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REGULATORY AFFAIRS

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Introduction - Charlotte

• Biomedicine program - 2006

• Ferring pharmaceuticals, Copenhagen - originals

• EQL Pharma, Lund - generics
Layout

- Why regulate drug development
- Product Life Cycle - Regulatory Affairs Perspective
- Regulatory Affairs and its role in the Pharma company
- Regulatory documentation/tools
- A typical day in Regulatory Affairs
Development plan

http://www.linnaeus.uu.se/online/pharm/lakemedelutveckling.html
Why regulate?

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy (medicine)"

Paracelsus (1493-1541)
Why regulate?

To ensure quality, safety and efficacy of drug products in order to assure the continued protection of Public Health.

No drug product is completely safe or efficacious in all circumstances, but there is a moral, as well as legal, expectation that appropriate steps are taken to assure optimal quality, safety and efficacy by the producers concerned. Benefit versus Risk.
Pharmaceutical regulation – A recent Development?

• Pharmacopoeias define:
  – the requirements for the qualitative and quantitative composition of medicines
  – the tests to be carried out on medicines
  – the tests to be carried out on substances and materials used in their production
  – But - no evaluation of safety or efficacy of medicines

• First “modern” pharmacopoeias 16th century (e.g. Spanish Pharmacopoeia)
Pharmaceutical regulation – A recent Development?

• Modern medicines regulation 19\textsuperscript{th} century

• Unfortunate events development of medicines regulation

• 1937 – diethylene glycol poisoning, 100 people died US Federal Food, Drug and Cosmetic Act

• 1956 – thalidomide disaster Major trigger for the development of the modern controls on the sale and supply of pharmaceuticals
  • EU Directive 65/65/EEC
The modern era of drug regulation

Now a wealth of Regulations, Directives and Guidelines controlling the sale, supply and study of medicines.

Agencies such as

• FDA (Food and Drug Administration) in US (http://www.fda.gov/),
• EMA (European Medicines Agency) in EU (http://www.ema.europa.eu/ema/) and
• National agencies (Läkemedelsverket) in SE (http://www.lakemedelsverket.se/)

set up to administer these rules and to approve medicines before they can be sold.
The modern era of drug regulation

International Conference on Harmonisation (ICH)

- A network of the authorities in EU, US, Japan and industry organisations
- Provide guideline on Quality, Safety, Efficacy and CTD
- No authority – recommendations which will have to be regionally implemented
Why is Regulatory Affairs Needed?

• Drug development and commercialization is highly regulated.

• The path to drug registration (Marketing Authorization) is paved with good intention but can be complicated.

• Things change....constantly!
Product Life Cycle - Regulatory Affairs Perspective

Development Phase
- Advice on development
- Scientific Advice
- Clinical Trial Applications
- Project management / Strategy
- Product Information - Claims

Approval Phase
- Application Procedure
- Authority meetings/hearings
- Electronic submission
- Readability Testing / Labeling Support

Post Approval Phase
- Life Cycle Management/Compliance
- Post-approval Commitments
- Clinical Trial Applications
- New Indications
The role of regulatory affairs – development phase

- Ensuring that the legislative requirements are met
  - Arrange for Scientific Advice - authorities
  - Advice on development studies to demonstrate safety, quality and efficacy
    - Set up regulatory strategy
    - Participate in cross-functional project teams
    - Ensure application of guidelines
    - Preparation of submission of application to conduct clinical trials
    - Managing the preparation of the regulatory submission
The role of regulatory affairs – development phase

• Minimize time to market (every day counts!)
  • Advice on a global development plan
    – Optimize submission strategies

• Efficiency in dossier preparation
  – Format, document re-use
  – Electronic submissions
  – Internal company relationships, project management
  – Review high-level documents/reports

• Interact with commercial side of business such as pricing and reimbursement
High-level documents?

- In all submission dossiers there will be a non-clinical, a quality and a clinical overview.
  - It is an introduction to the data with a critical assessment of the results.
  - It justifies any deviations from guidelines
  - It justifies the development and testing strategy.
Product Information - SmPC and package leaflet

SmPC – Summary for the prescribers
Package leaflet – Information for the patient

- Indication and dosing
- Precautions and warnings
- Interactions with other drugs
- Undesirable effects

The claims in the Product Information needs to be supported by scientific data in the dossier.

