Bennett Pharma *Solutions*

Using “Risk Assessment” to Put the “Design” into QbD

GMPs for the 21st Century . . .

- The FDA introduced their *"Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach"* (Aug 2002) to reassess their approach to regulation
- They stated the two-pronged approach of review of applications and inspection of facilities needed to be changed in order meet demands which were fast outstripping agency resources.
- The first two stated goals were to ensure
  - *the most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality*
  - *the latest scientific advances in pharmaceutical manufacturing and technology are encouraged*

GMPs for the 21st Century . . .

- They proposed to completely rethink their approach to identify methods which would not only meet the challenges of new technology, but also ensure they would get the most bang for the buck!
- The rethinking process was based on key principles:
  - Risk-based orientation
  - Science-based policies and standards (particularly with respect to assessment of risk)
  - Integrated quality-systems orientation
  - International cooperation
  - Strong Public Health Protection
- The FDA had come to the realization that they were committing the error of assessing compliance by measurement of the result, not of the process!

GMPs for the 21st Century . . .

- Such an approach would never let them get "ahead of the curve" because the old approach told nothing about future compliance!
  - From a risk-assessment point of view, without changing the approach there could be no hope of success!
- The FDA changed the strategy of inspections into the systems-based approach of today and prioritized sponsors for inspection according to risk, stating "*efficient risk management* [was] the primary way to make most effective use of Agency resources"
- In adopting a more strategic approach to compliance management, it was recognized that the sponsors' approach to compliance would need to change too!

The Challenges

- **The Regulatory Challenge**

1. FDA's *GMPs for the 21st Century* (2002) and introduction of real-time process analysis (PAT) (2003).
2. Implementation of "Quality by Design" (QbD) and pharmaceutical "Risk Assessment" via a comprehensive Quality System (ICH Q8 – Q10 and 2006 Guidance on Quality Systems Approach to cGMPs)
3. Life Cycle concept of Process Validation (FDA Draft Guidance on Process Validation and ICH Q11 whitepaper

- One difficulty is that this guidance is strategic in nature, the details of application are still unfolding . . .
  - Compliance has evolved from what was done to how/why it was done. . .from documentation of tasks to demonstration of knowledge, control and ongoing improvement.
  - Sponsors must now help shoulder the burden to define Compliance.

The Challenges

- Additionally, these and other recent guidances have recurring themes we need to address, namely
  1. to take a quality-by-design and life-cycle approach to pharmaceutical development which is directed (and re-directed) through risk management
  2. to provide a solid base of science, data and design for the CMC dossier and get away from a prescriptive or "fill in the blanks" type of approach.
  3. to task the QAU and senior management with applying the same continuous assessment and risk evaluation to compliance that are devoted to business and profitability
- The good news is
  - we DO know how to do this
  - it makes good sense and is good business
  - regulators and industry are figuring it out together

QbD and Risk Assessment

- This talk is about the integral role risk management plays in the process and product design process, both during development and in ongoing commercial cost reduction and process improvement.

  "Quality should be built into the product, and testing alone cannot be relied on to ensure product quality"

- The question we are all wrestling with is HOW it should be "built in" and what tools are necessary

- It is very slick to talk about Quality "by Design", but I have yet to see a design – of a formulation, a process, or a manufacturing plant – that worked the right way the first time without being challenged!

QbD and Risk Management

- Good design is not something that is created out of the blue, but is crafted and refined through a number of challenges. This thought repeated throughout Q8:
  - "The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process."
  - "The aim of the pharmaceutical development is to design a quality product and the manufacturing process to deliver the product in a reproducible manner."
  - "Information from pharmaceutical development is a basis for risk management and recognizes that quality cannot be tested into products. Quality has to be built in by design."
  - "…quality risk management principles can be helpful in prioritizing additional pharmaceutical development studies ."

