Risk Management: Practical Implications for Pharmaceutical Manufacturers

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The Bar is Being Raised Across the Industry for Formal Risk Management Planning

- While approval times are decreasing, industry has experienced high profile drug withdrawals within the past 5 years
- There are increased public expectations regarding product safety
- Product liability suits are spiraling
- Regulators are directing a significant shift by industry from a passive information oriented role to one of action and accountability toward greater safety assurance
  - FDA Risk Management Framework Document (5/99)
  - EMEA Proposals (5/02), Heads of Agencies (HOA) Summary Report 1/03
  - PDUFA III provides funding to FDA for dedicated Risk Mgt. resources, and stipulates that RM Plans may be a part of NDAs/BLAs submitted post October 1, 2002
  - FDA Public Forum to review Concept Papers (4/03)
  - FDA draft Guidance Documents (5/04)
  - CPMP/ICH/5716/03 – Pharmacovigilance Planning – adopted 12/04, effective 6/05
  - FDA final Guidance Documents (3/05)
- Industry is moving quickly to design and implement Risk Management processes
- Risk Management Programs can enable challenging products to stay on the market (by supporting the appropriate use of products that will maximize benefit and minimize risk)

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Challenge to Industry…..

- Pharmaceutical companies have established processes for collection, evaluation and reporting of safety data, both for investigational drugs and marketed drugs.
- The new era of Risk Management requires a shift from standard pharmacovigilance to a more active role geared toward proactive Risk Assessment and Risk Minimization.
- Companies must acquire the expertise and develop processes to meet these new standards.

Risk Assessment
Clinical Development

- **Pre-Marketing Risk Assessment:**
  - Risk Assessment should be planned.
  - Consider results of preclinical safety assessments, clinical pharmacology
  - Consider characteristics of target population, indication, other drugs in class
  - Consider known risks and theoretical risks
  - Safety database should be diverse and appropriately sized to detect serious adverse events.
  - Clinical trials should address the potential for certain serious adverse events such as drug related QTc prolongation, liver toxicity, drug-drug interactions, etc.
  - Coding of adverse events should be accurate, using one coding convention or dictionary.

Risk Assessment
Clinical Development

- **To meet these new expectations, Industry must bring additional expertise to the table when planning clinical trials.**
  - Earlier involvement of Safety group
  - Critical role for Epidemiology
  - Discussion of known risks and theoretical risks as part of clinical trial design.
  - Commitment to dialogue with FDA and other agencies.

- **In addition, there should be frequent evaluation of safety data and additional assessment (changes to study design, additional studies) of emergent safety issues if necessary.**

Risk Assessment
Clinical Development

- **Industry must develop processes to ensure that Risk Assessment activities are planned, performed and communicated during clinical development.**
  - SOPs
  - Define Roles and Responsibilities
  - Training
  - Documentation/Review
  - Governance bodies

- **Risk Assessment Activities should be integrated with other ongoing processes including management of the IB, Development Labeling, etc.**

