people
 - Knowledge, experience and understanding of equipment, processes and external factors.
 - 2. Unskilled people
 - No or limited knowledge, experience and/or understanding of equipment, processes and/or external factors.

3. Bad actors

 Skilled or unskilled people who on purpose mislead others and/or mistreat products including theft, counterfeiting and exposure to extreme temperatures.



• Risk Sources – People

Types of Human Error

- 1. Misunderstanding Teach your written policies and procedures repetitively
- 2. Forgetfulness Create a checklist or a Poka Yoke
- 3. Wrong identification Mark, label, color, etc., for easy recognition
- 4. Lack of experience/skill Improve your hiring or training systems
- 5. Willful ignoring of rules or procedures Hold people accountable
- Slowness Remove bottlenecks; create standards of performance; measure results
- 7. Inadvertent or sloppiness Apply an improvement methodology
- Lack of standardization Reduce and simplify; create procedures, templates, etc.
- 9. Intentional/sabotage/not caring Warn or terminate the person immediately
- Surprise Unexpected, infrequent and random causes are more difficult to eliminate

- Risk Sources External factors 外在環境因素
 - 1. Environmental factors
 - Natural disasters
 - Storms
 - Flooding
 - Bush fire
 - Earthquake
 - Volcanic eruption
 - Extreme cold / hot weather
 - Diseases / pandemic
 - 2. Geopolitical factors
 - 3. Economic factors
 - 4. Technological factors
 - Power supply
 - Power failure
 - Power surges (temporary increase in voltage in power lines)
 - Brownouts (power falls below the given amount from the utility)
 - Load shedding (rotating the availability of electricity between all customers)

Contingency plans are critical to handle external risk factors.



Risk Sources – External factors



Daily temperature variation



Schiphol Airport - The Netherlands

Altitude (-6.5 °C per 1000 m)



Sun insolation versus latitude



When to apply Risk Assessment



5. Risk Assessment Tools – Process map



- Identify each way the process can fail
- Identify the possible consequences of each failure mode
- Assign numerical rankings

• Quantitation of Risk: Severity 嚴重性

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action

• Quantitation of Risk: Probability 發生率

Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect

• Quantitation of Risk: Detectability 可偵測性

Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection (i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

Risk Evaluation Score

Probability

õ

Severity

ncrease

(Severity X Probability X Detectability = RPN)

Decrease Detectability

	1	3	5	7
1	1	3	5	7
3	3	9	15	21
5	5	15	25	35
6	6	18	30	42
7	7	21	35	49
9	9	27	45	<mark>6</mark> 3
15	15	45	75	105
18	1 <mark>8</mark>	54	90	126
21	21	<mark>6</mark> 3	105	147
27	27	81	135	189
30	30	90	150	210
42	42	126	210	294
45	45	135	225	315
63	63	189	315	441

Risk Level	RPN Range
Low	PRN < 30
Medium	$30 \le \text{RPN} \le 90$
High	$90 \leq \text{RPN}$

Risk Evaluation – Risk Acceptance?

ncrease

Probability õ Severity

Decrease Detectability

Risk Level	RPN Range
Low	PRN < 30
Medium	$30 \le RPN < 90$
High	$90 \leq \text{RPN}$

How to design a FMEA table

<u>Category</u>	<u>Failure mode</u>	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	Probability	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	<u>Remediation</u> action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
ſ												

Risk sources (phenomena and root cause)

Based on the historical data (e.g. deviations), interview, experience, and etc.

