Integrating Compliance with Business: Developing and Implementing the Tysabri Risk Map Reintroduction of a Breakthrough Medical Product

November 09, 2006

Juan Torres, Vice President Global Quality, Biogen Idec

Erika Cawthron, Associate Director, TYSABRI Services, Biogen Idec

Melissa Seymour, Director, Corporate Drug Compliance, Biogen Idec

Gregory Page, PhD, FDA Life Sciences Practice Leader, Deloitte & Touche, LLP

TYSABRI (natalizumab)

Objectives

- Regulatory Expectations
- TOUCH Prescribing Program
- Quality System Approach of Implementation
- Compliance and Monitoring

TYSABRI™ (natalizumab)

Regulatory Expectation

TYSABRI™ (natalizumab)

FDA “Risk Management” Process Definition

- An Iterative Process
  - Assessing benefit-risk balance
  - Use of tools to minimize risk and preserve benefits
  - Evaluation of tools, risks, and benefits
  - Reassessment of benefit-risk balance
- Risk Assessment and Risk Minimization

TYSABRI™ (natalizumab)

March 2005 Guidance Documents

- Three final guidance documents issued
- Premarketing Risk Assessment (Premarket Guidance)
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)
- Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)

TOGETHER THESE CONSTITUTE RISK MANAGEMENT

TYSABRI™ (natalizumab)

Premarketing Risk Assessment (Premarket Guidance)

- Robust clinical trial safety database
- Focused on Phase III of drug development
- Important role of Phase II and IV safety studies
- Recommendations for Quantity (patients) and Quality (study design/assessments)

TYSABRI™ (natalizumab)

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)

- Not possible to identify all issues during clinical trials
- Commercial Marketing may identify issues
  - Significantly larger patient population
  - Co-morbid conditions
  - Concomitant medical products
- Postmarketing safety data collection and assessment are important to enhance risk minimization

TYSABRI™ (natalizumab)

Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)

- Risk-Benefit is continuous through product lifecycle – Need for RiskMAP could be determined premarket or postmarket
- Sponsors are primarily responsible for determining necessity of a RiskMAP, however FDA may recommend
- Guidance covers
  - Elements of the Plan
  - Selection of risk Tools
  - Evaluation strategy

TYSABRI™ (natalizumab)

FDA Risk Minimization Action Plan (RiskMAP) Definition

A strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits.

Toni Piazza-Hepp, Pharm.D.

CDER Office of Drug Safety

TYSABRI™ (natalizumab)

Risk Minimization Tools

- Targeted Education and Outreach
  - Prescriber Education
  - Continuing Medical Education
- Reminder System
  - Patient Consent Forms
  - Physician Training documenting physician understanding
  - Specialized Product Packaging
- Performance Linked Access System
  - Systems that link product access to lab results or other documentation

TYSABRI™ (natalizumab)

TOUCH Prescribing Program

What is the TOUCH Prescribing Program?

TOUCH™ PRESCRIBING PROGRAM

TYSABRI Outreach: Unified Commitment to Health

A program that makes TYSABRI available only to prescribers, infusion centers, pharmacies associated with infusion centers, and patients who are enrolled in the program

TYSABRI™ (natalizumab)

What was the TOUCH Prescribing Program designed to do?

- Promote informed benefit-risk decisions between prescribers and patients regarding the use of TYSABRI in relapsing MS
- Minimize morbidity and mortality due to PML through early detection with clinical vigilance
- Minimize the risk of PML by treating patients who are not immunocompromised
- Warn against concurrent use with antineoplastics, immunosuppressants or immunomodulators
- Determine the incidence and risk factors for PML and other serious opportunistic infections in patients treated with TYSABRI, as well as the overall safety of TYSABRI in the clinical practice setting

TYSABRI™ (natalizumab)

TOUCH Prescribing Program Components

There are 3 main components of the TOUCH Prescribing Program

Enroll

- Prescribers and Patients
- Infusion Sites
- Central Pharmacies
- Specialty Pharmacy Providers

Infuse

- TYSABRI is only administered to enrolled and authorized patients
- Pre-infusion Patient Checklist is completed and faxed to TOUCH Prescribing Program

Track

- Patient status is tracked longitudinally to gather important safety information

NOTE: This overview of the TOUCH Prescribing Program components does not include a complete list of the program requirements.