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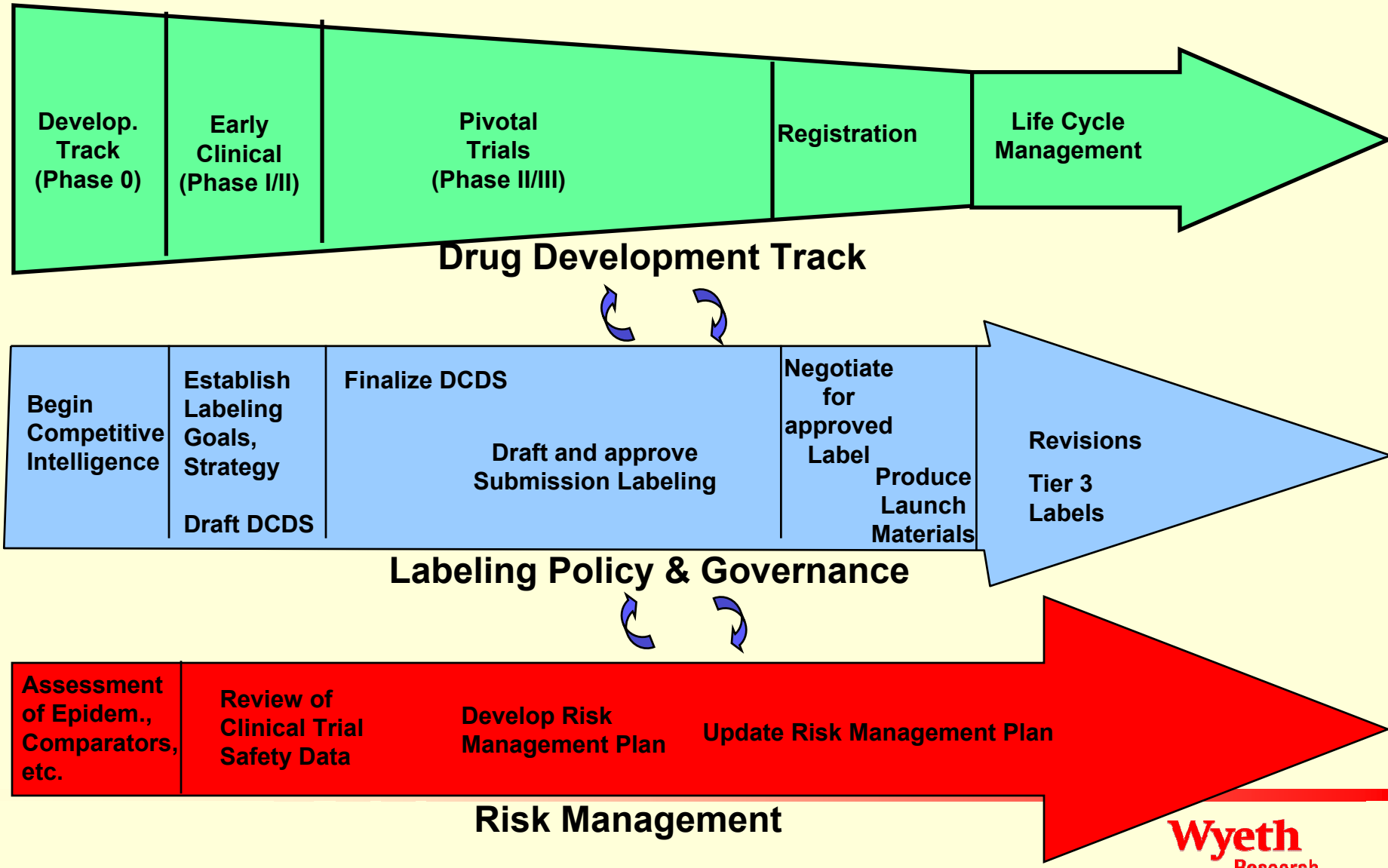
Integration of Risk Management, Labeling with Drug Development Timelines & Decision Points



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Risk Minimization Action Plans

- **FDA Guidance Document stresses that for for most products, routine risk minimization measures are sufficient. (Product label,pharmacovigilance).**
- **RiskMAPs should be considered for a small number of products – case by case basis.**
- **RiskMAP tools may include:**
  - Targeted Education and Outreach
  - Reminder Systems
  - Performance-Linked Systems

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Use of Risk Minimization Action Plans Implications for Industry

- **Design and implementation of RiskMAPs will require collaboration and expertise of various departments across a pharmaceutical company including:**
  - **Safety – continuing pharmacovigilance, input into development of RiskMAPs**
  - **Epidemiology – expertise in design and implementation of pharmacoepidemiology studies**
  - **Medical Affairs – Communication to Health Care Professionals/Patients re: Risks and Benefits, implementation of RiskMAPs, educational materials and activities.**
  - **Marketing – dissemination of efficacy and safety information.**
  - **Market research – (evaluation)**
    - **Usage data/prescription databases**
    - **Surveys.**
  - **Public Affairs**
  - **Global Affiliates**

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Use of Risk Minimization Action Plans

- **Additional challenges –**
  - How does Industry implement RiskMAPs on a global basis?
    - Practical considerations – drugs may be marketed in many countries.
    - Legal/Regulatory considerations
  - In order to change prescribing behavior and effectively communicate risk – what additional expertise is necessary ?
    - Use of behavioral experts
    - Use of process experts – FMEA, etc

Post-Marketing Risk Minimization Activities

- **Industry must develop processes for design, implementation and evaluation of Risk Minimization Plans.**
  - Establish “ownership” – group, department, person.
  - Standard processes, training, communication
  - Governace bodies
- **Ideal process should be “end to end”.**

