Overview of Regulatory Affairs and its Role in the Biotech and Pharmaceutical Industry

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Pfizer, Inc.,
Focus on Six Therapeutic Areas + Biosimilars
Global Commercial Organization/Business Units

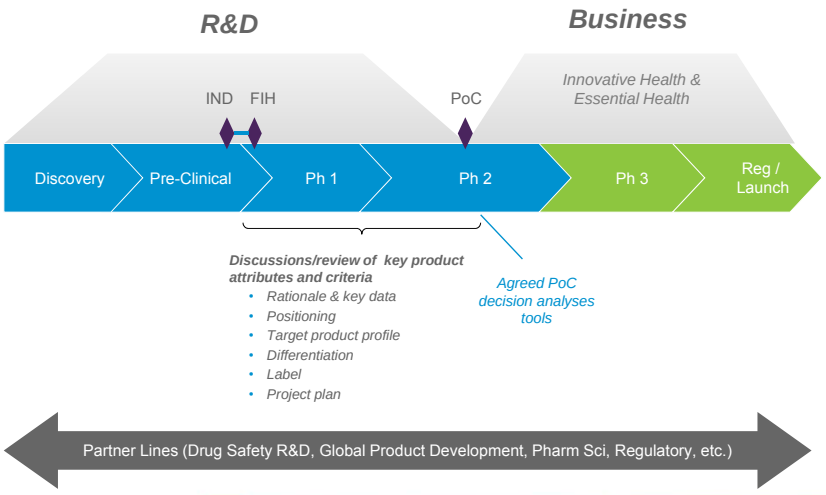
Pfizer Essential Health

- Brands and branded generics across key therapeutic areas including anti-infectives, women's health, and cardiovascular
- Sterile Injectables & generics
- Biosimilars
- Medical devices
- Policy & Intelligence

Pfizer Innovative Health

- Consumer Healthcare
- Inflammation & Immunology
- Internal Medicine
- Oncology
- Rare Disease
- Vaccines

Regulatory Affairs partners with Business and Research Units to position products for compliance and approval success



Success of Global Regulatory Affairs (GRA) Pfizer, Inc.,

12

functional lines/groups providing integrated safety and regulatory expertise

STAFF IN NEARLY

90

countries around the world

SUPPORTING

173

markets where Pfizer has products

WSR capabilities include strategic development and execution of regulatory pathways for assets potentially selected for New Drug Applications and maintaining global Pharmacovigilance standards for development compounds and mature products

751

launched products* maintained globally
(including 189 Consumer products)

3,650+

colleagues, contractors, and vendor staff worldwide

Overview of Regulatory Affairs and its Role in the Biotech and Pharmaceutical Industry

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Overview of Regulatory Affairs and its Role in the Biotech and Pharmaceutical Industry

Regulatory bodies such as the FDA and the EMA play an important role in the drug development lifecycle, from drug discovery, through clinical trials, to commercial production. This introductory overview of regulatory affairs will cover a brief history of drug development regulations as well as the drug development lifecycle. The presentation will also look at what happens when a manufacturer is not compliant with GMP standards, and the possible repercussions from a regulatory standpoint. The different regulatory challenges between large and small pharmaceutical companies will be discussed, as well as the future of the industry from a regulatory perspective.

Let's start at the very beginning...

A definition

Pharmaceutical regulatory affairs...

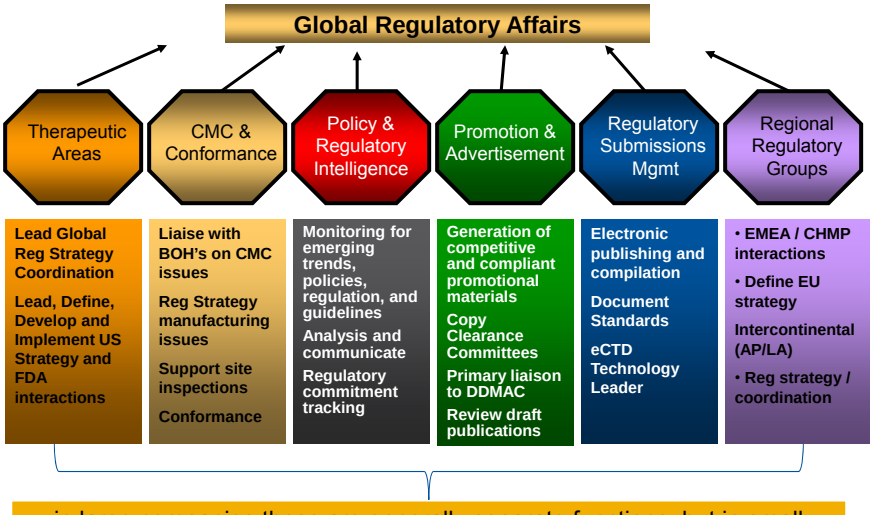
...operates at the interface of science, law, and business,

