THINKING RISK IN A DEVELOPMENT ENVIRONMENT – AN INDUSTRIAL VIEW

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Overview

- Understanding risk in Development
- Usefulness of current regulatory framework – strengths and weaknesses
- Adaptation of Risk Management concept for early Development
- Integration of Risk Management into design space model

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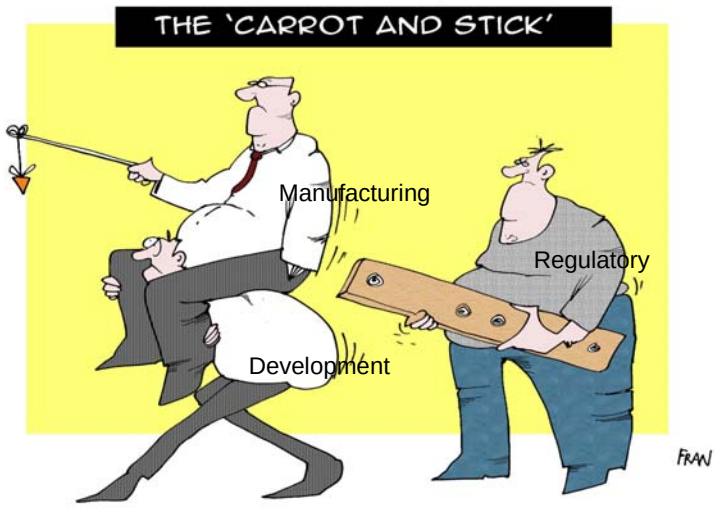
Development's view of Risk Management drivers



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Why understanding risk so important in Development?

- Drug development based fundamentally on minimising and managing risk

  "Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm"

- Risk management enables probability of harm to be qualified and/or quantified and appropriate actions to be established to minimise occurrence and impact

- Objective in Development is to integrate risk management into overall product design lifecycle

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How does risk feature in a Development framework?

- Long been "informal" practice within Development environment
- FDA initiative "GMP for 21st Century" sought to formalise risk-based approach for entire product development life-cycle
- ICH Q8, Q9 (and Q10) provide guidance for integration of quality risk management (QRM) into product design, development and manufacturing processes
- Excellent reviews also provided by PQRI Working group Dec 2006 on Process Robustness and Leyseele 2007 (Pharma Insight) on QRM
- So does it work in practice?

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Reality more complex can theory…?

- Linkage between ICH Q8, Q9 and Q10 exist in principle but challenging to reduce to practice for Development setting

1. ICH (Q8?) and Q9 centric on late phase development and NOT enough on early Development practices…?
2. Little practical guidance for conducting risk assessment in Early development
3. Risk management tools that work well for manufacturing needs adapting for R&D (not facile!)

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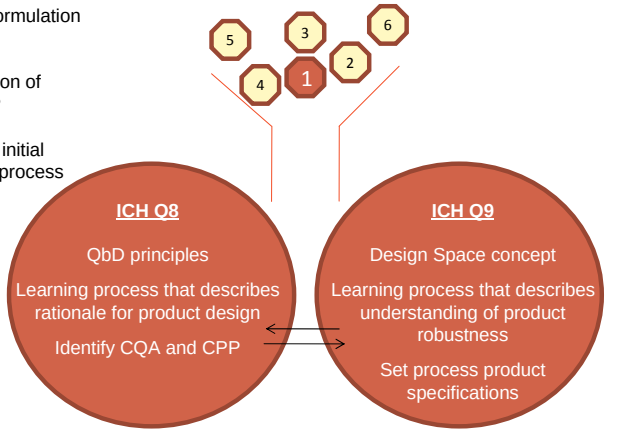
Relationship between ICH Q8, Q9 and Risk concept

RA of early formulation systems?

Standardisation of Approaches?

Rationale for initial formulation / process selection?