Ensure input from different parties.

FASS
The role of regulatory affairs – approval phase

• Check progress of evaluation and anticipate questions (prepare answers to expected questions)

• Clarify raised questions, plan response and strategies with other departments

• Plan and manage agency meetings/hearings

• Negotiate approval and Product Information with agencies
Marketing authorisation (MA)

An agreement with the authorities

- Valid for a period of 5 years.
- After 5 years renewal required
The role of regulatory affairs – post approval phase

- Compliance
  - Submission of variations/amendments
- Renewals
- Pharmacovigilance
- Product information review
- New indications / New formulations
  - Regulatory input to development plans!
- Regulatory Intelligence
  - What does the future hold?
Regulatory documentation/tools

• In the past the regulatory documentation presented to the authorities was printed on paper and organized in binders.

• Common Technical Document (CTD) is the standard format used for Marketing Authorisation Applications (MAAs, EU) and New Drug Applications (NDAs, US)

• Common agreed structure for the main sections (SAFETY, QUALITY, EFFICACY) of a regulatory submission
The common technical document - CTD

- The Common Technical Document is divided into five modules:
  - Module 1 Administrative and prescribing information
  - Module 2 Overview and summary of modules 3 to 5
  - Module 3 Quality (Pharmaceutical documentation)
  - Module 4 Preclinical (Pharmacology/Toxicology)
  - Module 5 Clinical - efficacy (Clinical Trials)
Modular Structure of Common Technical Document

Module 1
- Administrative and prescribing information
  (not harmonized)

Module 2
- Quality overall summary
- Nonclinical overview
- Clinical overview
- Nonclinical summary
- Clinical summary

Module 3
- Quality data

Module 4
- Nonclinical study reports

Module 5
- Clinical study reports
Tools - Electronic submission
Regulatory Intelligence

- Is a systematic process initiated by a defined need
- It is a collection of data and analysis of the data linked to a strategy
- It is legal and ethical (not espionage/hacking)

- So much information available on websites/databases

- Typical question – what other modified release products with indications x and y exist in Europe? What clinical trials supported the approval?
The role of regulatory affairs - Summary

• **GET THE PRODUCT ON THE MARKET QUICKLY**
  (Meet the legislative requirements and present the company position in the best light to maximise competitiveness)

• **KEEP THE PRODUCT ON THE MARKET FOR A LONG TIME**
The various roles within Regulatory Affairs

- Project management
- Submission management
- Maintenance management
- CMC specialist
- Pre-clinical/Clinical specialist
- Labelling expert
- Regulatory intelligence

- Global versus local Regulatory Affairs
An average day at work

• Computer work
• Read, review and also write documents
  – Interpret legislation, guidelines etc.
• Communication/collaboration – meetings/e-mails/TC
  – Colleagues
  – Business Partners
  – Medicines Agencies
• Deadlines
• Small details versus bigger picture
• Fast but still precise
Regulatory Affairs – what I like

• Writing, updating documents

• Reading & interpreting text

• Collaboration

• Diversity

• Learn new things

• Deadlines
Thank you!
Pharmacovigilance

• Pharmacovigilance

  – WHO’s definition: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

  – The word pharmacovigilance arises from the Greek word "pharmakon" – pharmaceutical and latin word “vigilare” – vigilant
Why do we need pharmacovigilance?

- To protect the patients
- To comply with the legislation
Adverse Reaction

• A response to a medicinal product which is noxious and unintended

• Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility

• Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.
Serious Adverse Reaction

• An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect
Authority Requirements

• MAH must have a system in place to ensure that all information concerning adverse reactions are collected evaluated and reported

• On-going pharmacovigilance evaluation

• Collate and write different types of reports to the authorities

• Electronic reporting of side effects
A valid case

- Patient (year and date of birth, gender OR initials)
- Medicine
- Event
- Reporter

Make sure that you always collect this information!

+ the date when you receive the information!
Timeframes – reporting to the authorities

• Serious adverse reactions - within 15 calendar days

• Non-serious side effects within 90 calendar days

The clock starts when the first person in the company receives the minimum information (the 4 criterias)

Compliance!
Serious adverse reactions within 15 calendar days

Non-serious side effects within 90 calendar days

The clock starts when the first person in the company receives the minimum information (the 4 criteria).