How to create a FMEA table

檔案常	常用 插	人 版面配置 公式	資料 校閱 檢視										a 😮 🗆 🖶 🛛
■ よ剪 い い い い い い い い い い い う い う い う い う い	下 製 -	Geneva - 10	- A [*] A [*] = = = >> -	■ 自動換列 通用格式		· 設定核式化格式化為 Warping	2 T	otal 2 Total 3	•		格式	Σ 自動加總 ▼ ■ 填滿 ▼ 北京の飾選	(1) (1) (1) (1) (1) (1) (1) (1) (1) (1)
✓ ∛ 複	製格式	B I <u>U</u> + ⊞ + <u>∞</u> •	· <u>A</u> · ф2 · ≡ ≡ ≡ ≡ ⊈ ≇	■ 跨欄置中 * * % ,	.00	→ 的條件 × 表格 ×		17 T	-		*	②清除▼ 17777平142	選取、
	012	字型	5 到臀方3	に 「「」」「」」 「」 「」 「」 「」 「」 「」 「」 「」 「」 「」 」 「」 」 「」 」 「」 」 「」 」 「」 」 」 一 一 一 一		Gi	禄 式			儲存格		編輯	
12 4	A	в	C	D	E	F	G	Н	1	J	K	L	M
1 (Category	✓ Failure mode	Potential Cause	Potential Effect(s) of Failur -	everi 🚽	Current Control	Probabili 🖵	Detection Strategy 🚽 🛽	Detecting Wi	Detectabili 🗸	<u>RP</u> 🗸	Remediation action	RNP After Remediati
2 Impax	TW Wareh	ouse Control Spec.: Temperat	ture: 20-25 °C, Relative humidity: 65%										
• Tempe	erature	lemparature variation leads to product exposure under unacceptable condition	Environmental effect (day and night switch)	Impurity, AS	3	Warehouse HVAC control system	1	Temperature monitored by RMS	automatic	1	3	Not required	<u>N/A</u>
· _ Tempe	erature	High excursoin during Summer	Seasonal environmental effect	in purity, AS	3	Warehouse HVAC control system	1	Temperature monitored by RMS	automatic	1	3	Not required	<u>N/A</u>
· Tempe	erature	Low excursoin during winter	Seasonal environmental effect	Impuny AS	1	Warehouse HVAC control system	1	Temperature monitored by RMS	automatic	1	1	Not required	<u>N/A</u>
• Vibratio	on	Drum breakage during packaging	Dropping or bumping of the drum	Appearance	1	Drums are wrapped by wraping plastic	1	1. Checked by packaing personnel at MFG site 2. Checked by QA at packaging site	Manual	3	3	<u>Not required</u>	<u>N/A</u>
• Vibratio	on	Bulk product breakage	Dropping or bumping of the drum	Appearance	1	Bubble wrap application in the inner drum	1	1. Monitored by packaing operator at packaging site 2. Packaging site QA sampling	Manual	3	3	<u>Not required</u>	<u>N/A</u>
Humid	lity	High excursion	Environmental effect (sunny and raining day)	Impurity, AS	3	1. Warehouse HVAC control system 2. Product is double-bagged 3. Desiccant application	1	Humidity monitored by RMS	automatic	1	3	Not required	<u>N/A</u>
• Humid	lity	Low excursoin	Environmental effect (sunny and raining day)	Impurity, AS	3	1. Warehouse HVAC control system 2. Product is double-bagged	1	Humidity monitored by RMS	automatic	1	3	Not required	<u>N/A</u>
Proces	5S	Drum or lid cracking	Improper packaging (piling) of the drums leads to drum or lid cracking	Appearance	1	SOL for equipment safety operation process	3	1. Checked by packaing personnel at warehouse personnel 2. Checked by QA at packaging site	Manual	3	9	Not required	N/A
	Checked by GA at Each and Second Control of the creating of th												
							~~~						

Process

#### How to create a FMEA table

<u>Category</u>	Failure mode	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	<b>Detectability</b>	<u>RPN</u>	<u>Remediation</u> action	RNP After Remediation (S x P x D = RPN)

Evaluation standard for Severity

Example 1, Drum appearance: Severity = 1

Example 2, API Degradation: Severity = 3

**Example 3, Low toxic impurity: Severity = 6** 

Example 4, High toxic impurity: Severity = 9

Score	Risk Severity
1	No or negligible harm/ quality alert
3	Loss of product activity/ drug appearance or package damage
6	Injury to patient/ batch loss
9	Death or extremely serious injury to patient/ product recall or regulatory action

#### How to create a FMEA table

<u>Category</u>	<u>Failure mode</u>	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	<u>Remediation</u> action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
						ノ						
-			1						1			

**Evaluation standard for Probability** 

Example 1, Temp controlled: Probability = 1 Example 2, Softbox during Spring: Probability = 3 Example 3, Softbox during Summer : Probability = 5

Example 4, N/A during Summer: Probability = 7

Score	Risk Probability
1	Not observed, extremely unlikely to occur/ proactive control
3	Not anticipated, but possible/ passive control
5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect
7	Very likely to occur, almost certain/ no control with harsh environmental effect

#### How to create a FMEA table

<u>Category</u>	<u>Failure mode</u>	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
									ノ			
-	I	1		1							1	

Evaluation standard for Detectability

1

Example 1, Temp logger: Detectability = 1

Example 2, QA and Operator checking: Detectability = 3

**Example 3, Operator checking: Detectability = 5** 

**Example 4, N/A: Detectability = 7** 

Score	Risk Detectability
1	Almost certain- Failure detected in every instance (i.e. automatic detection)
3	Very likely detection ( i.e. checked by multiple personnel)
5	Moderate chance of detection (i.e. detected by one personnel)
7	Essentially Undetectable

#### How to create a FMEA table

<u>Category</u>	Failure mode	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)

**Risk Control**: implement control actions to reduce risk (Risk Reduction)

#### 5. Risk Assessment Tools – FMEA How to create a FMEA table

Elimination Process Steps, Transfers, etc.