Risk-based development concept starts at ICH Q8

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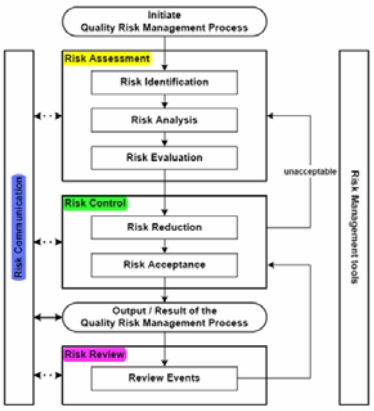
ICH Q9 Risk Management Framework



- Usually straight-forward to apply once initial formulation and preliminary process train has been established
- Perceived high-risk areas can be engineered out during formulation composition design
- Does not take account of multiplicity of substrates
- Difficult to work in practice due to lack of data and broadness of RA matrix

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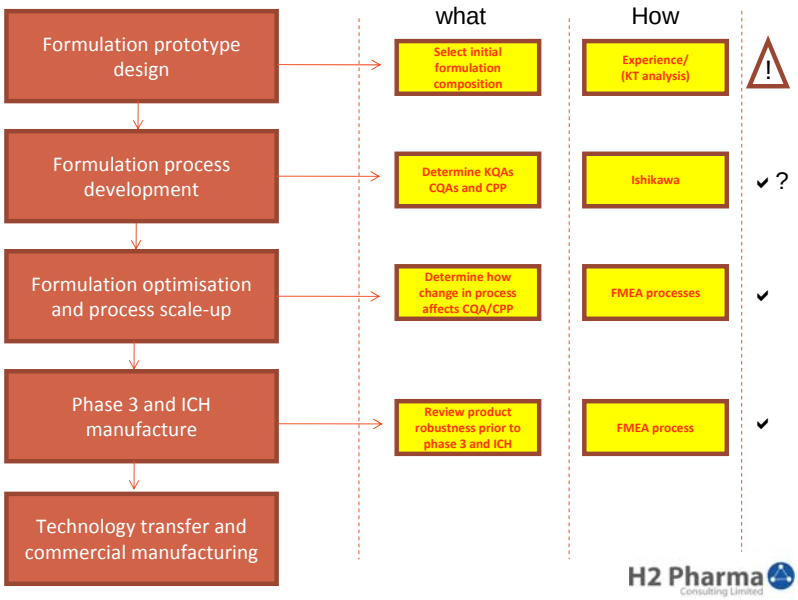
Risk assessment processes in Development



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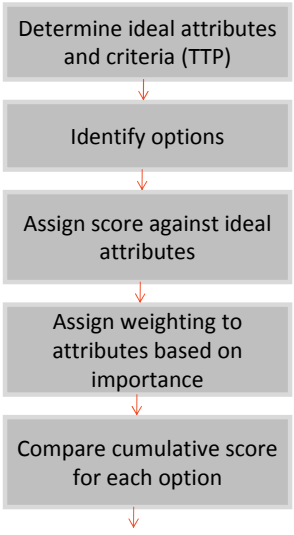
Application of risk assessment tool – Kepner-Tregoe



- Logical decision analysis for initial formulation/process selection
- Enable assignment of weighting to critical attributes
- Can compare across large matrix o formulation and process options
- Still heavily dependent on quality and consistency of starting input

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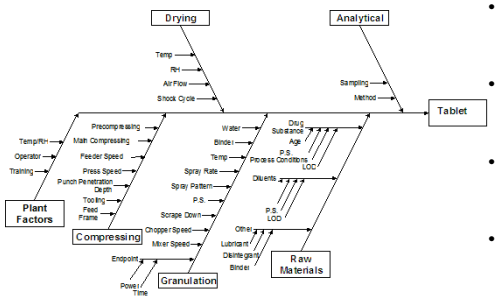
Application of risk assessment tool - Fishbone



- Excellent tool for risk identification
- Methodical reduces chance of missing critical parameters
- End out-put can very wide and requires significant triaging
- Needs additional tool for risk evaluation (FMEA)
- Can be difficult to work with in early development

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Application of risk assessment tool - FMEA

Key parameters	API particle size	MCC	Lac	DCP	Disintg	MgSt	Blending	RC	WG	DC	Milling	Lube	Compress/n	Film coating
Appearance	H	L	L	L	L	L	L	L	H	H	L	L	L	L
Identity	L	L	L	L	L	L	L	L	L	L	L	L	L	L
Assay	L	L	L	H	L	L	L	L	L	L	L	L	L	L
Impurities	H	L	H	L	L	L	L	L	L	L	L	L	L	L
Content uniformity	H	L	L	L	L	L	L	L	L	L	L	L	L	L
Disintegration	L	L	L	L	H	L	H	L	L	L	L	L	L	L
Dissolution	H	L	L	L	L	L	L	L	L	L	L	L	L	L

