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IPA
Innovation, Quality and Global Reach

Formalized Risk Assessment for Excipients

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Vice President, Scientific & Regulatory Affairs

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About PDA

- The Parenteral Drug Association (PDA) is the leading global provider of science, technology, and regulatory information. The PDA creates awareness and understanding of important issues facing the pharmaceutical and biopharmaceutical community and delivers high-quality, relevant education to the industry. Since its founding in 1946 as a nonprofit organization, PDA has been committed to developing scientifically sound, practical technical information and expertise to advance pharmaceutical/ biopharmaceutical manufacturing science and regulation, so members can better serve patients.

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PDA Vision

To maximize product quality, availability, and value by connecting people, science, and regulation within the pharmaceutical and biopharmaceutical community so that PDA is:

The preferred choice for professionals who seek specialized, innovative skills and knowledge enhancing their professional development

The premier educational partner for professionals in academia, industry, and government for the advancement of manufacturing, quality, and regulatory science

An organization that aligns its practices and resources in support of its core values of a basis in science (science based), integrity, and inclusion

PDA Mission

To advance pharmaceutical/biopharmaceutical manufacturing science and regulation so members can better serve patients.

PDA's Science-Based Activities

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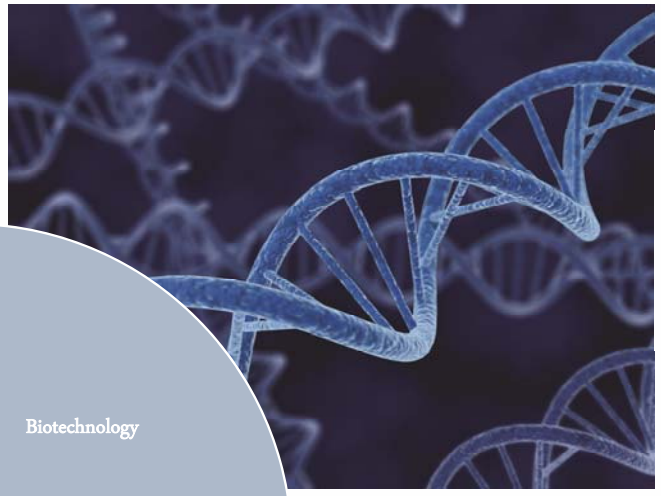

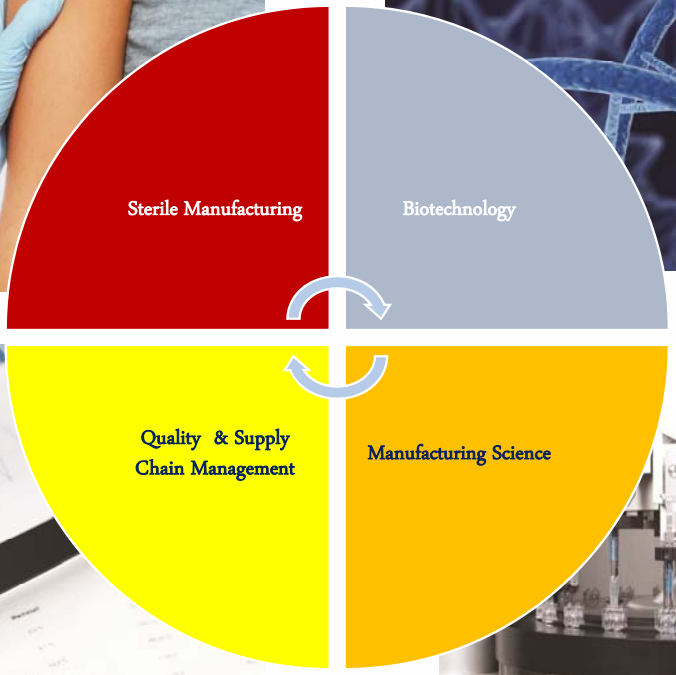

PDA Advisory Boards and their Interest Groups

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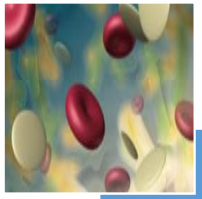

BioAB

- Advanced Virus Detection Technologies
- Biopharmaceutical Manufacturing
- Combination Products
- Vaccines
- Cell and Gene Therapy
- Biosimilar

SAB

- Applied Statistics
- Facilities and Engineering
- Filtration
- Lyophilization
- Microbiology/EM
- Packaging Science
- Pharmaceutical Cold Chain
- Pharmaceutical Water Systems
- Prefilled Syringes
- Process Validation
- Sterile Processing
- Visual Inspection

RAQAB

- **Data Integrity**
- GMP Links to Pharmacovigilance
- Inspection Trends
- Management of Outsourced Operations
- Pharmacopeial
- **Quality Risk Management**
- Quality Systems
- Regulatory Affairs
- Supply Chain Management
- Technology Transfer

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Today's Agenda

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- QRM Application – General Principles and the context of ICH Q9
- PDA's QRM work and case study library
- QRM for excipients and what that means in supply chain and manufacturing practice

Overview of a typical quality risk management process

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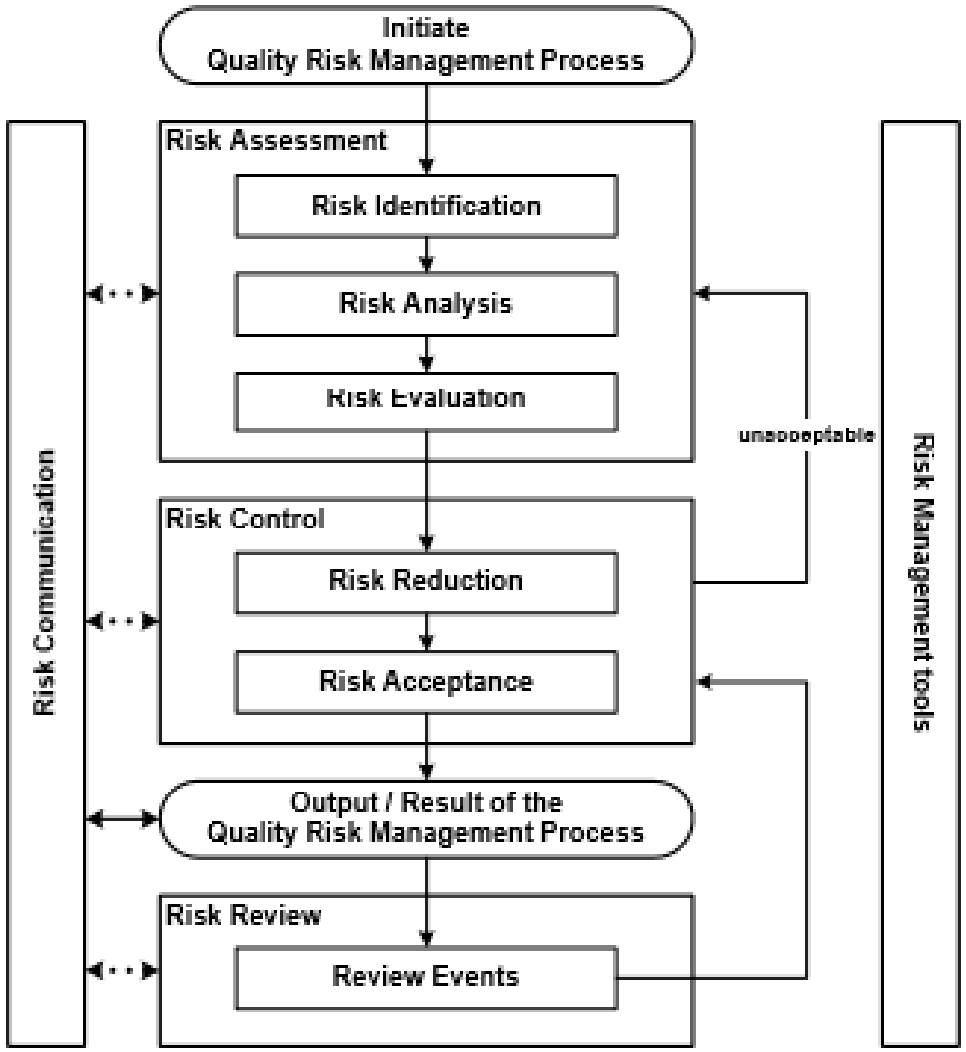