TYSABRI (natalizumab)

Development & Implementation

TYSABRI™ (natalizumab)

Biogen Idec's Quality System Approach

- Assure that each employee has the necessary tools to meet all required quality attributes
- Continuously evaluate each step of the process to ensure that it meets or exceeds internal and external standards and customer requirements
- Continuous improvement to meet customer needs by decreasing defects and striving for high efficiencies

TYSABRI™ (natalizumab)

Quality Plan

- Roles and Responsibilities
- Process Controls
- Identification of Risks
- Monitoring and Auditing
- Tracking and Reviewing of Key Data
- Corrective and Preventive Actions
- Management Review Process

TYSABRI™ (natalizumab)

Corporate Responsibility

- Compliance with all relevant regulations and commitments made in license applications or supplements
- Systems that assure control over the RiskMAP process, regardless of location
- Provide leadership in the Continuous Improvement Process leading to risk* reduction and improved customer satisfaction

***Probability and severity of harm.**

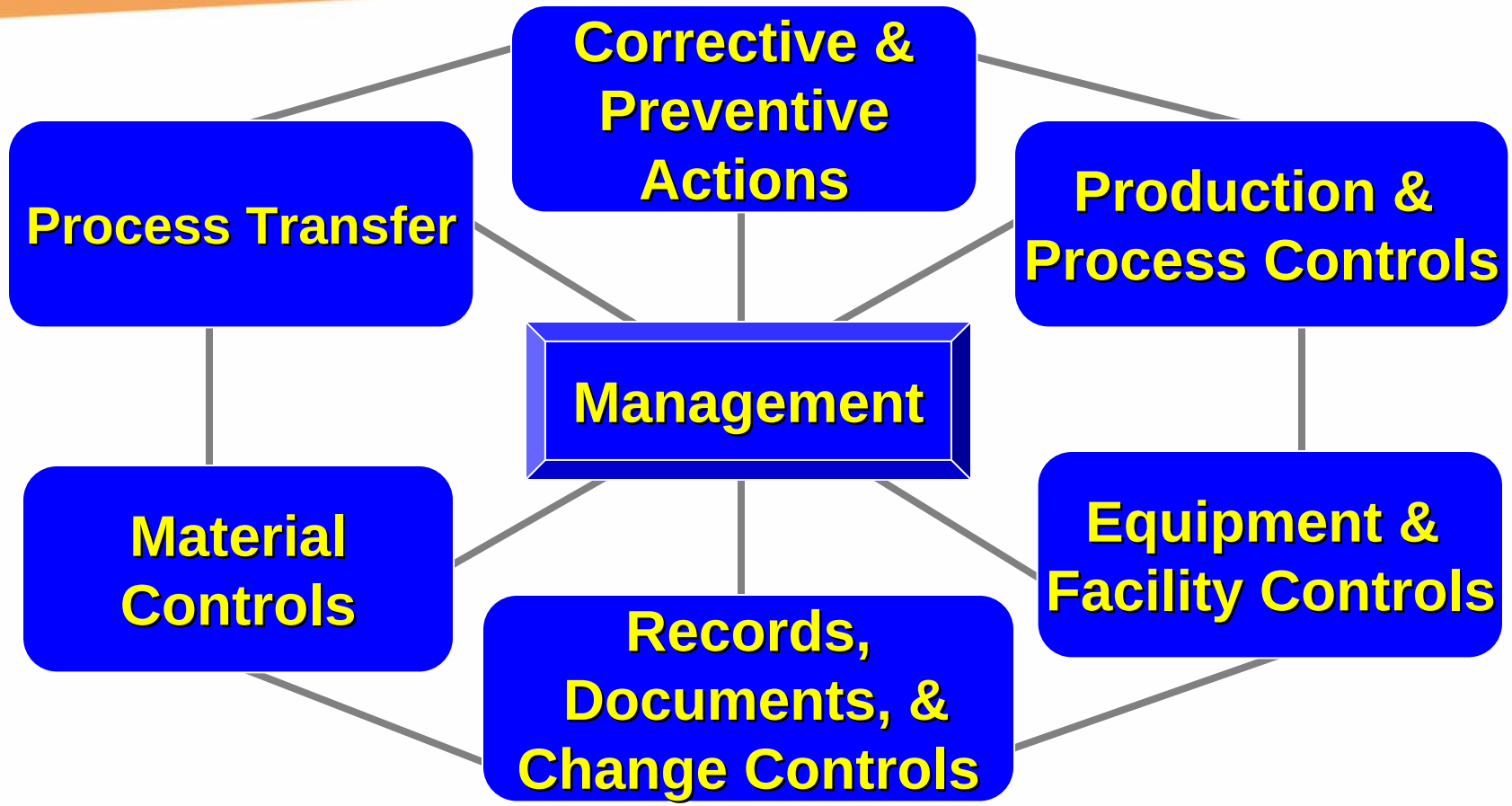
TYSABRI™ (natalizumab)