- Widely used as it allows direct reference to target parameters
- Enables weighting of likelihood of occurrence followed by analysis of impact severity to prioritise focus
- Enables prioritisation and focus of development studies
- Not ideal tool for triaging formulation composition selection as overall matrix can be very large (data also mostly unavailable to assess impact severity)

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Applying risk analysis in early development

Key issues:

- Initial formulation / process selection weakest link
- Process can be very subjective due to lack of data
- Limited cross-fertilisation of knowledge across groups/divisions
- RA process can be unnecessarily complex due to multiplicity of substrate

Impact:

- Potential for inappropriate and inconsistent formulation selection
- Emphasis on process to correct formulation design inefficiencies

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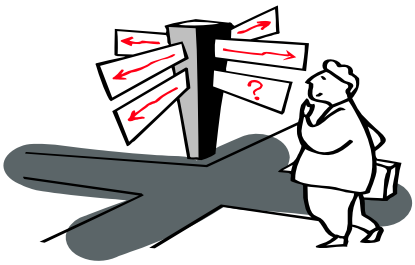
How can the process be improved…?



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Evolving industrial approach

- Institute more defined processes for formulation and process selection
  - Best practices, formulation manuals, internal guidance documents
- Minimise subjectivity during initial formulation/process development
- Encourage use of “targeted” and “rational” risk-assessment rather than blanket use of available tools
- Define risk category to determine downstream risk-assessment scrutiny

  (1) what is known → in the box
  (2) what is less known → out of the box

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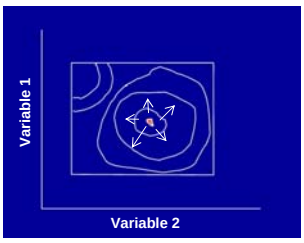
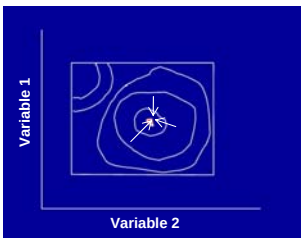
Defining the initial formulation

Existing design space model



Determine the design space for API in a given system

Simplified approach for initial formulation and process selection



Evaluate whether API fit pre-determined design space **(as a starting point)**

Design space developed with substantial dataset gained over many years with both development and commercial products

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Standardised "In-the-box" Route-map concept

API profile falls within pre-defined design space ?

YES

Standardised formulation system

+

Standardised process train

+

Standardised design space

=

Product with defined and reproducible quality

Adjust design space as more data becomes available

Generate key data for API and assess fit with standardised formulation/ process system

Undertake risk analysis in areas where API parameters not directly compatible with standardised system

Direct testing to quantify risk and define design space

Institute adequate level of control

Verify product performance in conventional manner

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Example I: Standardised "In-the-box" approach

For immediate release tablet dosage form development

New chemical entity

Discovery target product profile

Attributes	Response	Criteria	Pass/fail
Description	Standard immediate release tablet		Yes
Indication and usage	Duodenal ulceration		Yes
Dosage and administration	10-50mg twice daily given orally		Yes
Pharmacology	H-2 receptor antagonist, EC50 - 50ng/ml		Yes
	>1000-fold selectivity over H-1 receptor		Yes
	Rapid onset/offset		Yes
Pharmacokinetics	Linear PK, T1/2 - 6hrs, Vd - 0.8l/kxx		Yes
Metabolism	P450 microsomal isoenzymes		Yes
Toxicology	Negative in Ames		Yes
	HERG - no in vitro inhibition of patch clamp assay		Yes
	Irwin - no observable change over dose range		Yes