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Recognized Risk Management Tools and Approaches

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- Basic risk management facilitation methods (flowcharts, check sheets, etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP) • Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

Example of a Maturity Model for QRM

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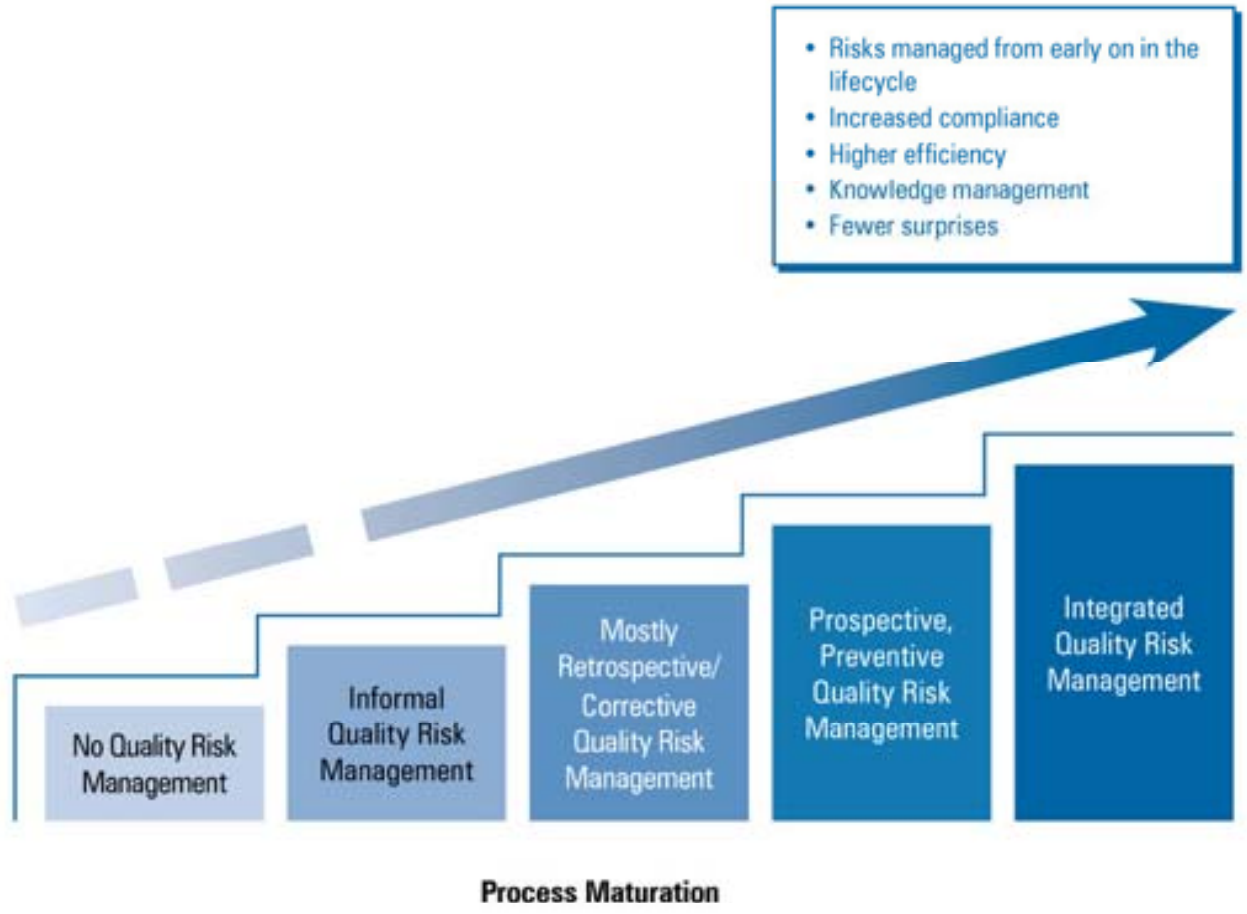

ICH Q9 and Q10 Context

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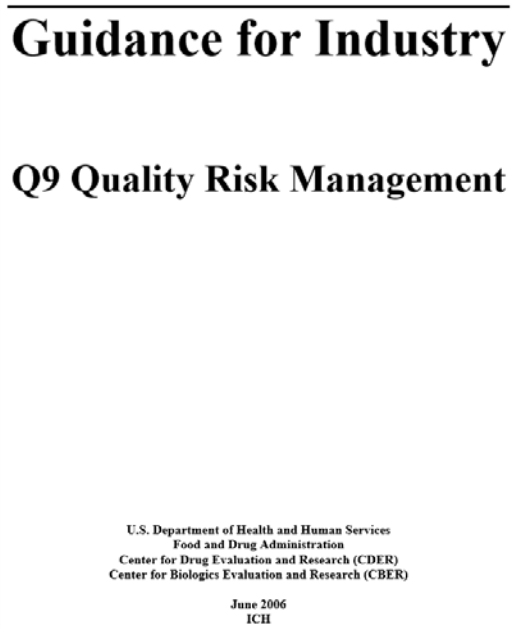

Guidance for Industry

Q9 Quality Risk Management

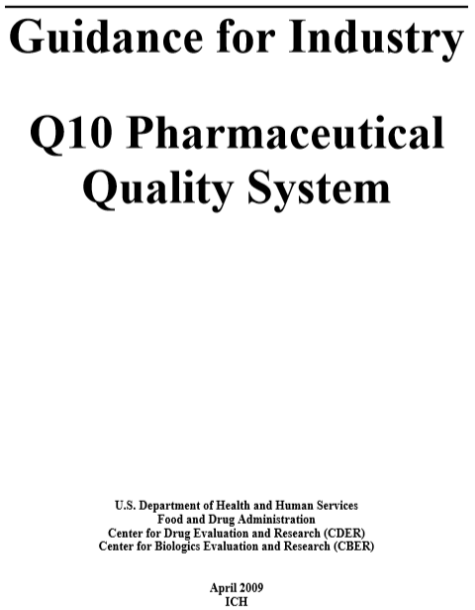
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2006
ICH

QRM is a PQS Enabler

2. Quality Risk Management (1.6.2)

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.


