A Risk Assessment of Pre-Licensure Manufacturing Changes

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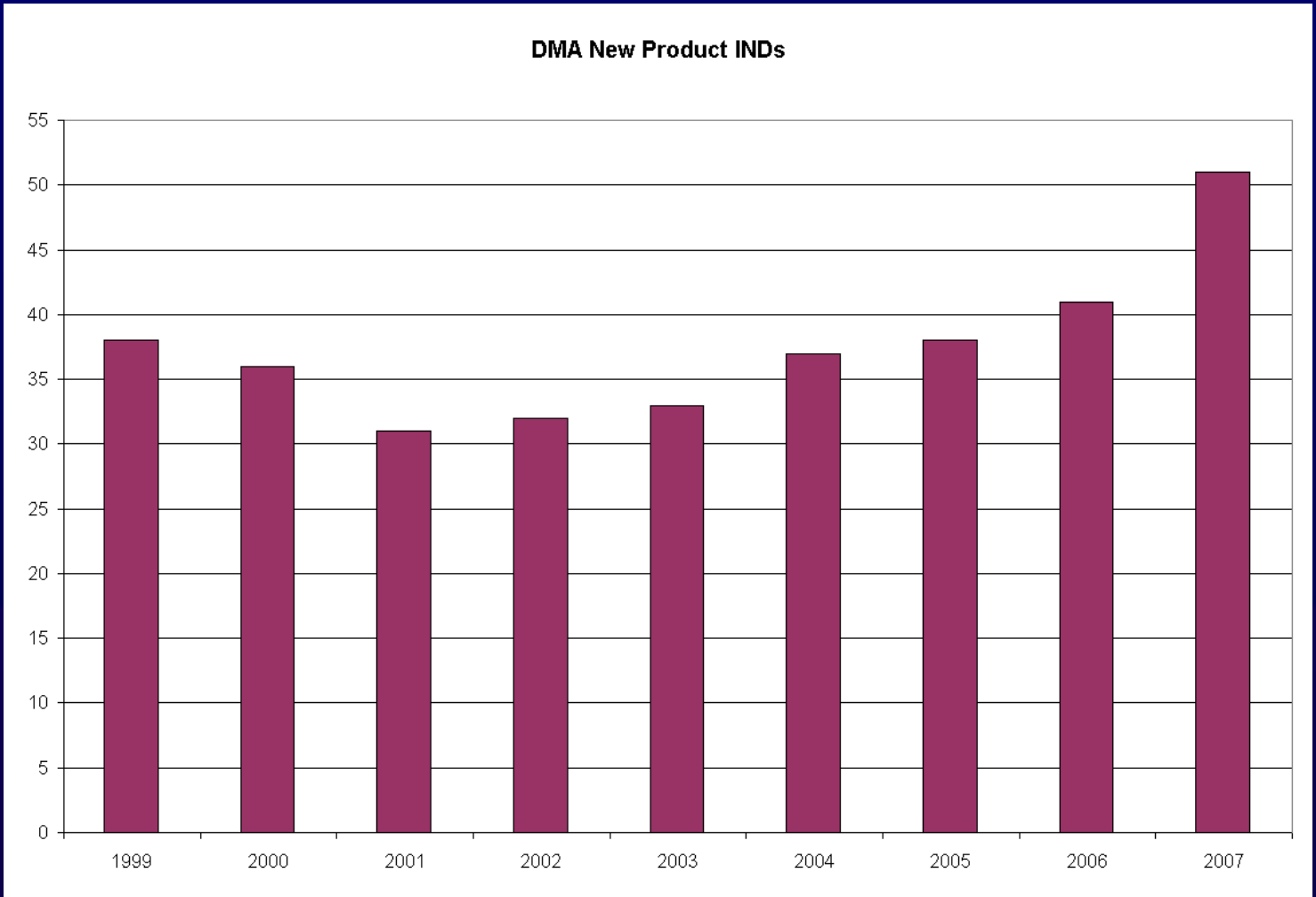
Overview

- Q5e + Q9 = ?
- A Proposed Risk Assessment for Drug Substance Manufacturing Changes during Phase 1 for Monoclonal Antibodies and Related Products
- Apply to examples of regulatory submissions describing various manufacturing changes

Why Pre-Licensure?