FDA's Expectations - ORA

- Systems that demonstrate Business is in appropriate control
- Management Oversight
- Proper delegation and administration
- Effective communication
- Audit, Monitor, Report
- Uniform enforcement, corrective actions
- Continuous improvement

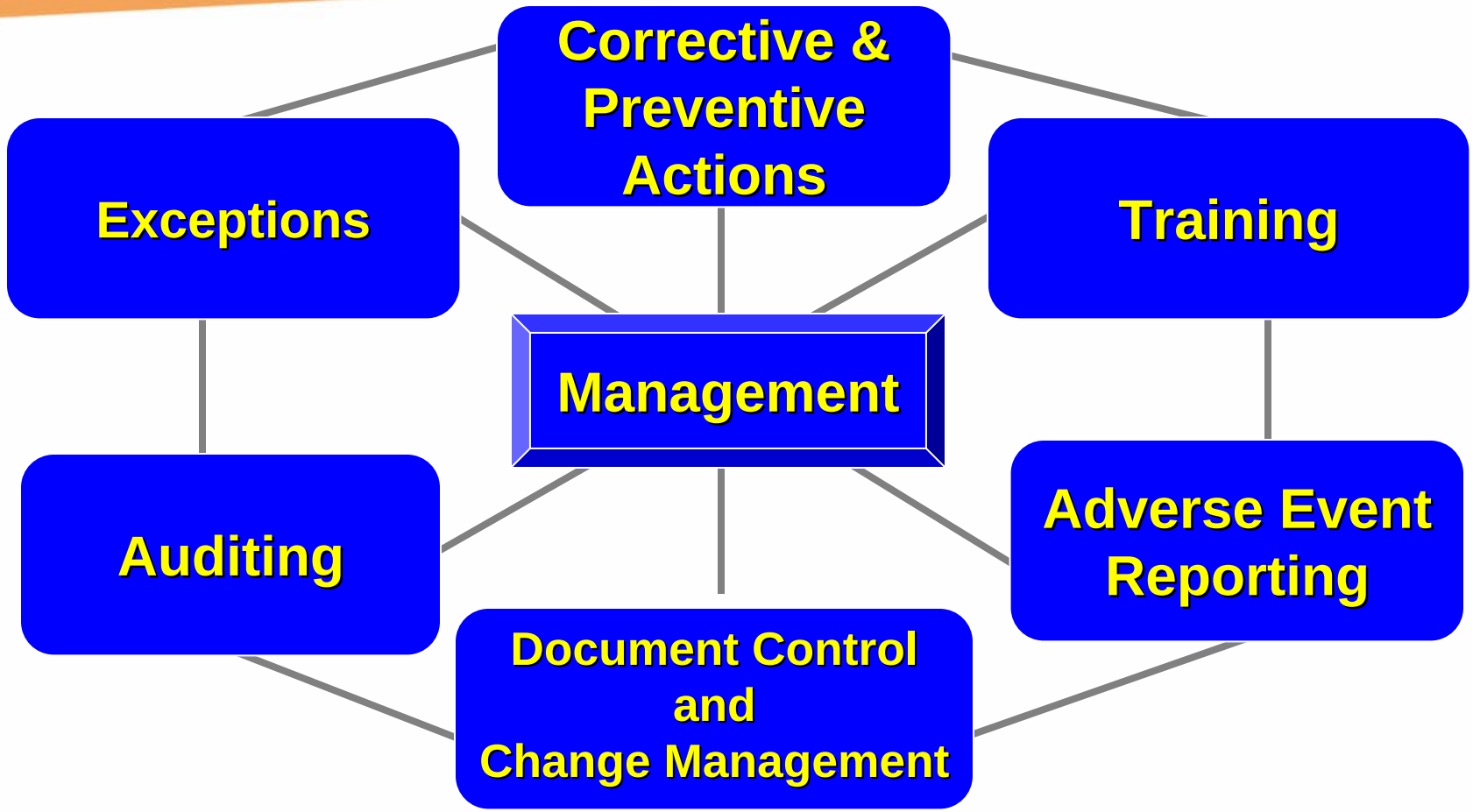
TYSABRI™ (natalizumab)