Guidance for Industry

Q10 Pharmaceutical Quality System

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2009
ICH

PDA Technical Report Series on QRM

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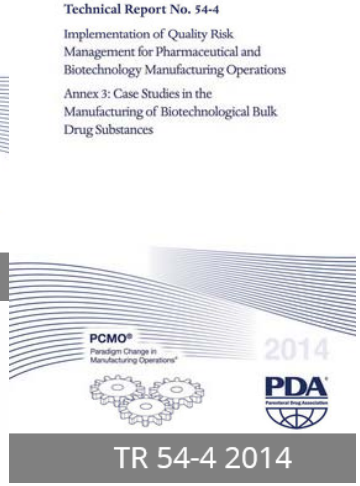
TR 54 2012

Foundational Report

TR 54-2 2013

TR 54-3 2013

Case Study Library



TR 54-4 2014

TR 54-5 2017

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New in 2020 – TR 54-6 Formalized Risk Assessment for Excipients

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Authors

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Expect publication in December 2019!

Identifying Whether an Excipient is Fit for Use

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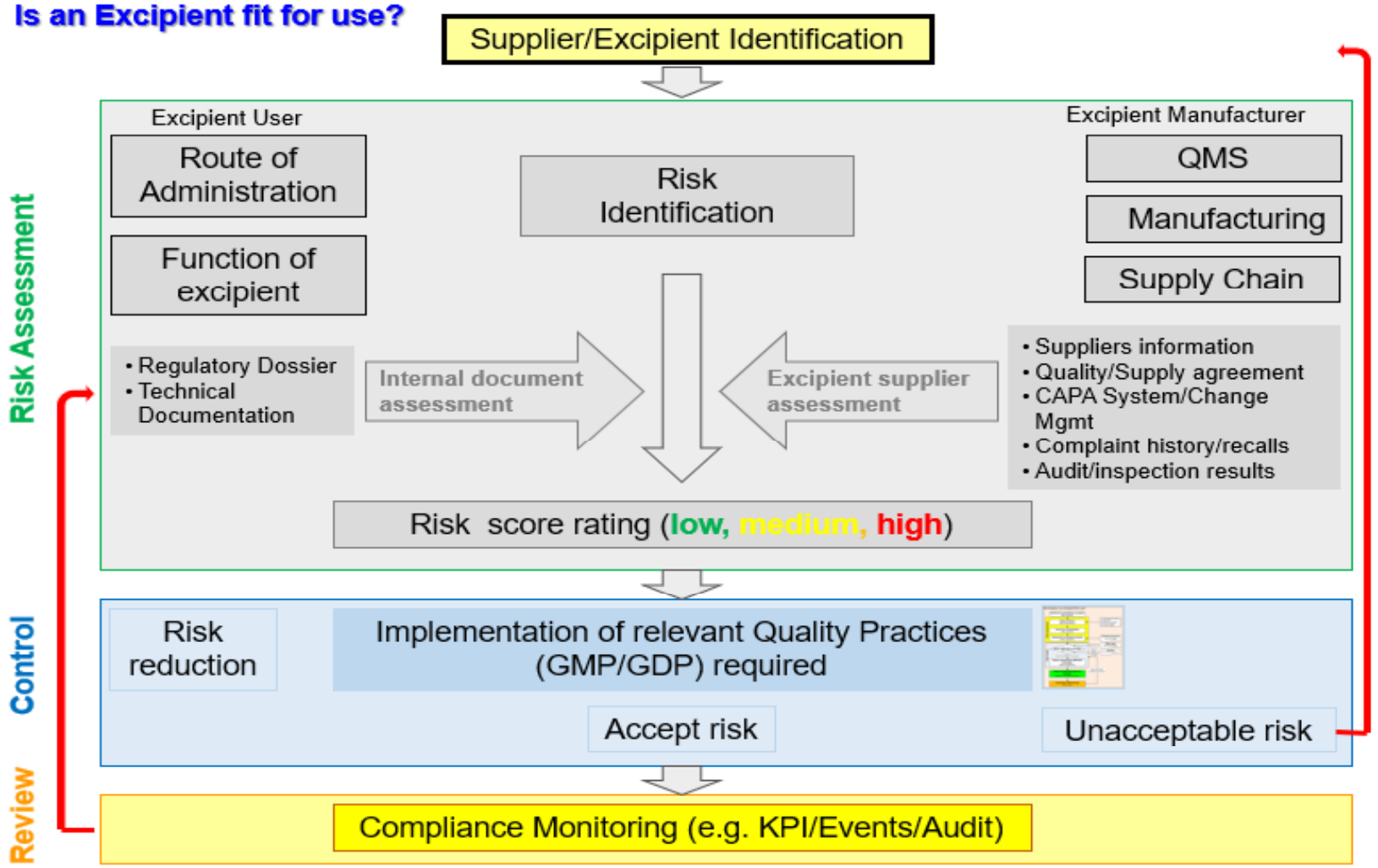

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Guides and Standards Most Widely Accepted for Excipient GMPs

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- EXCiPACT™: International Pharmaceutical Excipients Certification Standards for Pharmaceutical Excipient Suppliers
- NSF/IPEC/ANSI 363: Good Manufacturing Practices (GMP) for Pharmaceutical Excipients
- IPEC/PQG: The Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients
- USP: USP <1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients and <1059> Excipient Performance
- Japan: The Self-imposed Standard of GMP for Pharmaceutical Excipients

Risk Areas Beyond Quality

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- Excipient availability
- Business continuity risk
- Environmental,
- Socio-economic,
- Environmental, health and safety (EHS)
- Geographic risks
- General business data

Important, but out of scope for TR54-6

Supply Chain: Direct Supply from Manufacturer

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One of the lowest-risk arrangements due to the small number of intermediaries and the degree of control that can be applied.

Supply Chain: Supply via Distributors

- When an excipient moves from manufacturer to distributor, the distributor becomes the legal owner
- The distributor may repackage and/or relabel before ownership is transferred to the end user
- The distributor may have a marketing agreement with the original manufacturer, likely including a quality agreement
- This type of supply chain presents few more risks than the simple manufacturer-to-end user scenario; however, those risks may be magnified if the distributor engages in repacking or relabeling

Supply Chain: Supply via Repackager

- If the original manufacturer has not established agreements with distributors, it will be much harder to fully trace all parties in the supply chain, increasing the risks
- Other parties may repack and/or relabel the excipient
- The original manufacturer may change distributors from batch to batch without notice
- These supply chains are more complex to assess, and the attendant risks are higher than in the previous scenarios