Guidance for Industry

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

Scope: Protein products where manufacturing process changes are made **in development…..**

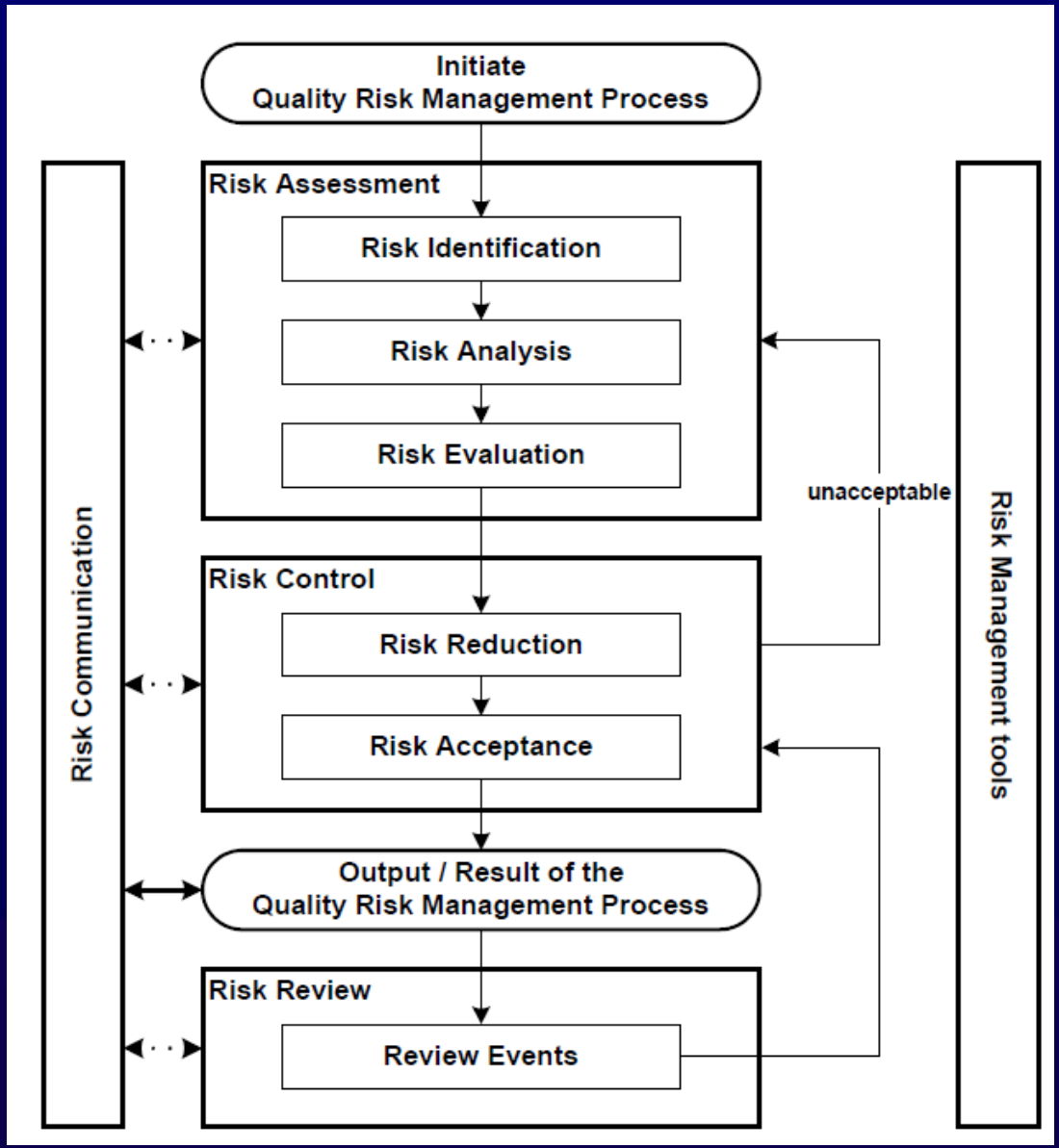
Guidance for Industry

Q9 Quality Risk Management

Annex II: Potential Applications

Quality Risk Management as Part of Regulatory Operations

- To evaluate impact of proposed variations or changes



Q9 - Figure 1: Overview of a typical quality risk management process

Q9: Quality Risk Management

- Risk Assessment
  - What might go wrong?
  - What is the probability it will go wrong?
  - What are the consequences?
- Identification - systematic use of information to identify hazards
- Analysis – Estimation of the risk
- Evaluation – Comparison against criteria

Failure Mode and Effects Analysis (FMEA)

- FMEA…provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance.
- “Failure Modes” means the ways, or modes, in which something might fail.
- “Effects Analysis” refers to studying the consequences of those failures.