QbD and Risk Management

- Design which has not been challenged by risk assessment tools is incapable of producing the desired quality of product and process.
  - those tools adapt the theoretical principles of pharmaceutical development and equipment operation to real-life production scenarios. Q10 calls them "enablers"
- This theme echoes throughout Q8 – Q10. The three pillars needed to produce a high-quality product and maintain it so throughout its life cycle are
  - Science- and data-based Pharmaceutical Development (the technology – "knowledge management")
  - Quality Risk Management (the tools to refine it, help define the controls, and facilitate continuous improvement)
  - Pharmaceutical Quality System (the framework that holds it all together and ensures you get the most "bang for the buck")

QbD and Risk Management

- Said another way in ICH Q6A

  "*The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, process validation, and by specifications applied to them throughout development and manufacture*"

- While risk management has only recently been promulgated by drug regulatory bodies, it is not new to those of us in development.

- Ironically though, one universal application of risk management in the past was to avoid anything that would result in increased regulatory "interest".
  - As the FDA correctly observed, this condition is counterproductive and stifles advancement of technology and continuous improvement

QbD and Risk Management

- This brings us to the question of what we mean by risk.
  - It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm.
  - The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk.
  - An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing.
- We in drug development want to bring a drug to patients which is efficacious, safe, and is consistent in (high) quality. So to us, “risk” is anything that endangers the successful completion of that task.

QbD and Risk Management

- As we in development have learned, risk assessment is essentially a proactive tool, whereas the GMP framework is essentially reactive.
- Using risk management, we test our knowledge of the situation, challenge our understanding of cause and effects, and project ourselves into a condition we may not be planning to "visit".
- How else could we achieve the goals stated in the FDA's 2008 draft guidance for process validation:
  - Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions, including those conditions that pose a high risk of failure.

Benefits of Risk Management

- …it is not a regulatory expectation that the process be developed and tested until it fails, but rather that a process be controlled within commercial manufacturing conditions, including those combinations of conditions posing a high risk of failure…
- Process controls address variability to assure the quality of the product.

- We can say that one benefit of risk management is to stretch the boundaries of our knowledge to cover conceivable (and some initially inconceivable!) sources of variation in materials, control methods, equipment operation and production technology.
  - Depending on the extent of the analysis, it can cover combinations of variance in all the factors above