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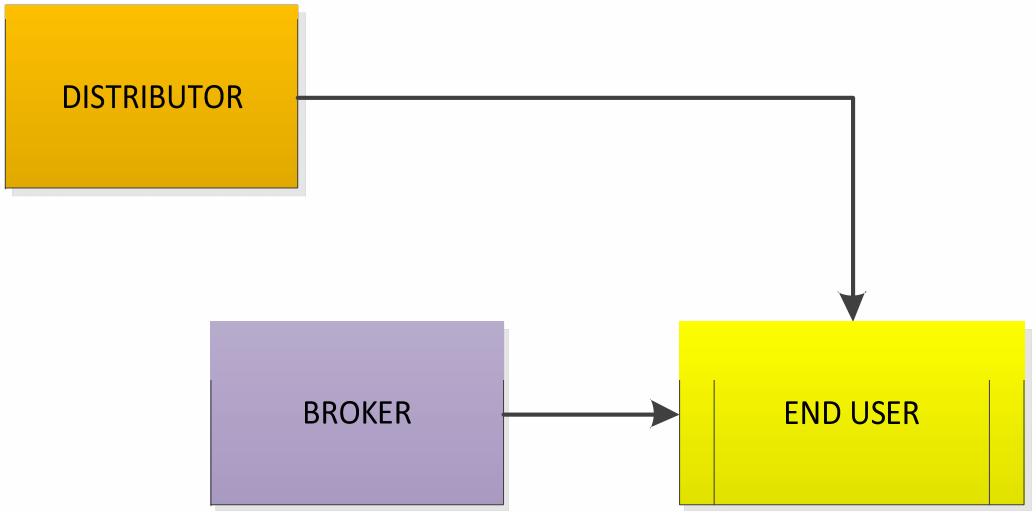
Supply Chain: Supply via Broker



- The ability to map the supply chain in this scenario will depend on the degree of transparency provided by the broker.
- When communications are totally open, the supply chain can be traced, and any risks can be assessed clearly.
- If the broker is fully transparent and the supplier is the original manufacturer, the risks may be as low as in the direct shipment scenario
- On the other hand, if the broker is less transparent, it may be very difficult to assess the risks

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Supply Chain: Manufacturer Exporting Excipient Directly to End User

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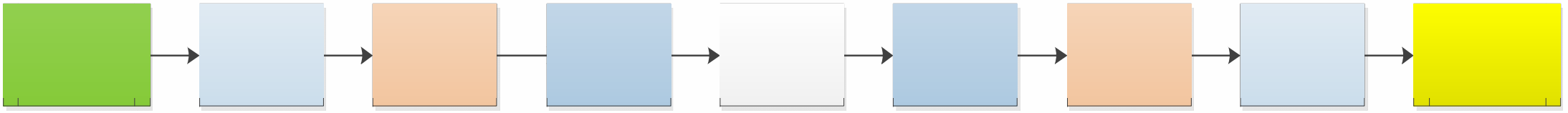

- International supply chain where parties may vary from shipment to shipment
- Quantifying risks may be difficult
- Fixed intermediaries and suitable inspection controls can reduce uncertainty

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Key Element – Transparency and Information Exchange

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Depending on the overall complexity of the supply chain, the participating parties have different roles and responsibilities, but critically have to collaborate in providing transparency, so risks can properly assessed and mitigated.

Information to support the excipient risk assessment process can be obtained using a variety of avenues:

- Meetings with manufacturers and suppliers
- Obligations placed in quality agreements or equivalent documents
- Chemistry, manufacturing and controls (CMC) documentation
- Excipient manufacturer customer portals
- Internet
- Manufacturing authorization holder supply chain management and quality oversight functions
- Health Authority portals
- Quality and technical collaborations between excipient manufacturer and end user

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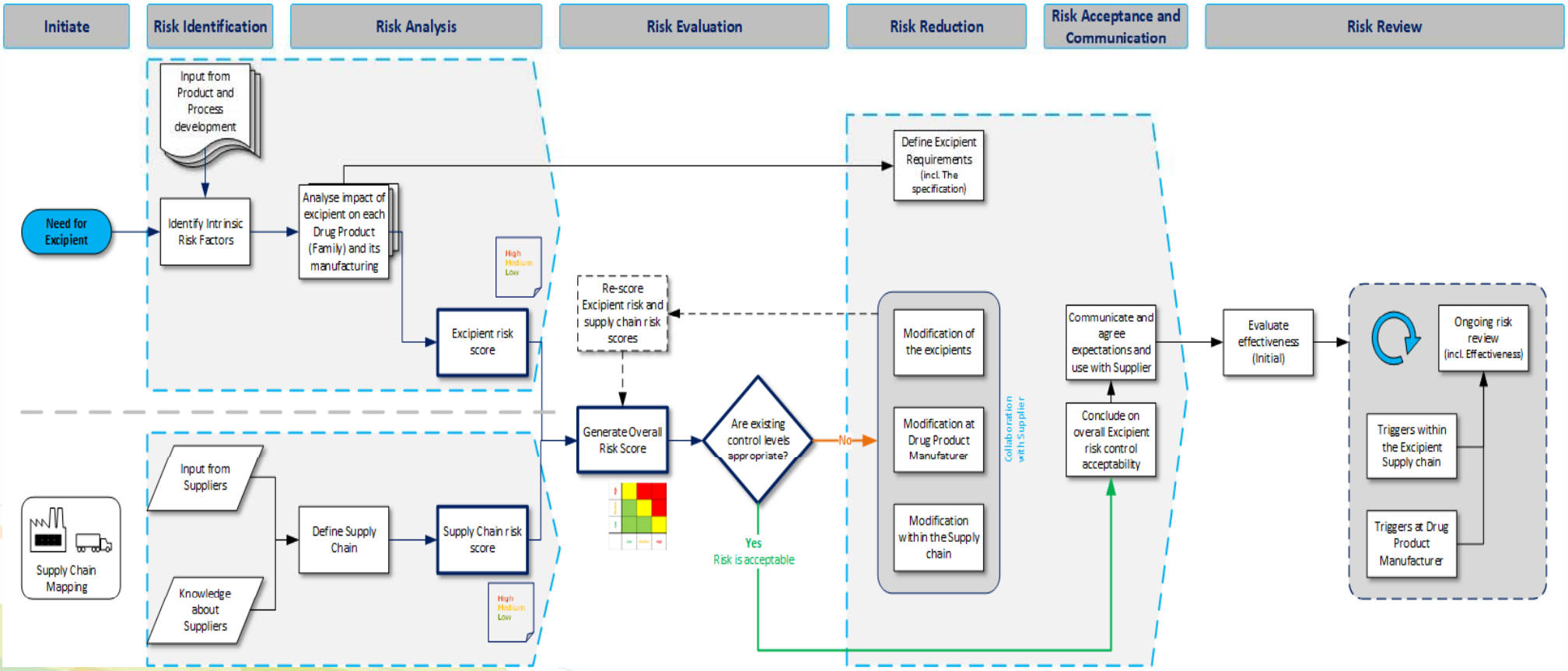
Complete Generic Risk Model for Excipients