Substitution Formulation of Process Method

**Reduction** via Enginering Controls, Closed Process, Transfer Devices, etc.

Administrative and Procedural Training, Technique, Time,

Location, etc.

Do not ship via this route

Change to a better packaging material

**Request VUN in the airport** 

**Revise SOP for personnel training** 

#### How to create a FMEA table

<u>Category</u>	Failure mode	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	<u>Remediation</u> action	RNP After Remediation (S x P x D = RPN)

	1	3	5	7
1	1	3	5	7
3	3	9	15	21
5	5	15	25	35
6	6	ĺδ	30	42
7	7	21	35	49
9	9	27	45	63
15	15	15	75	105
18	18	5-	5	126
21	21	63	105	147
27	27	81	135	189
30	30	90	150	210
42	42	126	2 9	> 4
45	45	135	225	315
63	63	189	315	441

**Risk Control:** reduce risk level to acceptable level (**Risk acceptance**)

<u>Category</u>	Failure mode	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
Impax TW Wa	arehouse Control Spec	.: Temperature:	20-25 ℃, Re	lativ	ve humidity: 65%							
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment- al effect (day and night switch)	Impurity, AS									

<u>Category</u>		Failure mode	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)		
Impax TW Wa	areho	ouse Control Spec	.: Temperature: 2	20-25 ℃, Re	lativ	ve humidity: 65%	I	1	l	I			Γ		
Temp.	Te var prc und cor	mperature iation leads to oduct exposure der unacceptable nditions	nperature ation leads to duct exposure er unacceptable ditions 6												
Score	)					Ri	sk	Severity	/						
1		No or neg	ligible ha	rm/ qı	ua	lity alert									
3		Loss of product activity/ drug appearance or package damage													
6		Injury to patient/ batch loss													
9		Death or extremely serious injury to patient/ product recall or regulatory action													

<u>Category</u>		Failure mode	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
Impax TW Wa	areho	ouse Control Spec	.: Temperature: 2	20-25 ℃, Re	lativ	ve humidity: 65%				r			
Temp.	Te vai pro uni coi	mperature riation leads to oduct exposure der unacceptable nditions	Environment- al effect (day and night switch)	Impurity, AS	6	Warehouse HVAC control system	1						
Score	2					Risl	k P	Probabili [.]	ty				
1		Not obser	ved, extr	emely	u	nlikely to	00	cur/ pro	active	cor	ntrol		
3		Not antici	pated, bu	it poss	sib	le/ passiv	'e	control					
5		Failure observed occasionally, likely to occur/ no control/ passive control with arsh environmental effect											
7		Very likely to occur, almost certain/ no control with harsh environmental effect											

<u>Category</u>		Failure mode	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
Impax TW Wa	arehou	use Control Spec	.: Temperature: 2	20-25 ℃, Re	lativ	ve humidity: 65%					1		
Temp.	Ten vari proc und con	Iperature ation leads to fuct exposure er unacceptable ditionsEnvironment- al effect (day and night switch)Impurity, AS6Warehouse HVAC control system1Temperature monitored by RMSAutomatic11Impurity, and night switch)6Warehouse HVAC control system1Temperature monitored by RMSAutomatic1											
Score	e		'		•	Risk	D	etectabil	lity		1		-
1		Almost ce	ertain- Fai	ilure d	et	ected in e	eve	ery instar	nce (i.e	e. a	utoma	tic detec	tion)
3		Very likely detection ( i.e. checked by multiple personnel)											
5		Moderate chance of detection (i.e. detected by one personnel)											
7		Essential	y Undete	ctable									

#### **Create a FMEA table**

<u>Category</u>	Failure mode	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	<b>Detectability</b>	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
Impax TW Wa	arehouse Control Spec	.: Temperature: 2	20-25 ℃, Re	elativ	ve humidity: 65%							
Temp.	Temperature variation leads to product exposure under unacceptable conditions	Environment- al effect (day and night switch)	Impurity, AS	6	Warehouse HVAC control system	1	Temperature monitored by RMS	Automatic	1	6	Not required	N/A