Benefits of Risk Management

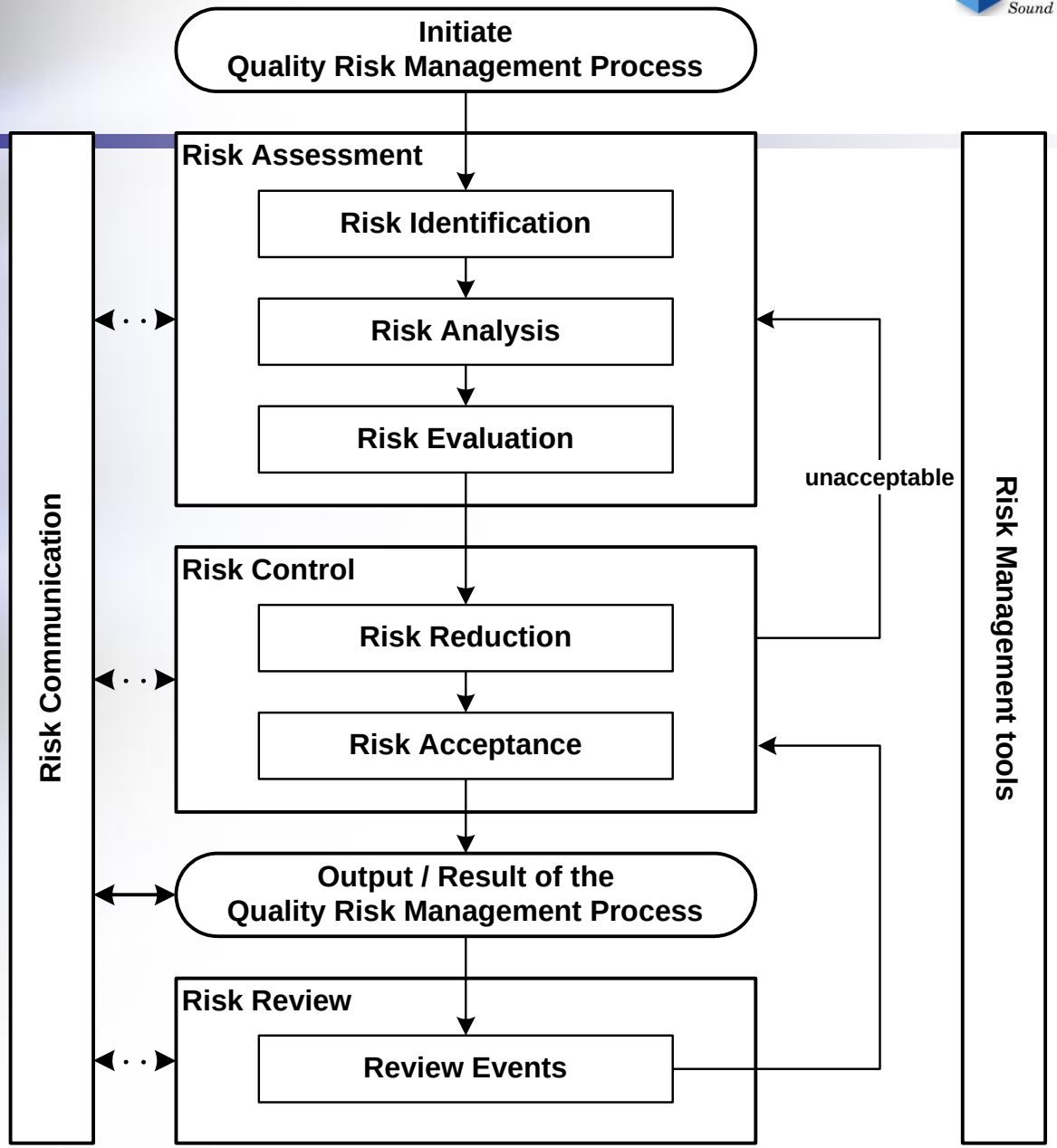
- Having made the case for risk management as an integral part of development and validation, let's see some stated uses
  - *can be used to screen for potential [critical] variables for DOE studies to minimize . . . experiments while maximizing knowledge gained*. (2008 PV Guidance)
  - *provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to. quality …useful in identifying the monitoring and control systems…identifying and prioritizing areas for continual improvement* (ICH Q-10)
  - managing outsourcing or distribution operations, materials suppliers, evaluation of suitability or competence of a 3rd party to function properly/provide reliably in the supply chain
  - establish process control strategy, including remediation steps
  - evaluate proposed changes (all ICH Q-9, 10)

Risk Management & Tools

"*Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle." (ICH Q-9)*

- The diagram provided in Q-9 to illustrate this is shown on the following page. It has the complexity you might expect of a regulatory document where nothing should be left out. I can briefly explain.
- In identifying and assessing a risk you figure out

1. what can go wrong
2. how likely it is for that to happen (what are the causes)
3. how bad the result will be and is it "curable"
4. how you will know if it did or is about to happen


Initiate
Quality Risk Management Process
Risk Assessment
Risk Identification
Risk Analysis
Risk Evaluation
unacceptable
Risk Control
Risk Reduction
Risk Acceptance
Output / Result of the
Quality Risk Management Process
Risk Review
Review Events
Risk Communication
Risk Management tools

Risk Management & Tools

- Starting: make sure you understand the scope and prepare yourself and your team accordingly
- Identification: definition of risk/issue, its causal agents, and consequences
- Analysis: severity of harm and likeliness of occurrence and ability to detect the failure has occurred
- Evaluation: Pulls it all together and determines actions
- Risk Reduction: Actions taken to minimize either cause, likelihood, severity of harm, or ability to detect and remediate
- Review: Confirm effectiveness and that actions taken have not introduced a new causal agent or risk

Risk Management & Tools

- There are mainly two types of tools associated with Risk Management
  - one kind to help you figure out all the things that can go wrong and what the causes might be
  - one kind to help you develop a pseudo-quantitative approach to ranking risk by taking the product of [severity], [likelihood or probability of occurrence], and [effectiveness of controls to detect and prevent the failure]
- Before we get bogged down in discussing techniques, the important thing to note is that it can be anything from a multi-day affair to 5 minutes.
- The focus of the guidance, AND the teaching of the school of hard knocks, is that it is much better to anticipate than react! Our outlook must change!