...applying scientific rationale along with statutory regulations and business demands

...to enable regulatory approval throughout drug development

...through interactions with government regulatory agencies who govern pharmaceutical approvals

What Comprises Global Regulatory Affairs



in large companies these are generally separate functions, but in small companies one person could be doing all these activities

Responsibilities of a Regulatory Affairs Professional

Serve as repository of regulatory policy knowledge

- Remain current with regulations, guidances, expectations & trends
- Review & provide comments on new draft guidances
- Understand regulatory history to current requirements
- Advise teams/company on impact of new requirements

Provide regulatory guidance to teams/management

- Contribute regulatory input to discussions, plans, problem-solving
- Develop regulatory strategy throughout drug development
- Communicate regulatory risks to teams and management

Responsibilities of a Regulatory Affairs Professional

Coordinate and/or author regulatory submissions

- Clinical trial applications
- Marketing applications
- Lifecycle management (e.g. label updates, new safety information, CMC changes, supply strategies)
- Responses to regulator queries

Represent company to global regulators

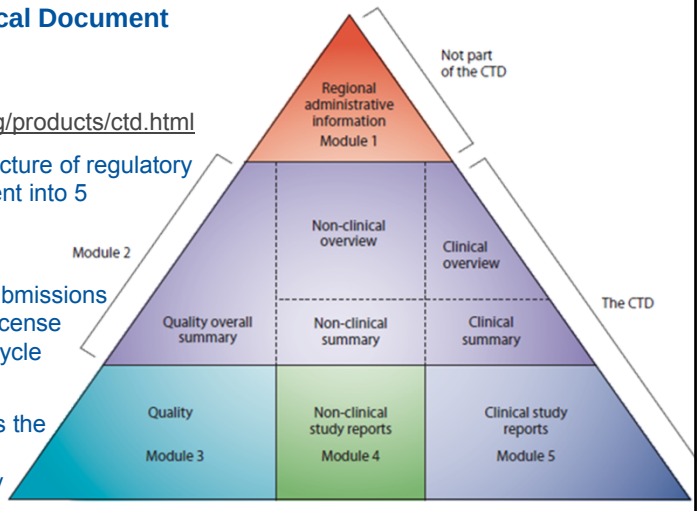
- Formal meetings as part of drug development; Informal teleconferences, phone calls, email

Most of the job is not black/white, its navigating every shade of grey – balancing risks / implications

Key ICH Guidances – CTD

Common Technical Document (CTD)

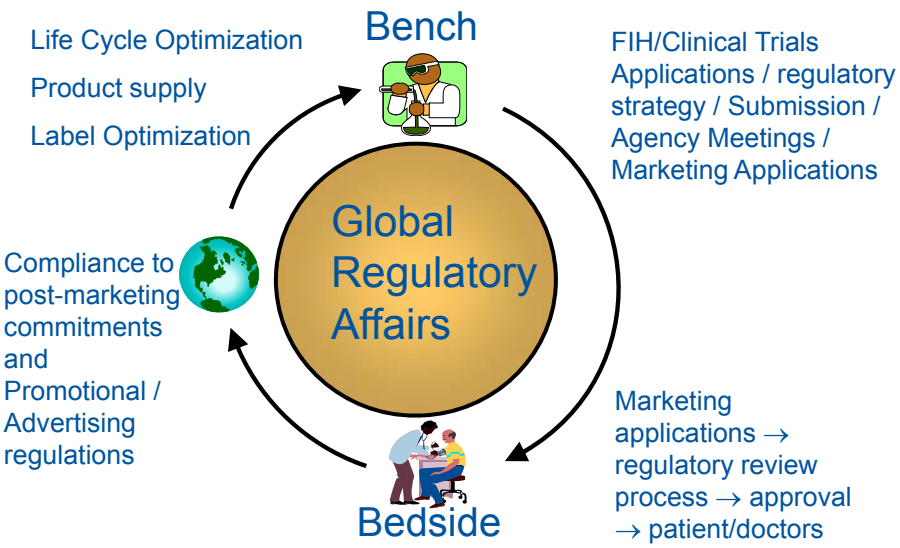
- http://www.ich.org/products/ctd.html
- Organization/structure of regulatory submission content into 5 Modules
- Used for both investigational submissions (IND, CTA) and license applications, lifecycle submissions
- ICH M4Q outlines the requirements for Module 3: Quality content