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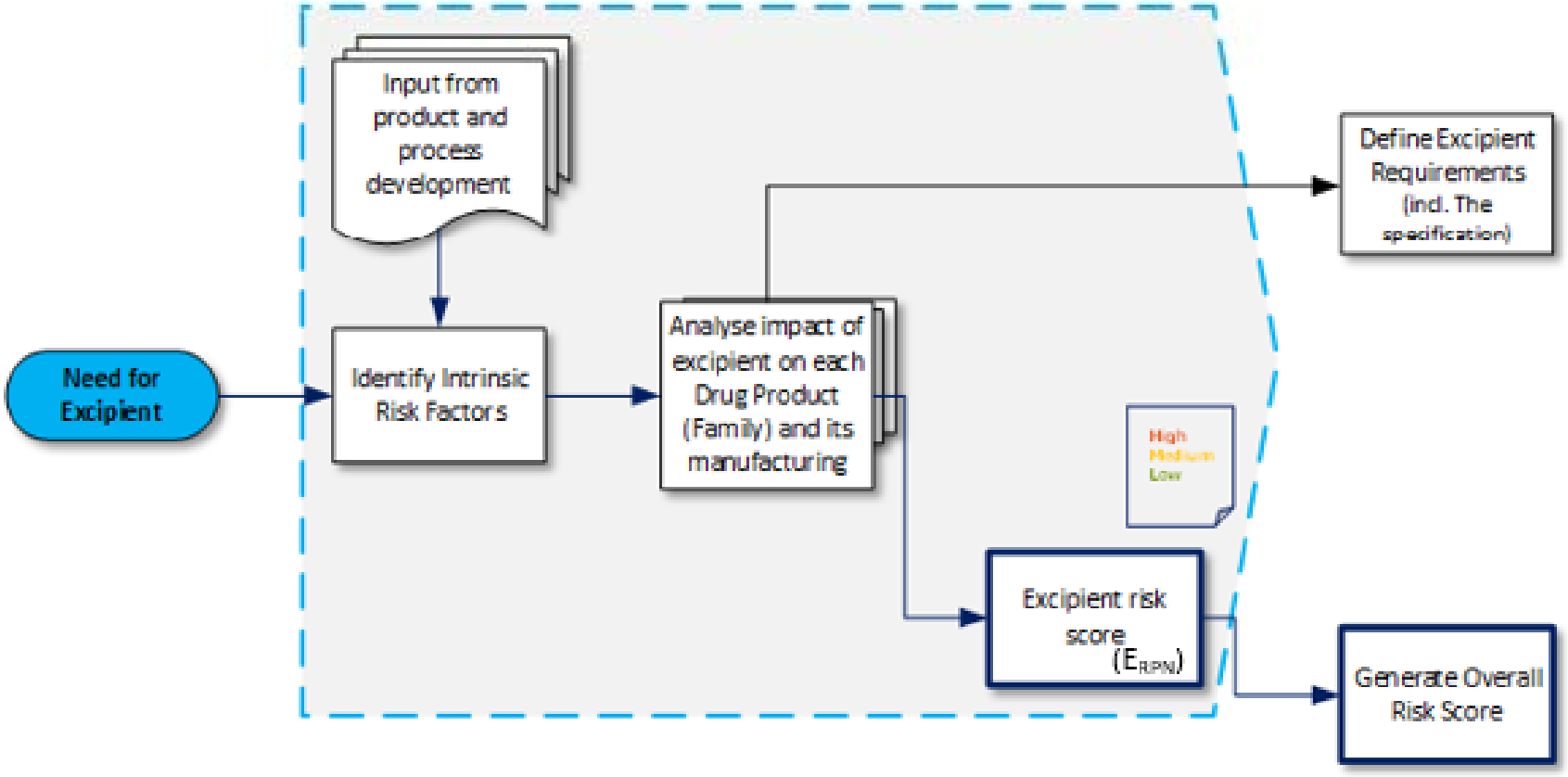
Steps in Excipient Risk Identification and Analysis



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Identification of Intrinsic Risk Factors

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Factors to be considered include:

- Characteristics of excipient needed for use in the drug product
- Manufacturer's excipient specifications
- Factors learned from the manufacture of the excipients
- Existence of multiple and or global manufacturers
- Lot-to-lot variability
- Risk factors listed in the EC Guidelines of March 19, 2015, such as—
  - Transmissible spongiform encephalopathy (TSE)
  - Potential for viral contamination
  - Potential for microbiological or endotoxin/pyrogen contamination
  - Potential, in general, for any impurity originating from the raw materials, e.g., aflatoxins or pesticides, or generated as part of the process and carried over, e.g., residual solvents and catalysts
  - Sterility assurance for excipients claimed to be sterile
  - Potential for any impurities carried over from other processes, in the absence of dedicated equipment and/or facilities
  - Environmental control and storage/transportation conditions, including cold chain management if appropriate
  - Excipient stability
  - Packaging integrity evidence

Illustration of an Excipient Impact Assessment to Provide Specification Input

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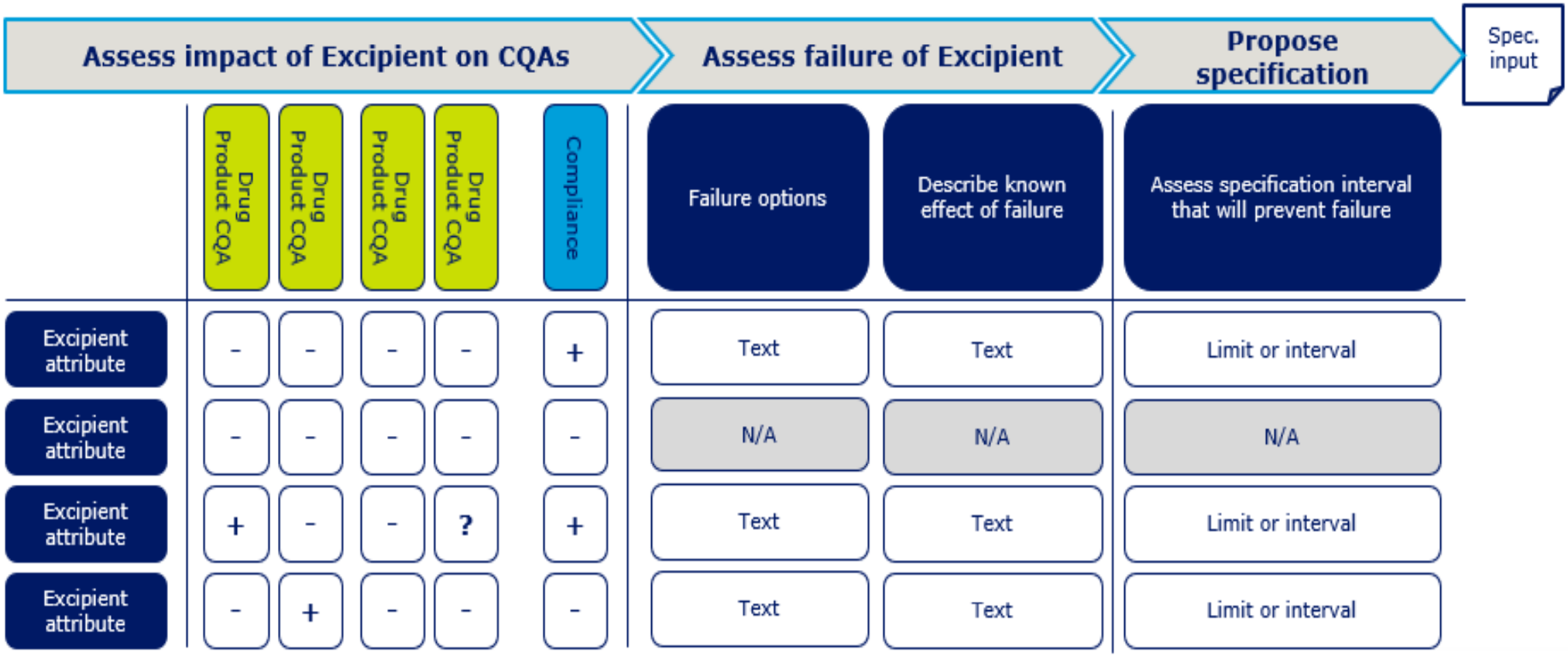