Risk Management & Tools

- Let's take examples from real life. How long does it take to make a risk assessment?
- So how is this different from our day to day interactions where we manage development, scale-up, materials sourcing or manufacturing operations? *Mainly in the need to be more formal and document the decisions!*
  - People are more likely to think something through when you are writing down their thought process!
  - *"It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/ or internal procedures) can also be considered acceptable."* (ICH Q-9)

Risk Management & Tools

- For a single task or two, it can be done rapidly. And if if you are just starting out, don't make it a massive undertaking. The important points are
  - define the risk/issue, likelihood and consequences clearly
  - record the actions taken and reasons, and follow up.
- For a complex program like formulation development, process scale-up or plant startup, then you must buckle down and do every detail.
  - you need a broad spectrum of attendees who can assess the consequence and severity of harm for various failure modes.
  - *"The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed."*

Risk Assessment – Getting Ready

- Now let's consider risk assessment techniques. Each has things it is a little better for. There are many out there and you must find one that fits your company culture! The important thing is you do it.
- No risk assessment is worth the effort if the available data are not organized and reliable. Some key tools you will need for your assessment are things like
  - Flowcharts and Process Maps
  - Check Sheets, Pareto Diagrams, or any other pertinent method of presenting data
  - Cause and Effect tables or diagrams (e.g., fishbone) and data to support the relationships
  - Information on occurrence of pertinent variances or failures or of severity of effect.

Risk Assessment – Getting Ready

- Preparation is key for the large number of people involved since most functional groups will need at least one representative.
- There is commercial software available for all the methodologies available. Some are customizable, some are less so. You can also use spreadsheets to record the analysis but getting the printed output you want may be something of a challenge.
- All these techniques involve brainstorming, discussion and some degree of subjective judgment. A high degree of discipline is required to keep the analysis on track You will need a strong moderator to get the analysis captured and move on.

Methods: FMEA / FMECA

- **Failure Mode, Effects (and Criticality) Analysis**
  - Inductive method used to determine all the ways a failure of product, system or equipment can occur. It was derived from quality tools developed in the 50s and is widely used by a variety of different industries..
  - The method can be applied to systems, products and devices, manufacturing processes, and equipment.
  - The objective is to define potential failure modes so (re-) design of the process or product can eliminate them, working off a prioritized set of failures.
  - The function of each unit, unit operation, or component is evaluated, all possible failure modes are identified, including various mechanisms of failure, and the RPN is calculated

Methods: FMEA / FMECA

- the RPN is a quantitative assessment of the criticality of the failure calculated as the product of the values assigned to Severity of harm, probability of Occurrence, and likelihood of Detection. Rankings are usually 1 – 10. May be 1 – 5.
- FMEA is one of the most commonly used risk-assessment tools in our industry since it is widely used by the medical device manufacturers. A design risk assessment is required for devices and a FMEA may likely be involved in a CAPA.
- FMEA is not particularly useful for evaluating impact of failure sequences or failures due to complex operations interactions between different systems.
- It can be particularly useful in evaluating operation of mechanized systems such as vial filling or capping machines
- Another evaluation of criticality can be made by comparing only severity and likelihood of occurrence.