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Role of RA in product development & lifecycle

From Bench to Bedside and Beyond…



Developing global regulatory strategy (GRS)

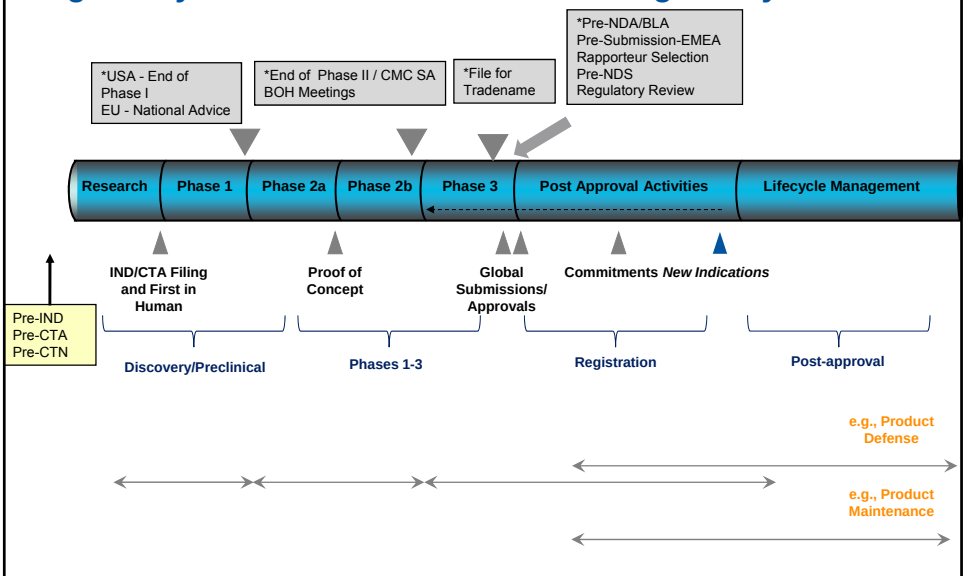
GRS – Initially prepared at Pre-Development Track, the GRS matures as the project advances toward submission to reflect study results, issues, specific country requirements

- Specific regulatory guidance for development
- Review of precedents – Regulatory Intelligence
  - SBAs, EPARs, ACM, Labels: What do competitor / regulatory precedents state in label and what data support available?
- Regulatory landscape and challenges / opportunities
- Key Regulatory milestones
- Includes CMC development strategies compatible with all countries (USP, EP, JP…) as usually there is one global product supplied to all countries
- Determine/request optimal regulatory status, ex: Orphan Status
- Filing strategy from FIH to post approval in all regions
- Strategy for interactions with regulatory authorities in US, EU, Japan

Developing the Global Regulatory Strategy

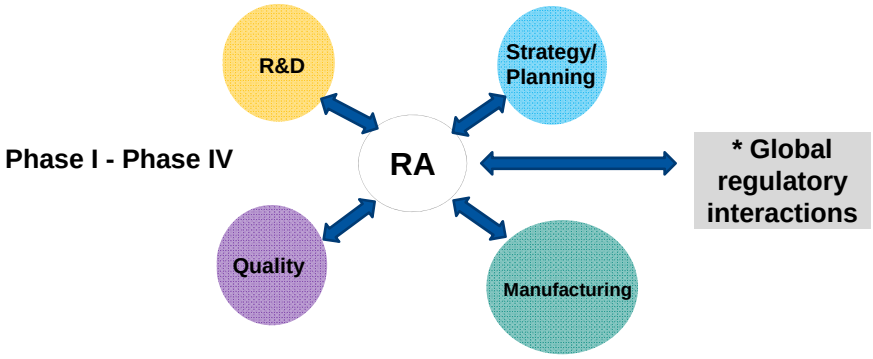
- What is the disease? What are the signs and symptoms and the patho-physiology?
- What is the product? Mechanism of Action. What will the new product do?
- What is the indication for product?
- Target Product Profile (TPP) / intended product positioning
- Regulatory guideline for developing product for indications
- Is program development plan able to support TPP / product positioning?
- **Regulatory / Competitive Intelligence**
  - Rigorous / detailed review of SBA, EPARs, Label
  - Benchmark product
- **What do current products offer?**
  - Efficacy / Safety / Metabolic / Convenience / Dosing, etc
- **Clinical Development Program – Global Regulatory Guidelines**
  - Key primary/secondary endpoints; Formulation / stability – DP/ DS issues