Criteria: Confidential

Illustration only

API/formulation target product profile

Category	Attributes	Method	Criteria	Pass/fail for DC	Pass/fail for RC	Pass/fail for WG
Biopharmaceutics	Dose	From Target profile		Pass	Pass	Pass
	Drug loading range	Projected		Pass	Pass	Pass
	Solubility	shake-flask		Pass	Pass	Pass
	Permeability	Caco-2		Pass	Pass	Pass
Chemical	Solid-state stability	Ambient and ccelerated conditions		Pass	Pass	Pass
	Stressed induced stability	Simulated compression		Pass	Fail	Pass
	Excipient compatibility	DoE matrix		Pass	Pass	Pass
Physical	Melting point	Differential scanning calorimetry		Pass	Pass	Pass
	Stability (hygroscopicity)	Dynamic vapour sorption / VTI Microbalance		Pass	Pass	Fail
	Particle size distribution	Laser diffraction / dry powder dispersion		Pass	Pass	Pass
	Particle morphology	Microscopy (light and electron)		Pass	Pass	Pass
	True density	Helium pycnometry		Pass	Pass	Pass
	Apparent density	Graduated cylinder/tap density tester		Pass	Pass	Pass
Mechanical	Ductility	Indentation hardness		Pass	Fail	Pass
	Tensile strength	Tensile test		Pass	Pass	Pass
	tableting indices	Compaction simulator		Pass	Pass	Pass
Flow	Uniform flow number	Shear cell		Pass	Pass	Pass

Illustration only

Choice of standardised formulation/process systems

Apply KT Decision Analysis

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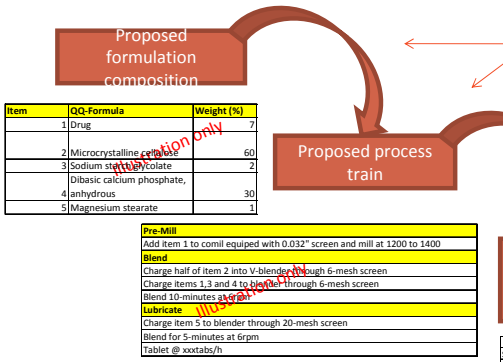

Apply FMEA/Fishbone analysis
To target RA on how API variation may impact on product quality/performance given defined formulation and process window

Item	QQ-Formula	Weight (%)
1	Drug	7
2	Microcrystalline cellulose	60
3	Sodium stearyl fumarate	2
4	Dibasic calcium phosphate, anhydrous	30
5	Magnesium stearate	1

Pre-Mill
Add item 1 to comil equiped with 0.032" screen and mill at 1200 to 1400
Blend
Charge half of item 2 into V-blender through 6-mesh screen
Charge items 1,3 and 4 to blender through 6-mesh screen
Blend 10-minutes at 20rpm
Lubricate
Charge item 5 to blender through 20-mesh screen
Blend for 5-minutes at 6rpm
Tablet @ xxxtabs/h

	Sieve analysis specification for product X tableting blend						
Screen size	20	40	80	100	200	325	>325
Max retained (%)	2	2	56	23	65	70	70
Retained (%)	0	0	5	6	25	16	48
	Target analytical specification						
Blend uniformity	Assay	Water	Bulk specific volume		Tapped specification volume		
(%RSD)	(%LC)	(%)	(cc/g)		(cc/g)		
<4.00	95-105	<4.5	1.5-2.5		1.1-1.7		
	Target tablet properties						
	10mgA						
Tablet shape	Round						
Target weight	400mg						
Average thickness	4mm						
Average hardness	13kPa						
Disintegration time	<200sec						
Friability	<0.2%						

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Non-Standard "Out-of-the-box" Route-map concept

API profile falls within pre-defined design space ?

No

Assess key risks within context of standardised formulation system

Undertake appropriate DoE to mitigate risk

Modify standard formulation/process with output from DoE

Generate key data for API and assess fit with standardised formulation/ process system

Provides justification on formulation and process design

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Example 2: Non-standardised "Out-of-the-box" approach

For immediate release tablet dosage form development

New chemical entity

Discovery target product profile

API/formulation target product profile

Attributes	Response	Criteria	Pass/fail
Description	Standard immediate release tablet	Confidential	Yes
Indication and usage	Duodenal ulceration		Yes
Dosage and administration	300-400mg twice daily given orally		Fail
Pharmacology	H-2 receptor antagonist, EC50 - 50ng/ml		Yes
	>1000-fold selectivity over H-1 receptor		Yes
	Rapid onset/offset		Yes
Pharmacokinetics	Linear PK, T1/2 - 6hrs, Vd - 0.5L, Cl XXX		Yes
Metabolism	P450 microsomal stability 30mins		Yes
Toxicology	Negative in Ames		Yes
	HERG - no in vitro inhibition of patch clamp assay		Yes
	Irwin - no observable change over dose range		Yes