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Excipient Risk Profile Based on Use and Intrinsic Factors

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Minimum Factors to be Considered:

- Excipient attributes and relevant specification
- Functionality of the excipient in formulation
- Intended patient intake (consider dose regimen, frequency of dose, strength of formulation)
- Route of administration
- Excipient origin and potential for contamination
- Excipient complexity (composite)
- Prior knowledge of and experience with excipient (e.g., known quality defects)
- Standard packaging size of the excipient (consider use in manufacture of drug product)

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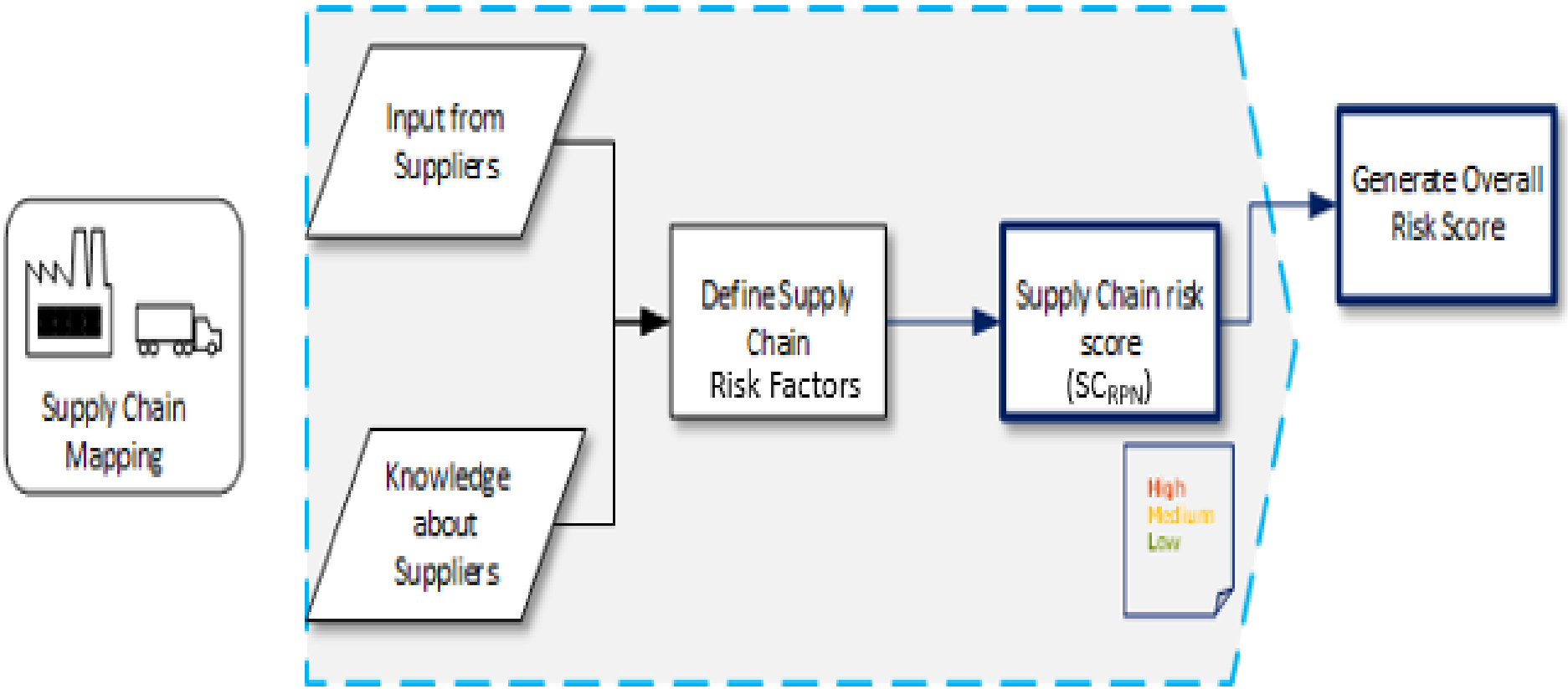
Steps in the Supply Chain Risk Analysis



Supply Chain Risk Analysis

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Minimum Factors to be Considered:

- Supply chain complexity—supplier, broker, manufacturer relationships, opportunity for fraud
- Prior knowledge of the supply chain—capability
- Organizational volatility
- Excipient manufacturer performance history—oversight knowledge such as customer complaints, changes, audits, trustworthiness, tailgate samples
- Packaging suitability—ability to protect excipient from fraud, moisture, heat, and similar elements
- QMS standard and certification

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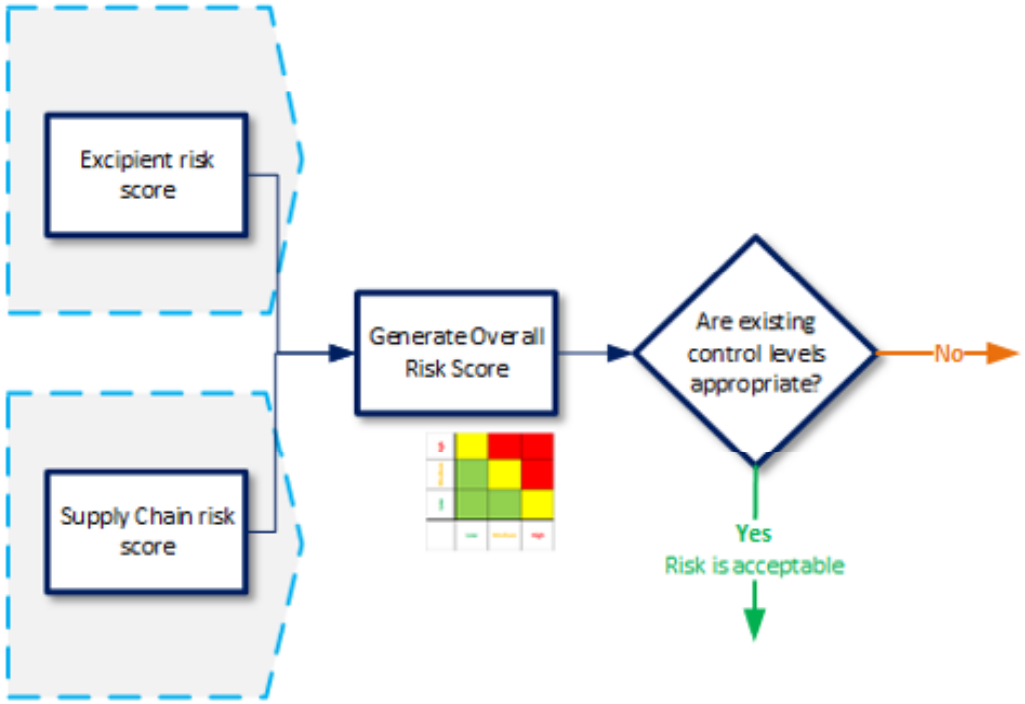
Developing the Matrix of Combined Excipient + Supply Chain Risk Evaluation