GMP Quality Systems



TYSABRI (natalizumab)

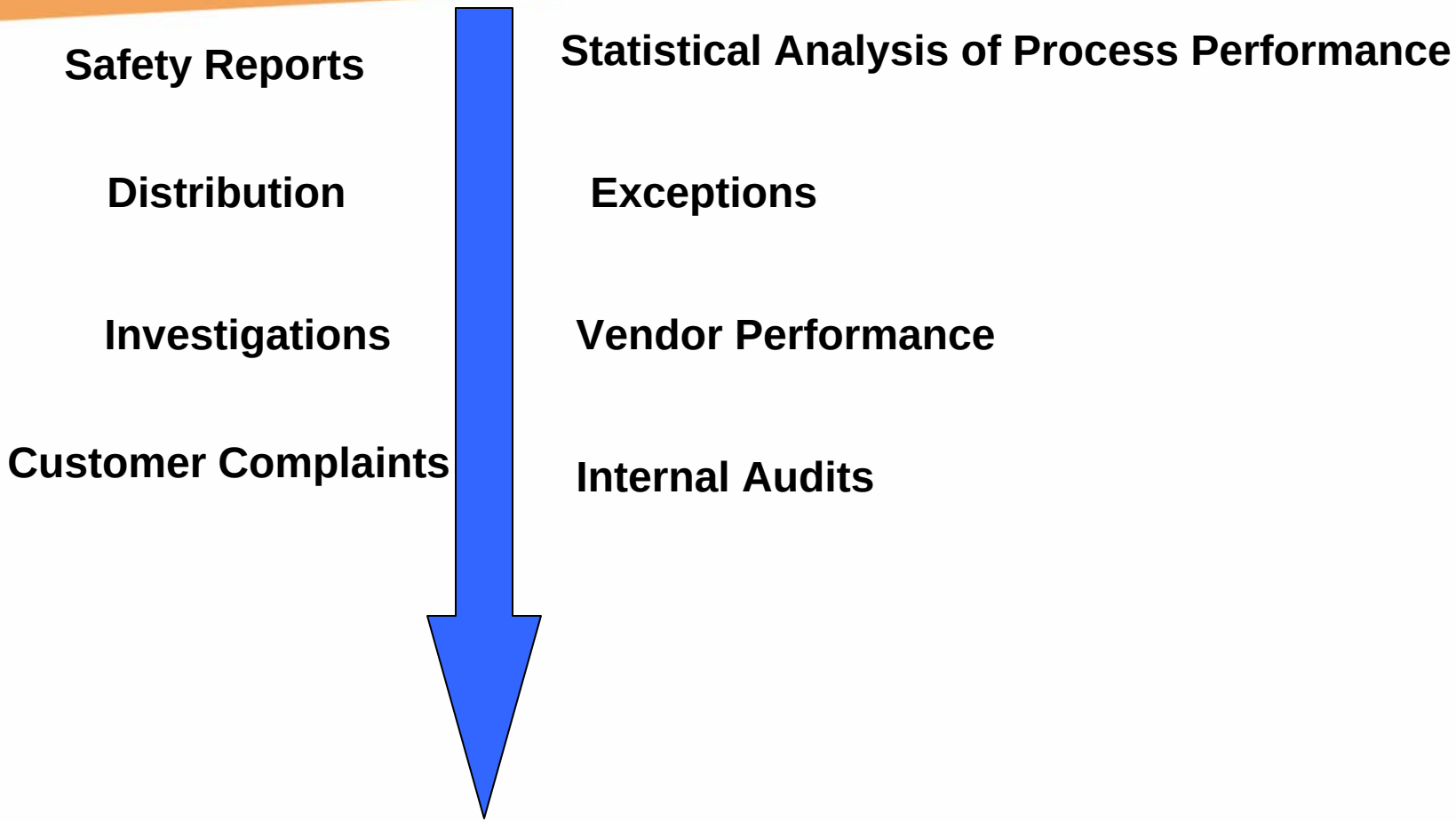
RiskMAP Quality Systems



TYSABRI (natalizumab)

Compliance and Monitoring

Surveillance Leads to Proactive Management of Operations



TYSABRI™ (natalizumab)

Exceptions

- Procedure that outlines the processes to identify, notify, investigate, review and track document exceptions
- Exceptions related to distribution, dispensing, infusion, and internal operations and requirements
- Exceptions are categorized by Quality based on impact
- Documentation includes at a minimum
  - investigation
  - root cause analysis, corrective and preventative action
  - impact assessment
- Appropriate level of review and approval

TYSABRI™ (natalizumab)

Exceptions – TYSABRI Compliance Review Committee

- Reviews Major and Critical Exceptions to determine corrective/preventive actions
- Trending of all exceptions to determine a systems issue that needs correcting
- Chaired by Quality
- Membership – Quality,Regulatory, Legal, Drug Safety, Supply Chain, and IT

TYSABRI™ (natalizumab)

Audits

- **Developed an Audit Plan Document**
  - Roles and Responsibilities
  - Location and Timing
  - Audit Coverage
  - Reporting and Tracking

- **Scope**
  - Internal Systems
  - Infusion Sites
  - Central Pharmacies
  - Specialty Pharmacies

TYSABRI™ (natalizumab)

RiskMAP Governance

- TYSABRI Risk Management Review Committee
- TYSABRI Safety Review Committee
- TYSABRI Compliance Review Committee

TYSABRI™ (natalizumab)

Safety Review

- Monitors, reviews, evaluates and discusses potential drug safety issues Safety Data
  - Potential and/or pending safety issues
  - Risks of drug use in special populations
  - Results from interim analysis of clinical trials
  - Proposed regulatory actions related to safety (recommendations to update core labeling)
  - Potential safety issues related to a possible product recall
