The EU Risk-Based Approach: What Does It Mean?

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Risk Management

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

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EudraLex

The Rules Governing Medicinal Products in the European Union
Volume 4

Good Manufacturing Practice

Medicinal Products for Human and Veterinary Use

Part II: Basic Requirements for Active Substances used as Starting Materials

Document History	
An amendment is made to Part II of the GMP Guide to incorporate principles of Quality Risk Management in line with the ICH Q9 guideline on Quality Risk Management. Amendments correspond to similar changes made to Part I Chapter 1 of the Guide and published in February 2008. A new section on Quality Risk Management is introduced as section 2.19. The remaining sections of chapter 2 are renumbered. A minor change is made to section 2.21. No other changes have been made.	September 2007
Public consultation	April 2008 until October 2008
Adopted by the European Commission	31 January 2010
Deadline for coming into operation	31 July 2010

Recent amendment to incorporate principles of Quality Risk Management in line with ICH Q9

ICH Q9 – Quality Risk Management

- EU GMP guideline specifically identifies the need for QRM with biological medicinal products
- The need for QRM must therefore be greater for Cell-Based Medicinal Products

Risk-Based Approach

"Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products…"

15.9.2009 EN Official Journal of the European Union L 242/3

DIRECTIVES

COMMISSION DIRECTIVE 2009/120/EC

of 14 September 2009

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

(4) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee for Medicinal Products for Human Use,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Risk-Based Approach

European Medicines Agency

London, 17 December 2009
Doc. Ref. EMA/CHMP/CPWP/708420/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE RISK-BASED APPROACH ACCORDING TO ANNEX I, PART IV OF DIR. 2001/83/EC APPLIED TO ADVANCED THERAPY MEDICINAL PRODUCTS

AGREED BY Cell Products Working Party, Gene Therapy Working Party and Biologics Working Party	November 2009
ADOPTION BY CAT/CHMP FOR RELEASE FOR CONSULTATION	17 December 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2010

Risk-Based Approach

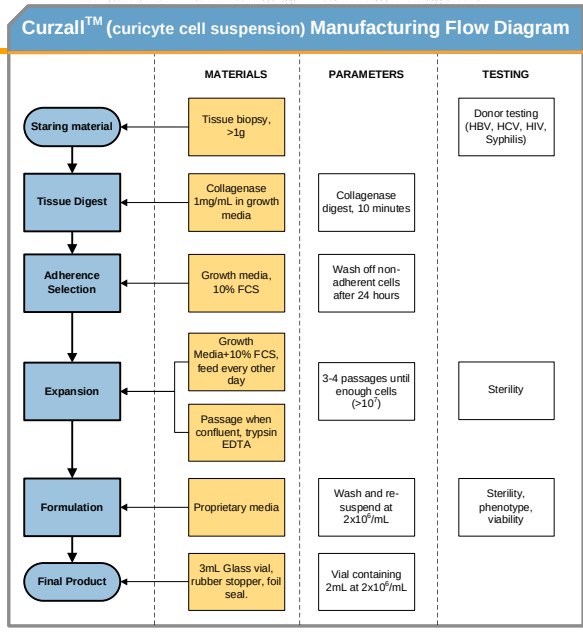
Risk factors, e.g.

- The cells used including cell source, cell type and differentiation status
- All aspects of the manufacturing process including manipulation
- The non-cellular components
- The specific therapeutic use including mode of administration, duration of exposure

What does this really mean?

Thinking about risk: Manufacturing

Case Study Example



What are the manufacturing risk factors?

- Materials (starting and raw)
  - Quality of materials
  - Toxicity/immunogenicity
- Manufacturing process (of product)
  - Contaminants, e.g. sterility
  - Inability to include viral reduction/elimination
  - Mistakes (esp. patient-specific products)
- Consistency
  - If you can't make a consistent product you won't get consistent clinical data – the trial won't achieve it's endpoint.

Note: This is not an exhaustive list

Example: Starting and Raw Materials

Risk Factors: Safety	Risk Mitigation: Safety

• Bacterial/viral/ TSE	• Source of material
	  ◦ Animal > vegetable > chemical
	  ◦ Animal: species, country/region, husbandry/health status
	  ◦ Animal: collection (facility, technique etc)
	• Material Manufacture
	  ◦ Aseptic handling/sterility
	  ◦ Viral reduction/elimination steps
	  ◦ Purification/removal of impurities
	  ◦ Consistency of material
	  ◦ Manufacturing quality system, e.g. GMP

Note: This is not an exhaustive list

Example: Starting and Raw Materials

Risk Factors: Safety	Risk Mitigation: Safety

• Bacterial/viral/ TSE	• Testing
	  ◦ Sterility, endotoxin, appropriate viruses
	  ◦ Process impurities like residual solvents
	  ◦ Product impurities like break-down products (e.g. dead cells, released/truncated proteins, etc)
	  ◦ Biological activity

Note: This is not an exhaustive list

Consulting on Advanced Biologicals

Example: Starting and Raw Materials

Risk Factors: Consistency	Risk Mitigation: Consistency

	• Source of material
	  ◦ Continuity of supply
	  ◦ Supply agreements
	  ◦ Need to know if/when the material changes
	  ◦ Need enough notice to manage change

Note: This is not an exhaustive list

Example: Starting and Raw Materials

Risk Factors: Consistency	Risk Mitigation: Consistency

	• Material Manufacture
	  ◦ Need to confirm batch to batch consistency of the material
	• Testing
	  ◦ Is the supplied testing (CoA) adequate for your needs?
	  ◦ Do you need to do additional testing routinely/qualification period?

Note: This is not an exhaustive list

Example: Starting Materials

Risk Factors: Consistency	Risk Mitigation: Consistency

	• Control of donation process
	  ◦ Training/quality assurance
	  ◦ Device to standardise collection
	• Initial processing
	  ◦ Training/quality assurance
	  ◦ Device/automation standardise collection
	• Testing
	  ◦ [Tight] Acceptance criteria
	  ◦ BUT needs to be balanced against need to ensure product supply

Note: This is not an exhaustive list

Example: GF raw material (e.g. for cell expansion)

- Critical material in process so high priority
- Biological origin
- Expression system
  - Bacterial, plant, insect, animal (e.g. CHO)
  - Manufacturing process (of raw material)
    - Culture media animal free/animal components (e.g. FCS, transferrin etc)
    - Viral inactivation/removal steps

Note: This is not an exhaustive list

Example: GF raw material
Continued..

- Biological Activity
  - Gycosylation needed for (*in vitro*) activity or not?
  - Correct amino acid/folding sequence for activity?
  - Stability, raw material batch consistency and quality
- *In vitro* biological activity:
  - If Same – use non-animal expression system
  - If Different:
    - compensate (e.g. concentration)
    - alternatives (different GF, media composition)
    - Use, BUT needs justification and greater focus on manufacturing quality/safety.

Note: This is not an exhaustive list

Conclusions

- Whether you submit a rationale for your risk based approach or not you NEED to consider development in this way in order to be able to plan/focus your development.
- A formalised process should ensure a consistent approach and avoid a single ‘view’ of risk predominating.
- Since it makes commercial and regulatory sense to record your approach/reasoning you may as well share this with the regulators since it should reduce the number of questions received during review of the MAA by helping them understand why you did or didn’t do things.