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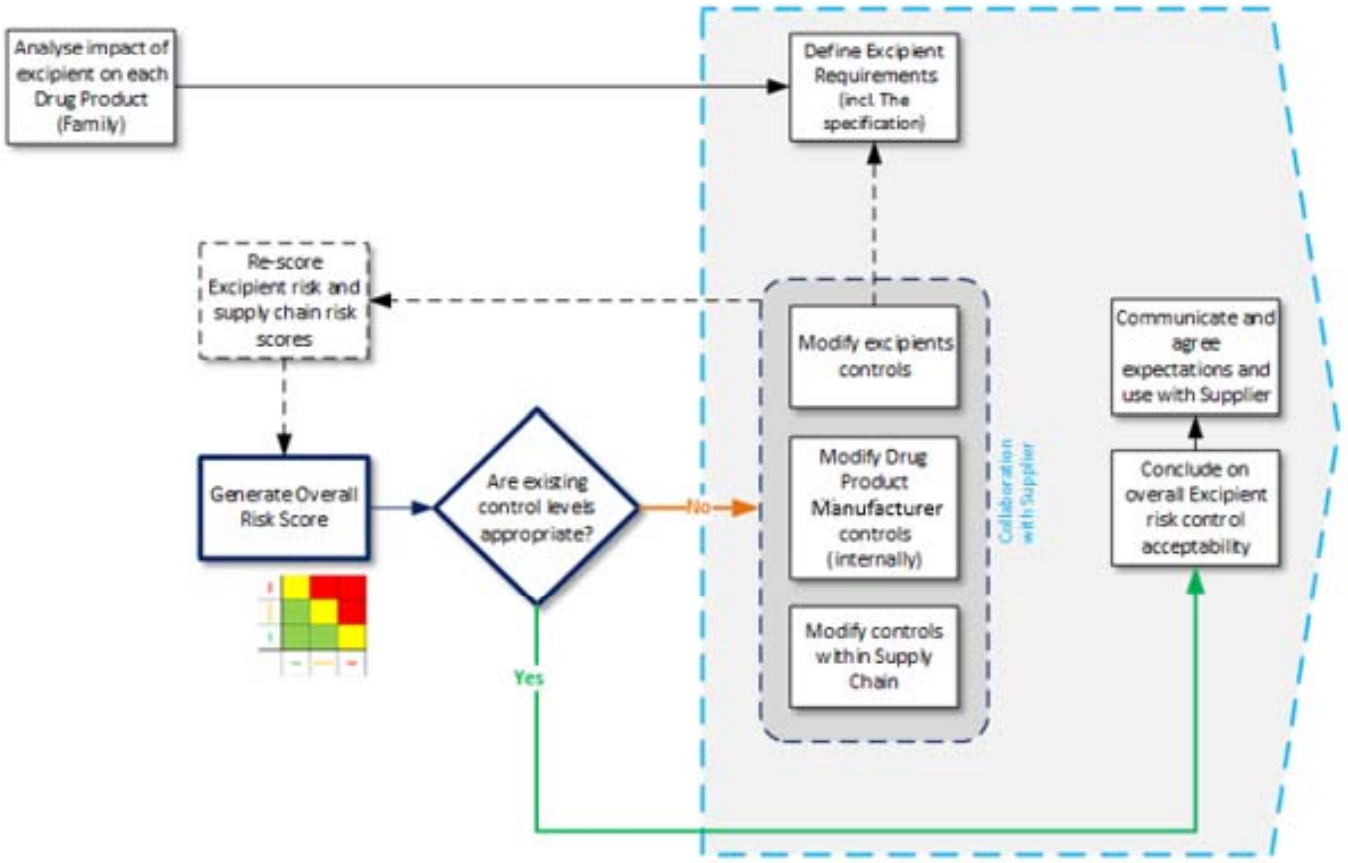
Identify Further Mitigation Actions to Reach Acceptable Risk Control, and Communicate



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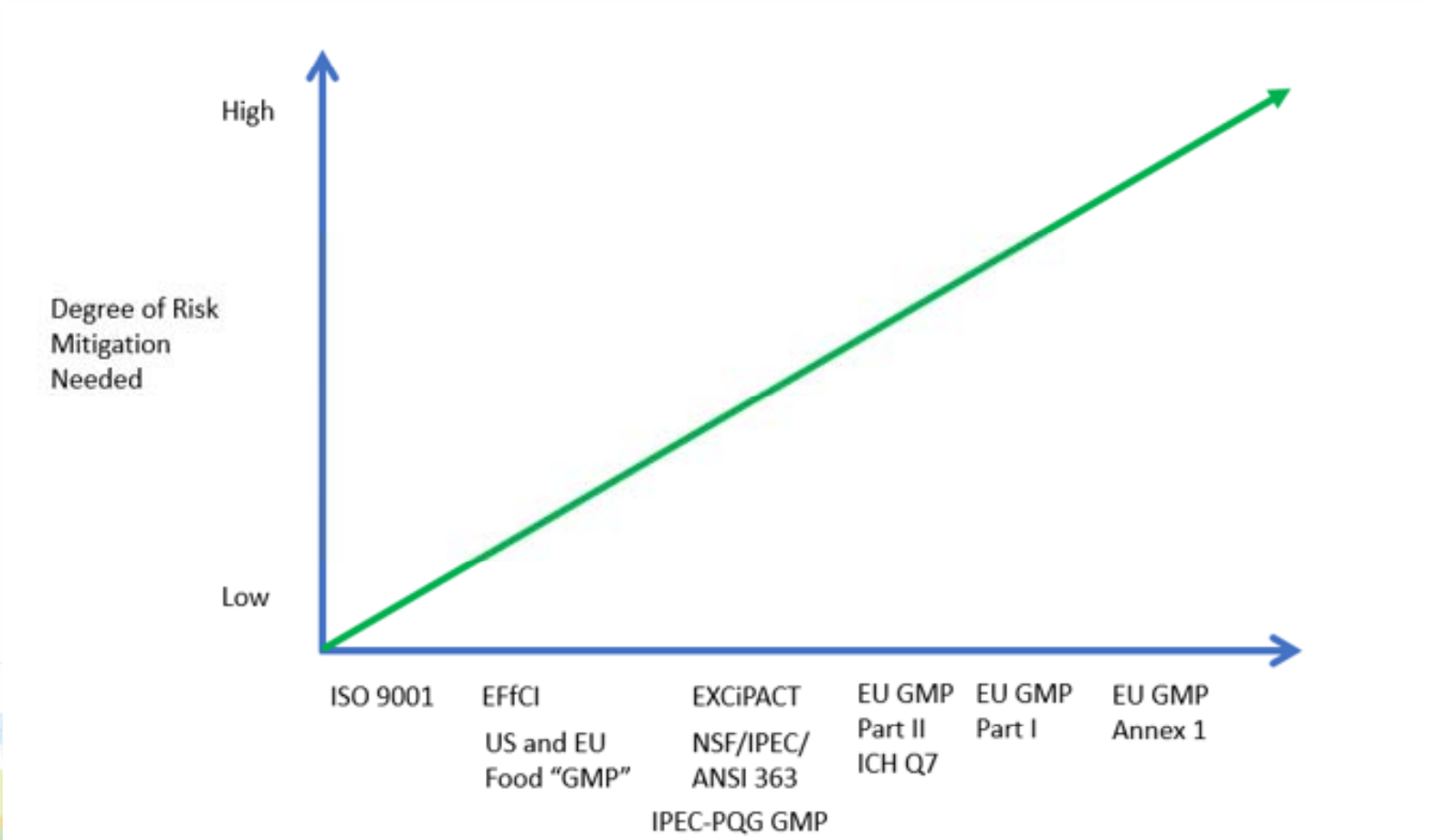
Degree of Risk Mitigation Required Based on the Nature of the Manufacturing Controls Required for the Excipient