Category	Attributes	Method	Criteria	Pass/fail for DC	Pass/fail for RC	Pass/fail for WG
Biopharmaceutics	Dose	From Target profile	Confidential	Fail	Pass	Borderline
	Drug loading range	Projected		Pass	Pass	Borderline
	Solubility	shake-flask		Pass	Pass	Pass
	Permeability	Caco-2		Pass	Pass	Pass
Chemical	Solid-state stability	Ambient and ccelerated conditions		Pass	Pass	Pass
	Stressed induced stability	Simulated compression		Pass	Fail	Pass
	Excipient compatibility	DoE matrix		Pass	Pass	Pass
Physical	Melting point	Differential scanning calorimetry		Pass	Pass	Pass
	Stability (hygroscopicity)	Dynamic vapour sorption / VTI Microbalance		Pass	Pass	Fail
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	Particle morphology	Microscopy (light and electron)		Fail	Pass	Pass
	True density	Helium pycnometry		Pass	Pass	Pass
	Apparent density	Graduated cylinder/tap density tester		Pass	Pass	Pass
Mechanical	Ductility	Indentation hardness		Pass	Fail	Pass
	Tensile strength	Tensile test		Pass	Pass	Pass
	tableting indices	Compaction simulator		Pass	Pass	Pass
Flow	Uniform flow number	Shear cell		Fail	Pass	Pass

Illustration only

Apply FMEA
Assess risks in context of standardised formulation / process approaches

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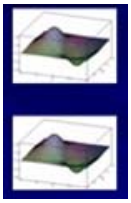
Example 2: Non-standardised "Out-of-the-box"

Risk assessment of standardised formulation systems

DoE to underpin formulation design



Modify standard formulation/process with output from DoE

Item	QQ-Formula	Weight (%)
1	Drug	35
2	Lactose monohydrate	25
3	Sodium starch glycolate	5
4	Dibasic calcium phosphate, anhydrous	30
5	PVP	4
6	Magnesium stearate	1

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Non-standardised complex "Out-of-the-box" approach

- Apply exactly same principles and activity flow
- In-the-box: use standardised formulation / process approaches
- Out-of-the box: supplement with detailed guidance on formulation and processing options to accompany risk assessment

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Example 3: Complex MR formulation development

Defined formulation for MR osmotic formulations

	"In-the-Box"	"Out-of-the-Box"
Dose	1-150mg	> 150mg
Release Rate	6h < $T_{80\%}$ < 16 h	$T_{80\%}$ < 6 h or $T_{80\%}$ > 16 h
API Form	Crystalline drug	SDD, drug+ solubilizer
Loading in the SCT		
Drug Layer (weight-%)		others
Drug layer formulation	Direct compression	Aqueous fluid-bed
Drug layer processing	Solvent high-shear wet granulation	Aqueous high shear wet
	Roller compaction	granulation
Sweller layer		others
formulation		Aqueous fluid-bed
Sweller layer	Direct compression	Aqueous high shear wet
processing	High-shear wet granulation	granulation
		Phase III - to
Scale of Manufacture	Phase I and Phase II	Commercial
	Solvent based CA/PEG	others
Coatings		
Delivery Port		

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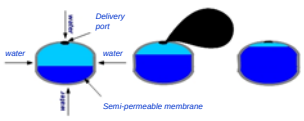

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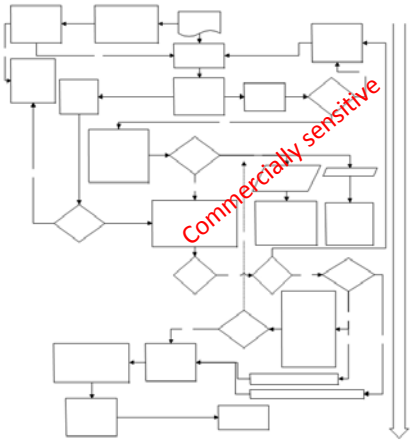
Example 3: Complex MR formulation development

Process decision tree fully mapped out to provide starting point for design space



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Summary

- Risk assessment is a crucial part of drug development process
- Current guidelines provide good initial framework but can be difficult to implement in practice for early development
- Institution of best practices reduces subjectivity of the risk assessment and can help to direct focus

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