Disclaimer

- **The views expressed in this presentation are my own, and do not necessarily reflect the official views of the FDA.**
- **"The FMEA is a team function and cannot be done on an individual basis".* This is only a proposal at this point.**

*D. H. Stamatis, *Failure Mode and Effect Analysis: FMEA from Theory to Execution* (Milwaukee: American Society for Quality, 2003).

A Proposed Risk Assessment for Drug Substance Manufacturing Changes during Phase 1 for Monoclonal Antibodies and Related Products

- Manufacturing changes are common during the development of monoclonal antibodies and related products under IND.
- Can we use the FMEA method for the assessment, communication and review of risks associated with phase 1 manufacturing changes?

The 10 Steps for an FMEA[1]

1. **Review the process**

- **This proposal is based on process FMEA with focus not on particular products or manufacturing processes but on *changes* in the drug substance manufacturing process for monoclonal antibodies and related products in general.**

[1]The Basics of FMEA; McDermott, Mikulak & Beauregard, 1996

The 10 Steps …

2. **Brainstorm potential failure modes**

- **Manufacturing changes are not considered failures as they are necessary for continuous improvement.**

- **The failure modes assessed here are manufacturing changes that result in a deleterious change in product quality attributes.**

The 10 Steps …

3. List potential effects of each failure mode

- Effects analysis references the potential change in product's safety/efficacy profile.

Step 4: Assign a Severity Rating

Rating	Description
1	No differences have been observed and no adverse impact on safety or efficacy (S/E) profiles is foreseen.
2	Some differences have been observed but it can be justified that no adverse impact on safety/efficacy is expected.
3	Some differences have been observed but it can be justified that no adverse impact on safety is expected. Impact on efficacy is unknown.
4	A possible adverse impact on safety cannot be excluded. Additional studies are needed.
5	Change results in conclusion that post-change material is a new product. Safety and efficacy data with prechange material is not applicable

Step 5 – Assign an Occurrence Rating

Rating	Description
1	No known occurrence
2	Possible, but no known data
3	Documented but infrequent
4	Documented and frequent
5	Documented, almost certain

Step 6 – Assign a Detectability Rating

	Detectability
1	Robust CMC analytical tools sensitive to **all** relevant changes and attributes
2	Critical Quality Attributes (CQA) known. WCBP with robust CMC analytical tools sensitive to changes in CQA.
3	Prior knowledge of potential product class CQA and impact of process changes on some CQA ("platform"). WCBP with robust CMC analytical tools sensitive to potential changes.
4	CQA unknown. WCBP with robust CMC analytical tools sensitive to potential changes.
5	CQA unknown. Not WCBP. Changes are not detectable by CMC analytical tools.

Examples of classes of products and their detectability ratings

- Detectability rating # 1 can include defined molecular entities (e.g. small peptides).
- Detectability rating # 2 can include licensed monoclonal antibodies.
- Detectability rating # 3 can include some investigational IgG monoclonal antibodies.
- Detectability rating # 4 can include Fc-fusion proteins.
- Detectability rating # 5 can include complex biologics (e.g. IgM's).

The 10 Steps …

7. Calculate the ~~risk priority number~~ relative risk value for each effect
8. Prioritize the failure modes of action
9. Take action to eliminate or reduce the high risk failure modes.
10. Calculate the resulting RPN as the failure modes are reduced or eliminated.