Regulatory Affairs: Where the Work of Regulatory Gets Done

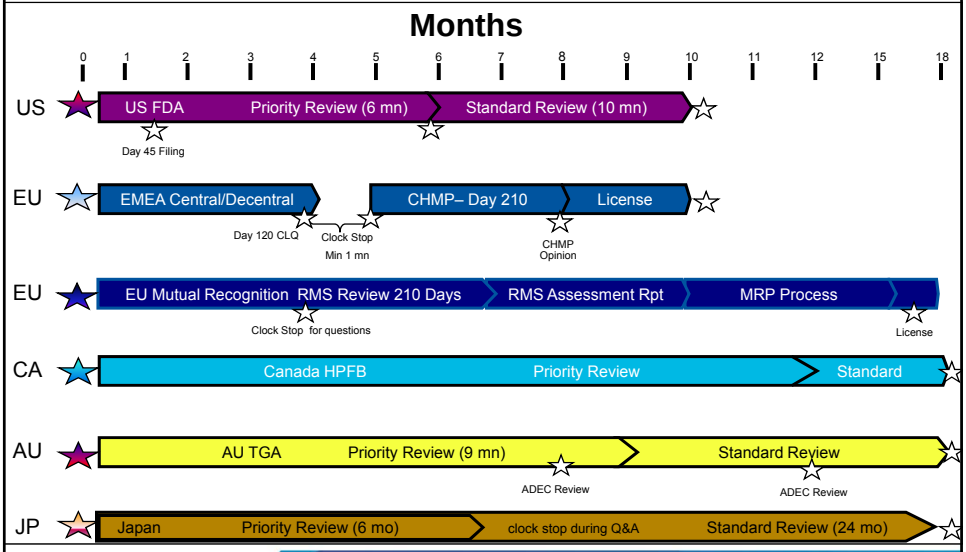


Regulatory Affairs: Where the Work of Regulatory Gets Done

Role of RA across teams



Regulatory Agency Review Timelines



FDA review process of a BLA

Pre-BLA Meeting

↓

Submission

Day 45-60 ↓

FDA determination if application can be filed

74 Days Letter*[1] ↓

120 days Post-Submission — 4 month safety update

↓

~ 8-10 months*[2] Post- submission — Advisory Committee

↓

12 months Post- submission

Queries (there are no set dates for FDA queries)

*[1]74 Day letter is the FDA acceptance to file letter. For biosimilars, the Agency could mention if AdComm would be required.
*[2] n Could be discussed at a pre BLA submission meeting

EMA review process of a MAA

Aim 20 days ahead of published EMA procedure start date

CLOCK STOP TO PREPARE RESPONSES: 3-6 months (recently approved etanercept biosimilar had 3 months clockstop)

CLOCK STOP TO PREPARE RESPONSES/ PREPARE FOR OE: 1 month clockstop

Submission	Validation (10 days post submission) RRT - depending on type of validation question	D 1 (procedure starts)	D80 RRT - preliminary Rapp/Co-Rapp AR	D120 (LOQ) RRT - Final D120 LOQ for responses	CLOCK RESTARTS - D120 responses submitted	D150 RRT - preliminary Joint Rapp/Co-Rapp AR	Approx D170 RRT - Updated preliminary AR (includes PRAC concerns)	D180 (Final LOOI) RRT - Final D180 AR / List of Outstanding Issues	D181 (OE) CLOCK RESTARTS - D180 responses submitted /OE takes place	D210 (CHMP opinion)	D277 (EC opinion)

Two types of validation questions possible:
- CTD based and needs to resolve before procedure starts (hence before EMA published start date)
- Written response – within 10 days of procedure starting

Preliminary Rapp/Co-Rapp AR. Will give a general understanding of D120 LOQ so can start drafting responses

RESOLVE all of the major objections and ensure that the minor questions ("other concerns") do not get upgraded to Majors through lack of resolution.