Methods: FMEA / FMECA

- Typically shown in grid of severity versus occurrence, all criticality factor in an unacceptable area of the grid are designated as high priority for remedy.
- One reason this method is often chosen is because of the quantitative element derived from the RPN number. Once a corrective action is chosen a new RPN number can be calculated, resulting in a very impressive X% lower risk!
- FMEAs require a good understanding of cause and effects. Consequently, the magnitude of the reduction of risk is only as sound as the understanding of the mechanisms of failure and the causes for those mechanisms.
- FMEAs are relatively straightforward to execute. But if the unit chosen for evaluation is too complex, it may have to be broken into subunits to make the evaluation of failure mode and causal effects more manageable.

Methods: FTA

- **Fault Tree Analysis**
  - FTA is a deductive and primarily visual method focusing on causes, or sequences of causes, which can potentially result in a defined failure. The goal is to reach the root cause(s).
  - Whereas FMEA (and most other techniques) look at function and situations in which that function can fail, FTA looks at failures which have been identified to be severe.
  - While it has strengths for examining a specific failure, it requires a high level of system specificity and strong knowledge of cause and effects.
  - It is particularly useful when attempts to correct a failure have been unsuccessful. It is very useful in linking up sequential causal factors which may not have been considered in other risk analyses. It is good for developing monitoring systems.
  - It can rapidly become visually complex. Buy the software.

Methods: HACCPs

- **Hazard Analysis and Critical Control Points**
  - This is a tool extensively used by and customized to the food industry and expected by the FDA for certain food producers.
  - It is more fundamentally a proactive risk management process than other methods. It also looks at the entire system, including distribution, in assessing if all identified risks have be either successfully mitigated or are monitored for.
  - It tends to require less technical information than HAZOPs or FMEAs because it is more concerned with the bigger picture -- identifying and controlling hazards and verifying the extent of the control. As such, it represent a current picture of the status and effectiveness of safety controls
  - Although historically used for food, HACCP has was adapted by WHO to an approach more fitting to pharmaceutical products. (WHO TechRpt No 903, 2003 Annex 7)

Methods: HACCPs

- HACCPs are based on analysis of a simplified but verified process flow diagram keeping in mind the specifications of the product, its intended use and special conditions which might apply (e.g., counterfeiting, thievery, etc).
- There are seven steps in a HACCP
  1. conduct a hazard analysis, determine if the hazard needs to be controlled, and identify preventive measures for each step of the process (food HACCPs are concerned only with safety)
  2. determine the critical control points where action must be taken to prevent or control a hazard
  3. establish critical limits (alerts, action, specification)
  4. establish a system to monitor the critical control points
  5. establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control
  6. establish system to verify that the HACCP system is working effectively (via records, sampling, complaints, quality metrics, etc)
  7. establish a record-keeping system.

Methods: HAZOPs

- **Hazards and Operability Reviews**
  - A primarily inductive systematic step-by-step review of the intended operation which identifies hazards or operational difficulties by assessing the impact of deviations from the target condition.
  - Primarily applied to manufacturing process, particularly scale-ups or new plants where the interaction of the process and the equipment has not been fully proven.
  - Primarily concerned with operational safety and/or failures. However, easily adapted to cover a much broader range of issues that can result in quality failures or deviations from the approved process.
  - The step by step analysis is facilitated by the use of “guidewords” which represent deviations from the target condition: “more, less, none, other, faster, slower, etc.”

Methods: HAZOPs

- The guide words are applied regardless of whether or not it seems “likely” that the condition can occur. The question of main interest is what will happen if it does occur.
- If the guide condition generates a hazard, the circumstances and causes which might generate the guide condition are explored.
- A great deal of information is needed to run a HAZOP including full P&IDs, batch records, process flow diagrams and the control logic diagrams.
- The use of the guidewords can make HAZOPs particularly tedious and care must be taken to avoid “autopilot”. Certain shortcuts can be applied by examining only particular “nodes” or areas of interest when transformations are occurring.

