Developing a Regulatory Plan for a New Product

Prof. Dr. Harald G. Schweim
Head of Department for Drug Regulatory Affairs
Institut for Pharmacy, University of Bonn

Former President of the German *Federal Institute for Drugs and Medical Devices* (BfArM)
Former Director of the German Institute of Medical Documentation and Information (DIMDI)
Structure of Presentation

• Basic Principles
  A regulated market, the R&D value chain …

• Key Elements & Tools
  Regulatory Plans & Strategy, Guidelines, Scientific Advice…

• Managing the Regulatory Process
  Input, Timelines…

• Summary
Basic Principles

• 12 or more years developing phase for a new product, from 500 to 1 000 million €
• Pipelines dry up on NCEs
• Generic competition
• Impact of Regulatory Strategies
  – Early submission is not always early approval
Key Elements & Tools

- Product differentiation:
  - Target Product Profile (TPP),
  - Project Development Plan (PDP)
- The Regulatory Plan (RP):
  - Strategy, Issues and Risk Assessment
- Standards & Guidelines
  - The External & Internal Match
- Regulatory & Scientific Advice
Product Differentiation (TPP, PDP)

- **Target Product Profile (TPP):** The « ideal » product for the target at the beginning
- To be aligned to data during development progression
- Real world & expectations should match at the end
- **Project Development Plan (PDP) to be structured to answer requirements of Target Product Profile (TPP)**
The Regulatory Strategy

- Element of Project Development Plan (PDP)
- Global, integrating requirements of major markets,
- Growing with project progression
- Anticipating future regulatory developments as science progresses
- Matching the Target Product Profile (TPP)
- Addressing regulatory risks & issues
- Interfacing with commercial items: pricing, reimbursement, co-marketing, co-promotion
The Regulatory Strategy

• Regulatory & Scientific Advice: when & from whom
• Regulatory Intelligence
• Scientific Dialogue: Meetings, hearings, oral explanations
• Dealing with objections, commitments & decision making
• Process planning: teams & responsibilities, expert involvement
• Practicalities: Translation resources, readability, labelling
The Regulatory Strategy

- European Union, Norway, Iceland, Liechtenstein:
  - selection of procedures (CP, MRP)
  - Co/Rapporteurs, Reference Member States, CMS
  - Timelines
  - Involvement of countries: where & where not
- USA
  - Meetings: Pre-IND, Pre-NDA, Advisory Committees
  - Dossier Management, pre-approval inspections
  - Local organisation & decision making process
- Japan
  - MHLM, Kiko & Co
- Other countries
  - Certificates (e.g.: C. of Free Sales) & Inspections
Implementation

• Regulatory teams:
  composition, competence & resources

• Networking:
  maintain the scientific dialogue of internal experts with regulators, prepare & organise hearings & briefing documents

• Define global submission formats:
  Clinical Trials & Marketing Authorisation Applications: Common Technical Document (CTD, e-CTD*)

• Address regional & national requirements
  E.g.: IND, EU IMPD, NDA, MAA (Abbr. explained later)

• Plan & monitor dossier distribution and submission timelines

• e-CTD = electronic CTD
Standards & Guidelines
The External & Internal Match

- Hierarchy of Law, Regulations, Directives, Guidelines & regulatory practices & standards
- International, regional & national regulatory framework
- How guidelines & standards are developed: guidelines are «frozen» science
- The hidden agenda: evolution of standards
- Fourth hurdle(s)
- Interpretation & derogation: when & how
- Internal Standards, Processes, Guidelines need to be consistent with regulatory requirements
Regulatory & Scientific Advice (SciA)

- Role of SciA in the R&D process
  A permanent regulatory & scientific dialogue to avoid surprises
- Obtain SciA: where (Europe, Japan & the USA)
  3 systems & philoso-fees
- Obtain SciA: when & how, by whom
  organise a structured, unequivocal dialogue
- How to use (or not) SciA
  derogations to be scientifically justified, progress of science & state of the art
Research & Early Development

- Progress of life sciences of today will be « frozen » in guidelines tomorrow
  The best guess: How will a guideline look like at submission, or how would we write the guidelines?
- « Environmental » regulations impact on research & discovery (Genetic Modified Organisms (GMO), stem cells, environmental & occupational toxicity …)
- Intellectual property protection
- Data privacy & disclosure
Development – Pre-clinical

PDP: Regulatory Elements
Objective: Fast track to Clinical Program
• Define Pre-clinical Safety Studies
  for intended duration, route & exposure, GLP, …
• Pharmaceutical particulars of investigational drug:
  formulation, stability, impurity profile, GMP …
• **Clinical Trial Authorisation Applications (CTAA)**
• Investigational **New Drug Application (FDA: IND)**,
  Investigational **Medicinal Product Dossier (EU: IMPD)**;
  Format & content, local requirements & procedures
  Investigator’s Brochure, Ethics Committees
• Scientific Advice (Pre-IND, EU, Kiko (JP) national
  Health Authority)
Development  –  Clinical I

First In Man (FIM):
• Establish data base clinical research program:
  Quality, Safety, Bio-availability (QSE), Pharmaco-kinetics & -dynamics
• Monitor data for regulatory reporting
• Quality Assurance: GMP, GLP & GCP compliance
• Shipment of Investigational Drug Supplies
  Export & Import Certificates, Customs, Inspections
• First TPP & global RP:
  where, when & how to apply for Marketing Authorisation (MA)
Development – Clinical II a & b

First Treatment of Patients:
- Demonstrate « biological signal » in disease state
- Define target patient groups, inclusion & exclusion criteria
- Monitor & report efficacy and safety
- Establish dosage, dose-finding and route of administration for large scale clinical trials
- Update TPP, draft SPC & global regulatory strategy for Medicinal Assistance Administration (MAA) USA
Confirmatory large scale clinical & special trials:

- Target patient population(s), patients at risk (elderly, renal & hepatic insufficiency, pregnancy, paediatric patients)
- Dosage & administration, route, conditions of use
- Final drug formulation(s), stability
- Risk/Benefit in selected indication(s)
- Labelling & Summary of Product Characteristics (SPC)
- Start of dossier compilation for global submission
- Regulatory Strategy & Risk Assessment
Registration, Launch

Filing and evaluation:
- Pre-Filing meetings
- Review, Assessment
- Clock stop
- Submission Team
- Expert availability & meetings, Advisory Committees
- Hearings, break-out sessions
- Scientific dialogue & networking
- SPC*s, labelling texts, Pack sizes
- Pricing & Reimbursement documentation

*Summary of Product Characteristics
Life Cycle Management

- Safety & Post Marketing Surveillance
  Pharmaco-vigilance, Post Marketing Surveillance (PMS) studies, labelling adjustments, Periodic Safety Update Reports (PSURs), EU community referrals
- Variations
- Co marketing & Co promotion
  Transfers of Marketing Authorisations (MA)
- Data Protection & Exclusivity Strategies
- Line extensions:
  new formulations, indications (e.g.: paediatric)
Summary

- Regulatory Affairs
  bridging R&D, life cycle management & interface to health authorities
- Regulatory planning & strategies
  optimise timelines and avoid registration pitfalls
- From data to knowledge & from clinical trial to authority decision
  tools and logistics of information transfer
- From Science to Guidelines
  Evolution of standards follows progression of science
Thank you for your kind attention!