#### Risk Evaluation Score: Severity X Probability X Detectability = RPN 6 X 1 X 1 = 6

Risk Level	RPN Range
Low	PRN < 30
Medium	$30 \le RPN < 90$
High	$90 \leq RPN$

### 6. Case Study II – Warehouse Humidity

<u>Category</u>	<u>Failure mode</u>	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	<b>Detectability</b>	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
Impax TW Wa	arehouse Control Spec	.: Temperature: 2	20-25 ℃, Re	lativ	ve humidity: 65%							

### 6. Case Study II – Warehouse Humidity

	<u>Category</u>	Failure mode		Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	<b>Detectability</b>	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
	Impax TW	Warehouse Contr	rol Spec.:	Temperature: 2	:0-25 ℃, Re	lati	ve humidity: 65%	1						
	Humidity	High excursion		Environmental effect (sunny and raining day)	Impurity, AS		N/A		Humidity monitored by RMS	automatic	I	42		
			Score	2					Risk S	Severity				
			1	No or neg	igible ha	m,	/ quality alert							
			3	Loss of pro	Loss of product activity/ drug appearance or package damage									
Risk	Level R	PN Range	6	Injury to p	atient/ b	atc	h loss			_				
Low	P.	RN < 30	9	Death or e	Death or extremely serious injury to patient/ product recall or regulatory action Risk Probability									
High	9	$0 \le RPN \le 90$ $0 \le RPN$	Score	2										
111gil			1	Not observ	ved, extre	em	ely unlikely to	осс	ur/ proactive	e control				
			3	Not anticip	pated, bu	tр	ossible/ passiv	e c	ontrol					
			5	Failure obs	served oc	cas	sionally, likely t	to c	occur/ no con	trol/ passi	ve c	ontrol wi	th harsh enviro	onmental effect
			/ Scoro	Very likely	to occur,	alı	most certain/ r	10 (	Control with r	harsh envir	ronn	nental eff	ect	
			1	Almost cer	tain- Fail	ure	a detected in a	ver	v instance (i d		tic d	etection		
			3	Very likely	detectio	n (	i.e. checked by	ver vm	ultiple person	nnel)	tic u	election		
				Madarata	chanco	f d	etection (i.e. d		ctod by ono	norconnol	<b>`</b>			
			5	woderate	chance c	i u	election (i.e. u	ele	cied by one	personner	)			

### 6. Case Study III – Warehouse Vibration

Category	<u>Failure mode</u>	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	Detectability	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
Impax TW Wa	arehouse Control Spec	.: Temperature: 2	20-25 ℃, Re	elati	ve humidity: 65%							
Vibration	Bulk product breakage	Dropping or bumping of the drum	Appearanc e	1	Bubble wrap application in the inner drum	1	1. Monitored by packaing operator at packaging site 2. Packaging site QA sampling	Manual	3	3	<u>Not required</u>	<u>N/A</u>

Risk Level	RPN Range	Score	Risk Severity						
Low	PRN < 30	1	No or negligible harm/ quality alert						
Medium	$30 \le \text{RPN} \le 90$	3	Loss of product activity/ drug appearance or package damage						
High	$90 \le RPN$	6	Injury to patient/ batch loss						
		9	Death or extremely serious injury to patient/ product recall or regulatory action						
		Score	Risk Probability						
		1	Not observed, extremely unlikely to occur/ proactive control						
		3	Not anticipated, but possible/ passive control						
		5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect						
		7	Very likely to occur, almost certain/ no control with harsh environmental effect						
		Score	Risk Detectability						
		1	Almost certain- Failure detected in every instance (i.e. automatic detection)						
3			Very likely detection ( i.e. checked by multiple personnel)						
		5	Moderate chance of detection (i.e. detected by one personnel)						
		7	Essentially Undetectable						