Methods: HAZOPs

- A difficulty of HAZOPs, as well as one of the strengths, is that the knowledge/experience of the causal elements in the manufacturing process, as well as the equipment and facility setup, is tested intensely through the use of the guidewords.
- Thus, a HAZOP will identify gaps in process knowledge or cause/effect relationships as well as errors in construction, assembly or process control missed in commissioning.
- In a HAZOP adapted to control quality issues, the limits of operating space and design space are challenged in this way.
- The output of a HAZOP generally is a revision of the operating procedures, equipment setup and control strategy which is more effective and efficient, as well as being safer.
- Critical action limits and controls are established for worker and facility safety.

Final Notes

- So we have briefly seen several different techniques which can be used for risk assessment/management. Each has strengths and weaknesses and there are less rigorous techniques listed in Annex I of ICH Q-9.
- As you get more familiar with techniques, you may begin to hybridize them – pulling aspects from one into the other, or modifying approaches
  - For example, even though HAZOPs don't rank defined risk to safety or quality, you can easily introduce a ranking system.
- Subjectivity affects risk assessment. People "filter"" information based on their understanding and so risk often remains invisible. This is why I say, part of the battle is to change people's thinking.

Final Notes

- I find that small risk assessment sessions can be very productive in a development or manufacturing program
  - It trains the thought process so that it is incorporated in every day thinking in design of experiments, prioritization of tasks.
  - I don't know if anyone here has ever noticed, but development people have their pet solutions to certain problems – maybe it worked once well in the past. They may be convinced the solution is effective even if data say a new approach is needed. Do a risk assessment!
  - It helps people think of the process boundaries and why they are there. It is much easier to show a regulator why you do what you do, what the critical parameters are, and why you are confident you can control the quality when you have the experience and documentation from many risk assessments under your belt.

Final Notes

Risk Assessment Record

Project		Attendees:		
Activity				
Date:				
Issues:				
Note Taker:				

Subtask	Risk or Issue	Consequence/Severity	Likley? How To Prevent/Detect	Actions To Be Taken

Final Notes

- In this way, "Design" is not just something we picked because we think "QbD" sounds cool. Our design has been refined and refocused by multiple challenges!
- If people are familiar with the thought processes, a comprehensive risk analysis session is likely to be greatly facilitated. A large formal risk assessment session takes a great deal of discipline to keep focused and on track.

- Documentation is critical to retaining the value of any risk assessment, particularly the high horsepower ones involving a cast of thousands. You have done it – now be able to show what you accomplished.
  - Someone needs to sift through everything and extract every nugget of value. These need to find their way into your Development Report and/or submission
  - Regulators may ask to see examples of your risk assessment techniques to gain confidence in your commitment to quality.

Final Notes

- I want to finish with a comprehensive listing of all the ways the ICH working group thought various activities could be improved by risk management.

Practical uses of risk management

- Integrated Quality Management
  - Documentation
  - Quality defects
  - Auditing/Inspection
  - Periodic review
  - Change management / change control
  - Continual improvement
  - To facilitate continual improvement in processes throughout the product lifecycle.

Final Notes

- Regulatory Operations
  - Inspection and assessment activities
  - To communicate risk management activities
- Development
  - To design a quality product and its manufacturing process to consistently deliver the intended performance of the product
  - Design Space
  - Technology (PAT)
- Production
  - Validation
  - In-process sampling & testing
  - Deviation Remedies
  - Production planning

Final Notes

- Facilities, Equipment and Utilities
  - Design of facility / equipment
  - Hygiene aspects in facilities
  - Qualification of facility/equipment/utilities
  - Cleaning of equipment and environmental control
  - Calibration/preventive maintenance
  - Computer systems and computer controlled equipment
- Materials Management & Supply Chain
  - Qualification of suppliers and contract manufacturers
  - Starting Materials
  - Use of Materials
  - Logistics

Final Notes

- Laboratory Control and Stability Studies
  - Out of specification results
  - Retest period / expiration date
- Part of Packaging and Labelling
  - Design of packages
  - Label controls
- If you can't figure out how risk management would help, go read Annex II of ICH Q-9. Then go out and make sure your QbD is based on a solid Design refined by the realities of commercial production and the challenges of Murphy's law!