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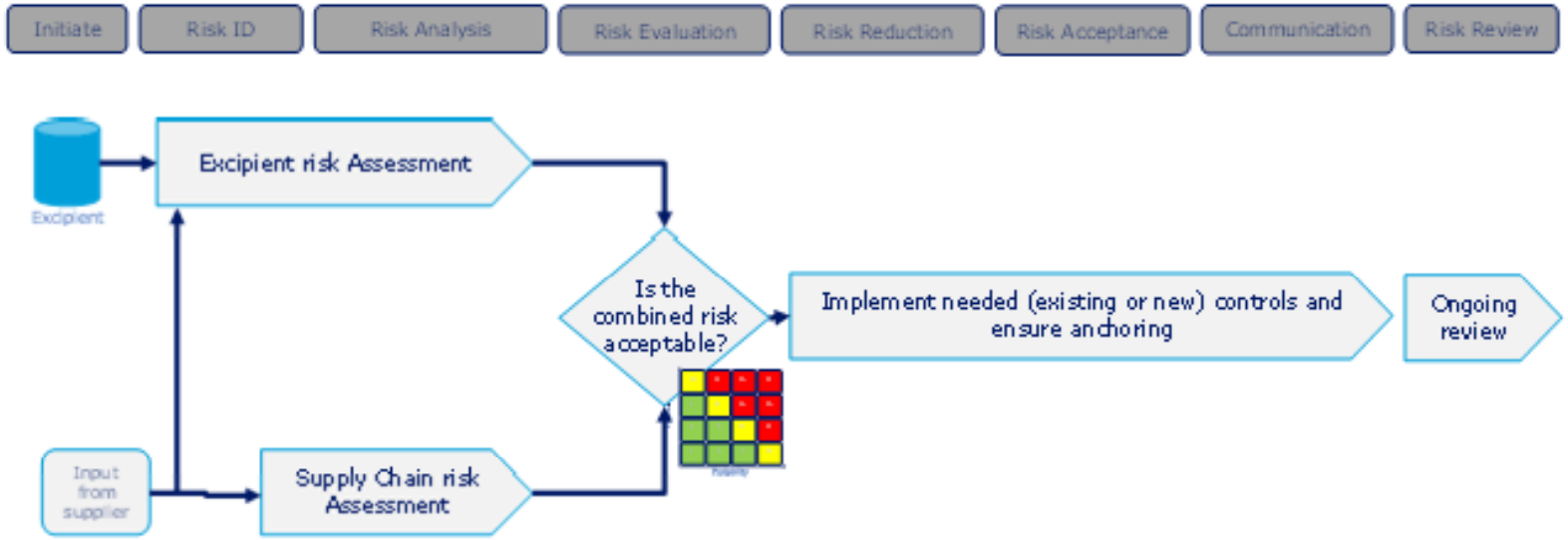
Simplified Overview of the Generic Lifecycle Model



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Triggers for Risk Assessment Review

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Internal procedures should define a periodic review and revision process that lists events that would trigger reassessment, such as:

- New product
- New formulation of existing product
- New manufacturer/supplier
- New excipient
- Change in notification from manufacturer/supplier
- Change in supply chain
- Change in GMP certification status or GMP status of manufacturer/supplier
- Change to site
- Geopolitical/socioeconomic/business changes
- Regulatory changes
- Pharmacopeial changes
- Quality events, industry-wide (e.g., TSE)
- Shifts/changes in trends
- New safety information

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Benefits and Value

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- Documented knowledge, in a structured manner, about the excipient supply chain
- Ability to rapidly and effectively evaluate the requirements for new products that use existing or new excipients
- Identification of supply chains that present lower risks and preferred supply chains with which to build relationships
- Focus on specific risk mitigation oversight activities for both manufacturer or supplier and user
- More detailed product knowledge and increased understanding of how the risks from excipients may affect product quality
- Formal assessment and database of risk review triggers, such as major changes and critical investigations
- Knowledge-based and proactive decision-making
- Provides a common language and approach for clear communication with stakeholders throughout the supply chain
- Opportunities for knowledge-sharing and comparative assessments between manufacturers or suppliers and end users

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Resources

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PDA Parenteral Drug Association
Connecting People, Science and Regulation ®

HOME EVENTS & TRAINING TOPIC AREAS

Upcoming Events

PDA Quality Risk Management Certificate Program

2019 PDA Quality Week
DEC. 9-13 | WASHINGTON, DC

https://www.pda.org/global-event-calendar/courses/pda-quality-risk-management-certificate-program

Required Training Courses

Track	Mon. November 11	Tues. November 12	Wed. November 13	Thur. November 14	Fri. November 15
QRM Foundations	Course 1 PREREQUISITE Foundations of Quality Risk Management *Trainers: Amanda B. McFarland & Lori Richter*				
QRM Decision Maker	Course 1 PREREQUISITE Foundations of Quality Risk Management *Trainers: Amanda B. McFarland & Lori Richter*	Course 2 Quality Risk Management: Risk Control and Risk-Based Decision Making *Trainers: Amanda B. McFarland H. Gregg Claycamp*			
QRM Application	Course 1 PREREQUISITE Foundations of Quality Risk Management *Trainers: Amanda B. McFarland & Lori Richter*	Course 2 Practical Application of Quality Risk Assessment Tools *Trainers: Patrick Mains Tiffany Baker*			
QRM Application + Elective	Course 1 PREREQUISITE Foundations of Quality Risk Management *Trainers: Amanda B. McFarland*	Course 2 Practical Application of Quality Risk Assessment Tools *Trainers: Patrick Mains Tiffany Baker*			ELECTIVE Course 3 TR 54-5: QRM for the Design, Qualification, and Operation of Manufacturing Systems *Trainer: Kelly Waldron*