  - Regulatory actions taken in one jurisdiction that may have global impact

TYSABRI™ (natalizumab)

Safety Review

- Determines strategic directions regarding risk mitigation, establish corporate medical position, and endorse recommended action concerning drug safety issues
  - Safety signal evaluation and confirmation
  - Risk-benefit assessment
  - Risk mitigation
  - Risk communication – including the need for labeling changes

TYSABRI™ (natalizumab)

Compliance Review

- Facilitate RiskMAP compliance and provides oversight for the effective execution of the Quality Plan by formal review of exceptions and noncompliance with TOUCH requirements
  - Distribution Data
  - Customer Service Data
  - Audit Data
  - Corrective and Preventive Actions
  - Trending of Exceptions
  - Critical and Major Exceptions

TYSABRI™ (natalizumab)

Management Review

- Evaluates the effectiveness of the risk management plan from a health outcomes perspective as well as a systems/process perspective
  - Safety Data
  - Performance Metrics
  - Audit Findings
  - Drug Surveillance Reports
  - Decisions from Safety Review and Compliance Review Committees
  - Exceptions Trending
  - Open regulatory commitments

TYSABRI™ (natalizumab)

Management Review

- Document agenda, attendees, reports, action items, decisions, and approved quarterly report to agency
- Chaired by Quality and Drug Safety
- Membership – SBU, Quality, Drug Safety, Supply Chain, Regulatory, Legal, and IT
- Representatives must have decision making authority and responsible for resource allocations

TYSABRI™ (natalizumab)

Summary

- Risk-Benefit is a continuous process through the life of a product
- Risk assessment and Risk Minimization constitute Risk Management
- Quality Systems approach to RiskMAP development and implementation ensures a robust and compliant program
- Continuous monitoring ensure effective implementation of the Quality Plan

TYSABRI™ (natalizumab)