### 6. Case Study IV – Warehouse Process

	Categ	gory	Failure mode		Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	<b>Detectability</b>	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
	<u>Impax</u>	TW Wa	arehouse Co	ntrol Spec.	: Temperature: 2	20-25 ℃, Re	lati	ve humidity: 65%		T	I		ľ	l	
	Process	5	Drum or lid cra	icking	Improper packaging (piling) of the drums leads to drum or lid cracking	Appearanc e	1	SOP for equipment safety operation process	3	1. Checked by packaing personnel at warehouse personnel 2. Checked by QA at packaging site	Manual	3	9	<u>Not required</u>	<u>N/A</u>
D' 1	 		D	Score						Risk S	everitv				
K1SK	Level	RPN DDN	Range	1	No or negli	gible har	m/	quality alert							
Med	ium	30 < 30 < 100	$\frac{< 30}{\text{RPN} < 90}$	3	Loss of pro	duct activ	, zitv	/ drug appear	anc	e or package	damage				
High	1	<u>90 ≤</u>	RPN	6	Injury to pa	atient/ba	tch		arre	e or puerio _{Be}	uunu _b e				
				9	Death or ex	tremelv	ser	ious iniury to i	oat	ient/ product	recall or r	egul	atorv act	ion	
				Score				·····		Risk Pro	obability	-0			
				1	Not observ	ed, extre	me	ely unlikely to c	оссі	ur/ proactive	control				
				3	Not anticip	ated, but	рс	ossible/ passive	e co	ontrol					
				5	Failure obs	erved oco	casi	ionally, likely t	0 0	ccur/ no cont	trol/ passiv	ve co	ontrol wit	h harsh enviro	nmental effect
				7	Very likely	to occur,	alm	nost certain/ n	0 C	ontrol with h	arsh envir	onm	ental effe	ect	
					Almost cor	tain- Eaile	ire	detected in a	ION	KISK Det		ic do	tection		
				3	Very likely	detection	i (i	.e. checked by	mı	ltiple person	nel)	ic ue			
				5	Moderate d	chance of	de	etection (i.e. de	ete	cted by one p	personnel)				
				7	Essentially	Undetect	ab	le							

### 6. Case Study V – Apron Temperature

<u>Category</u>	<u>Failure mode</u>	Potential Cause	Potential Effect(s) of Failure	Severity	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	<b>Detectability</b>	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
ULD Area A	pron in TPE Airport											
Temperature	High excursoin during Summer	Seasonal environmental effect	Impurity, AS	3	1. Night freight during the period of Apr to Oct 2. VUN requested. The time at the apron is controlled in 1- 3 hours 3. Insulated packaging to control temperatre variation	5	TT4 monitoring	Automatic	1	15	<u>Not required</u>	<u>N/A</u>

Risk Level	RPN Range	Score	Risk Severity						
Low	PRN < 30	1	No or negligible harm/ quality alert						
Medium	$30 \le \text{RPN} \le 90$	3	Loss of product activity/ drug appearance or package damage						
High	$90 \le \text{RPN}$	6	Injury to patient/ batch loss						
		9	Death or extremely serious injury to patient/ product recall or regulatory action						
		Score	Risk Probability						
		1	Not observed, extremely unlikely to occur/ proactive control						
		3	Not anticipated, but possible/ passive control						
		5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect						
		7	Very likely to occur, almost certain/ no control with harsh environmental effect						
		Score	Risk Detectability						
		1	Almost certain- Failure detected in every instance (i.e. automatic detection)						
		3	Very likely detection ( i.e. checked by multiple personnel)						
		5	Moderate chance of detection (i.e. detected by one personnel)						
		7	Essentially Undetectable						

### 6. Case Study VI – Your term

<u>Category</u>	<u>Failure mode</u>	Potential Cause	Potential Effect(s) of Failure	<u>Severity</u>	Current Control	<b>Probability</b>	<u>Detection</u> <u>Strategy</u>	<u>Detecting</u> <u>Way</u>	<b>Detectability</b>	<u>RPN</u>	Remediation action	<u>RNP After</u> <u>Remediation</u> (S x P x D = RPN)
		T	ſ					T				

Risk Level	RPN Range	Score	Risk Severity						
Low	PRN < 30	1	No or negligible harm/ quality alert						
Medium	$30 \le RPN \le 90$	3	Loss of product activity/ drug appearance or package damage						
High	$90 \le RPN$	6	Injury to patient/ batch loss						
		9	Death or extremely serious injury to patient/ product recall or regulatory action						
		Score	Risk Probability						
		1	Not observed, extremely unlikely to occur/ proactive control						
		3	Not anticipated, but possible/ passive control						
		5	Failure observed occasionally, likely to occur/ no control/ passive control with harsh environmental effect						
		7	Very likely to occur, almost certain/ no control with harsh environmental effect						
		Score	Risk Detectability						
		1	Almost certain- Failure detected in every instance (i.e. automatic detection)						
		3	Very likely detection ( i.e. checked by multiple personnel)						
		5	Moderate chance of detection (i.e. detected by one personnel)						
		7	Essentially Undetectable						

# 7. Summary



ICH Q9

# 7. Summary



[©] J. Arce, F. Hoffmann-La Roche

# Thank you for your attention

# **Questions?**