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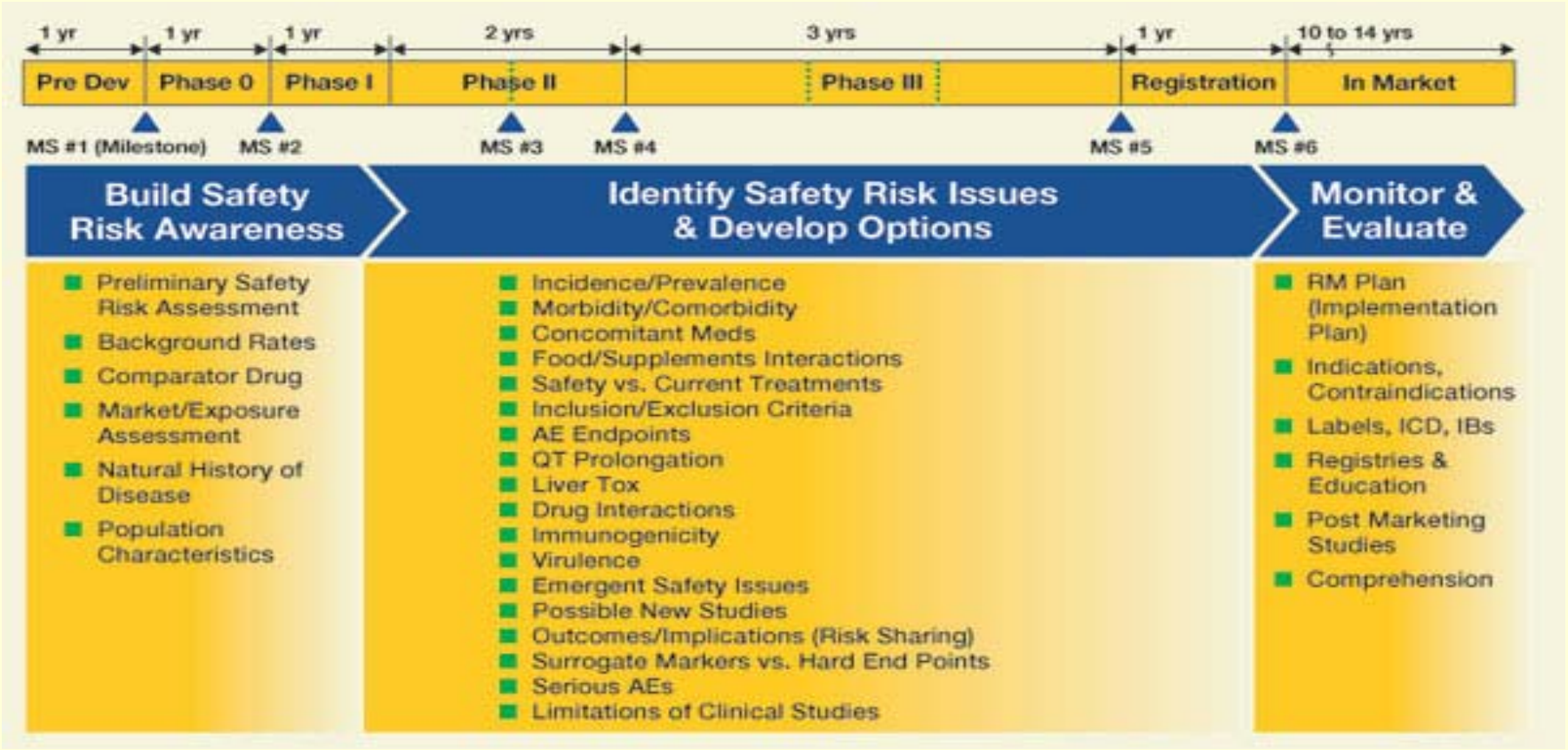
Design of an End-to-End Risk Management Process is Critical Toward Optimizing the Safe Use of Products



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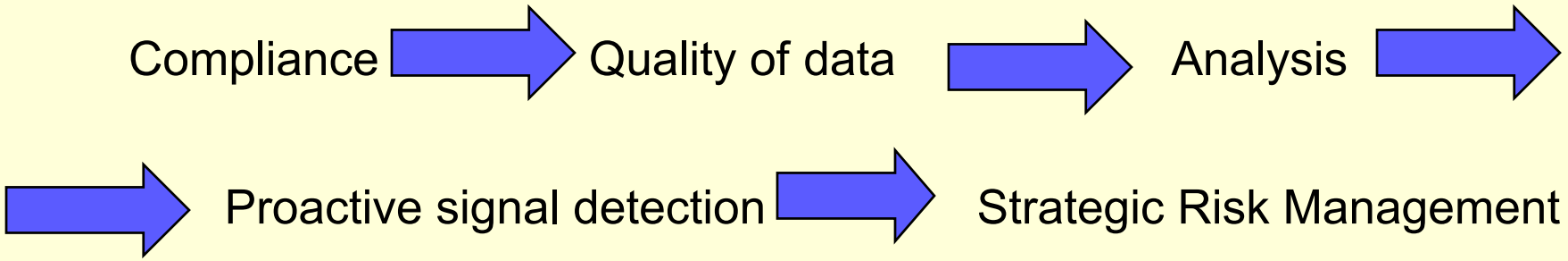
Pulling it all together….

- New regulations and guidances call for a more strategic approach to risk assessment and minimization.
- Safety and Risk Management planning activities should begin early in development and continue throughout the product lifecycle (end to end).
- Industry is working to develop expertise and processes to meet these new standards.
- Clear roles and responsibilities must be defined and communicated across the business.

Conclusion

- **The bar *has been* raised for the formal study of safety and risk, both during clinical trials and after product launch.**
- **Emerging regulations and guidances reflect the evolution of the field of Pharmacovigilance to the new era of Risk Management:**



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