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. explaind 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

Development – Clinical III

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!