Example 1- New Cell Line

- **Humanized IgG1 monoclonal antibody produced in CHO cell line. Prior to initiation of phase 2 studies, sponsor generated a new CHO cell line that produces higher titers of antibody.**

- **MCB tested and passed. FDA reviewer concurred that analytical results demonstrated comparability.**

Factor	#	Description	RRV
Severity	1	No differences have been observed…	9
Occurrence	3	Documented but infrequent	
Detectability	3	"Platform"	

Example 2 – Multiple Mfg Changes

- Human IgG1 monoclonal antibody produced in NS0 cells.
- Prior to Phase 2, multiple manufacturing changes were made including:
  - Phase 1 mfg process utilized a non-clonal cell line. Clone cell line. New MCB and WCB
  - Production Bioreactor scaled up
  - Change in DS manufacturing site
  - Cell Culture process modifications
  - Changes to affinity column resin
  - Introduction of linear gradient elution for IEC
  - Change to a different viral filter mfg

Example 2 – Multiple Mfg Changes

- Human IgG1 monoclonal antibody produced in NS0 cells.
- Reviewer concurred that CMC safety issues were addressed and *in vitro* analytical data supported comparability.

Factor	#	Description	RRV
Severity	1	No differences have been observed…	12
Occurrence	4	Documented and frequent	
Detectability	3	"Platform"	

Example 3 – Multiple Mfg Changes

- Human IgG2 monoclonal antibody produced in NS0 cells
- Prior to Phase 2, multiple manufacturing changes were made including:
  - Phase 1 mfg process utilized a non-clonal cell line. Clone cell line. New MCB and WCB.
  - Production Bioreactor scaled up
  - Change in DS manufacturing site
  - Cell Culture process modifications including removal of animal-derived raw materials
  - Change to the harvest process
  - Changed the order of downstream operations
  - Change to a different viral filter mfg

Example 3 – Multiple Mfg Changes

- Human IgG2 monoclonal antibody produced in NS0 cells.

- No data presented; only a plan.
- Plan did not provide sufficiently detailed acceptance criteria.
- Plan did not adequately address Q5a (viral safety) risks.

Factor	#	Description	RRV
Severity	4	A possible adverse impact on safety profiles cannot be excluded	64
Occurrence	4	Documented and frequent	
Detectability	4	All CQA unknown.	

Example 4 – Multiple Mfg Changes including a change in amino acid sequence

- Humanized IgG1 monoclonal antibody produced in NS0.
- Prior to Phase 2, sponsor noted a relatively high rate of immunogenicity and poor cell line productivity.
- Investigation revealed that murine sequence in the light chain constant region was inadvertently not removed during humanization.
- Multiple changes proposed including:
  - Substitute human amino acids for murine
  - Change from NS0 to CHO
  - Change from roller bottles to bioreactor
  - Add an additional chromatographic step
  - Change the viral filter

Example 4 – Multiple Mfg Changes including a change in amino acid sequence

- Humanized IgG1 monoclonal antibody produced in NS0.
- Primary sequence changes indicated that this is a new product and the applicability of previous non-clinical/clinical data to the development of the new product was called into question. A consensus was difficult to reach.

Factor	#	Description	RRV
Severity	5	Change results in conclusion that postchange material is a new product	75
Occurrence	5	Documented almost certain	
Detectability	3	"Platform"	

Summary Results

Example	S	O	D	RRV
1. New cell line, data provided	1	3	3	9
2. Cloned cell line etc, data provided	1	4	3	12
3. Cloned cell line etc, data not provided	4	4	4	64
4. New sequence, new cell line, etc.	5	5	3	75

Summary Results

Example	S	O	D	RRV
1. New cell line, data provided	1 2 3	3 2 3	3 2 2	9 8 18
2. Cloned cell line etc, data provided	1 2 3	4 2 3	3 2 2	12 8 18

Summary Results

Example	S	O	D	RRV
3. Cloned cell line etc, data not provided	4 4 4	4 3 4	4 4 4	64 48 64
4. New sequence, new cell line, etc.	5 4 5	5 3 4	3 3 4	75 36 80

Summary Results

Example				RRV
1. New cell line, data provided				9-18
2. Cloned cell line etc, data provided				8-18
3. Cloned cell line etc, data not provided				48-64
4. New sequence, new cell line, etc.				36-80

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Moving Forward

- Formalized risk assessments may be useful in planning for and evaluating manufacturing changes.
- Occurrence ratings would benefit from systematically collecting the results of comparability assessments.
- Consider weighing factors based on confidence (e.g. S >> O, D)
- Apply to other phases of development? Drug Product Manufacturing Changes?

More Information Needed?

Guidance can be found at :

http://www.fda.gov/cder/guidance/index.htm

AND

Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use

http://www.fda.gov/cber/gdlns/ptc_mab.txt

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