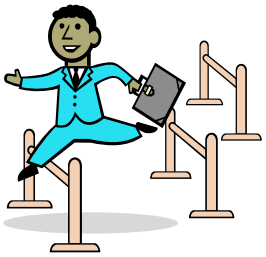
Preliminary Rapp/Co-Rapp AR. Will give a general understanding of D180 LOOI so can start drafting responses/ preparing for OE

Global Regulatory Agency Filing and Review Activities

1st Hurdle: Submission filed – 45 days post-submission or Refusal to File / Rejection

2nd Hurdle: Review Questions / responses
- timely turnaround

3rd Hurdle: Advisory Committee
FDA Open Hearing – EMEA/CHMP
Australia TGA ADEC – Oral Hearing
Japan – Bukai, Bunkakai



4th Hurdle: Regulatory Action
- Approval – 1st cycle
- Approvable – 2nd cycle review / additional information required
- Not approved / Application Withdrawn

Approval !

What happens if a company is non GMP compliant?

- Good Manufacturing Practices or GMPs are the pharmaceutical industrys fundamental guidance set up by regulatory authorities to describe what is necessary to manufacture safe and effective drugs.
- GMP refers to the Good Manufacturing Practice regulations enforced by FDA. cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. Assures that drug products meet their quality standards
  - USA, enforced under Title 21 CFR, WHO, UK…..
- To be compliant, drug manufacturers need to demonstrate to regulators that their drug-making processes within the production environment meet what the *industry* recognizes as best practice (GMPs guide pharma manufacturers on what they should do, not how they should do it)

What happens if a company is non GMP compliant?

- FDA inspects pharmaceutical manufacturing facilities worldwide, including facilities that manufacture active ingredients and the finished product
  - If a company is not complying with cGMP regulations, any drug it makes is considered "adulterated" under the law.
  - In rare cases, FDA regulatory action is intended to stop the distribution or manufacturing of violative product.
  - FDA's advice will be specific to the circumstances, and health care professionals are best able to balance risks and benefits and make the right decision for their patients
  - FDA, if during inspection any conditions that in their judgment which may constitute a violation is observed, 483 observations (official letters of sanction) to notify the company's management of objectionable conditions is issued. Company provides response, with timelines, to Agency within 15 business days….response may avoid a warning letter (with holding of product approval/shut down of the inspected plant.
  - The FDA Form 483 is considered, along with a written report called an Establishment Inspection Report, all evidence or documentation collected on-site, and any responses made by the company.

What happens if a company is non GMP compliant?

- MHRA (UK) may identify deficiencies during inspections (critical (license may be refused/suspended), major or other). After the inspection closing meeting, issue a post inspection letter confirming any deficiencies found. Company must respond to the inspector by email to confirm the proposed corrective actions and dates for when these actions will be completed. The inspector will review the response.
  - If accepted, a GMP or GDP certificate is issued with inspection report.
  - If rejected, an escalation process to support achieving compliance prior to regulatory action becomes necessary…..

In EU, non compliance can result in a huge fine – can be a certain percent of companies global earnings

Summary

- Pharmaceutical industry is highly regulated – the regulatory landscape is getting more complex
- Global Regulatory Affairs plays a pivotal leadership role in expedient and successful drug development
- Regulatory Affairs team is diverse and is involved in all aspects of drug development activities
- A strategic and proactive global regulatory team contributes in driving efficient and timely drug development, guiding to optimal global filing and successful registration
- The future for regulatory in our industry is necessary, continually evolving, provide interesting challenges….all provide for a very rewarding career.

Questions?

Please use the microphone indicated so our recording includes audio of your question

For more information

Pharmaceutical regulatory professional organizations

Regulatory Affairs Professional Society (US) www.raps.org

The Organization for Professionals in Regulatory Affairs (UK) www.topra.org/careers

Training courses

CfPIE, PERI, FDLI, Barnett International, DIA

Conferences

RAPS, IBC, AAPS

Degree & certificate programs

Some available to remote students

Sampling:

- Northeastern University
- Temple University
- Johns Hopkins University
- California State University
- Northwestern University
- University of Southern California
- San Diego State University

RAPS Regulatory Affairs Certification (RAC)

Comprehensive list on RAPS career development website

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