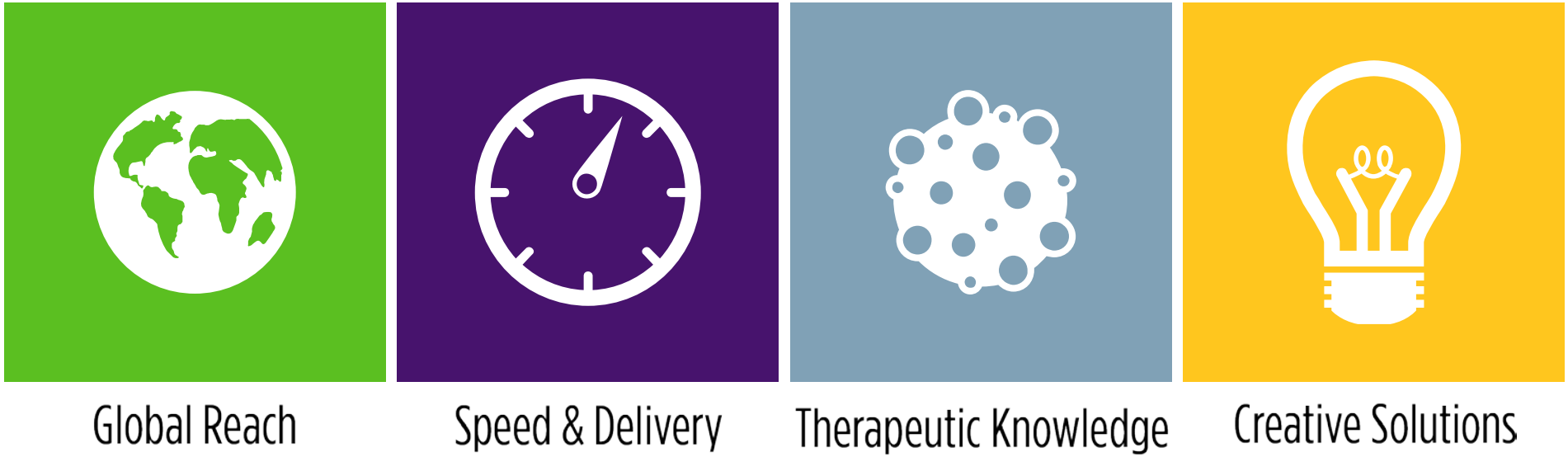


Regulatory Intelligence – Building Strategies for Drug Development

Kirsten Messmer & Charity Schuller

PPD®

Presentation Regulation

1. Introduction – Regulatory Intelligence
2. Application of Regulatory Intelligence
3. Regulatory Intelligence in Drug Development
4. Regulatory Intelligence Process
5. Case Study 1 – Biosimilar
6. Case Study 2 – Advanced Therapy
7. Case Study 3 – Pediatric Development Program

1 - Introduction – Regulatory Intelligence

Regulatory

- Regulate (transitive verb)
  - 1. To govern or direct according to rule
    - To bring under the control of law or constituted authority
    - To make regulations for or concerning (some industry)
  - 2. To bring order, method, or uniformity to (something)
  - 3. To fix or adjust the time, amount, degree, or rate of (something)

Merriam-Webster Dictionary

Intelligence

- Intelligence (noun)
  - 1. The ability to acquire and apply knowledge and skills
  - 2. The collection of information of military of political value
  - 3. Information in general – News (archaic)

Oxford Dictionary

Intelligence

Intelligence (noun)

- 1. The ability to learn or understand or deal with new or trying situations
  - The skilled use of reason
  - The ability to apply knowledge to manipulate one's environment or to think abstractly as measured by objective criteria
- 2. The act of understanding - comprehension
- 3. Information concerning an enemy or possible enemy or an area

Merriam-Webster Dictionary

Regulatory Intelligence

In general regulatory intelligence is the monitoring, gathering and analyzing of publicly available and experience based regulatory information to develop a strategy for time- and cost-efficient drug development.

Analysis of data to create actionable regulatory information → create advantage

2 - Application of Regulatory Intelligence

Who uses Regulatory Intelligence?

- Pharmaceutical/Biotech companies
  - Plan time- and resource efficient drug development
- Regulatory agencies
  - Consider precedents during approval decisions
  - Advisory Committee meetings
- Lawyers
  - Consider precedents to interpret the applicable law
  - Optimize legal proceedings

ansm
Agence nationale de sécurité du médicament et des produits de santé

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

MHRA
Regulating Medicines and Medical Devices

CFDA China Food and Drug Administration

Health Canada

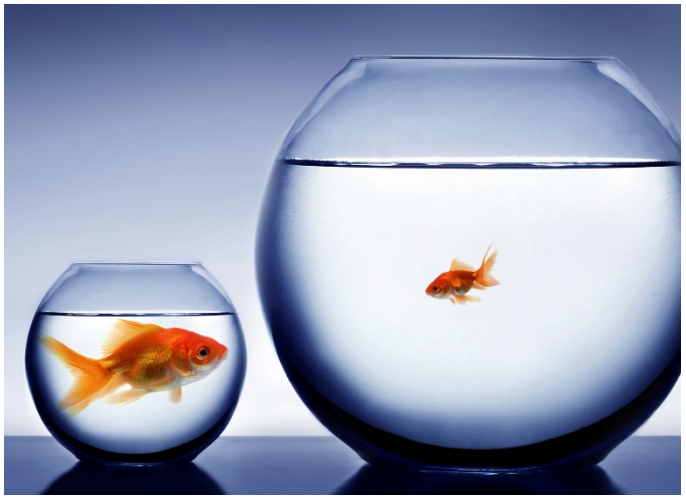
Pmda

Agência Nacional de Vigilância Sanitária

FDA

Who uses Regulatory Intelligence? - continued

+ Large companies
  + Dedicated regulatory staff
  + Well defined regulatory intelligence methodology
  + Proactive
  + Company internal or access to external structured databases



Versus

+ Small companies
  + Regulatory Intelligence part of a job function
  + One person, many hats → conflicting priorities
  + Reactive
  + Unstructured external information sources, needing to use consultants

Who uses Regulatory Intelligence? - continued

+ Large companies
  + Dedicated regulatory staff
  + Well defined regulatory intelligence methodology
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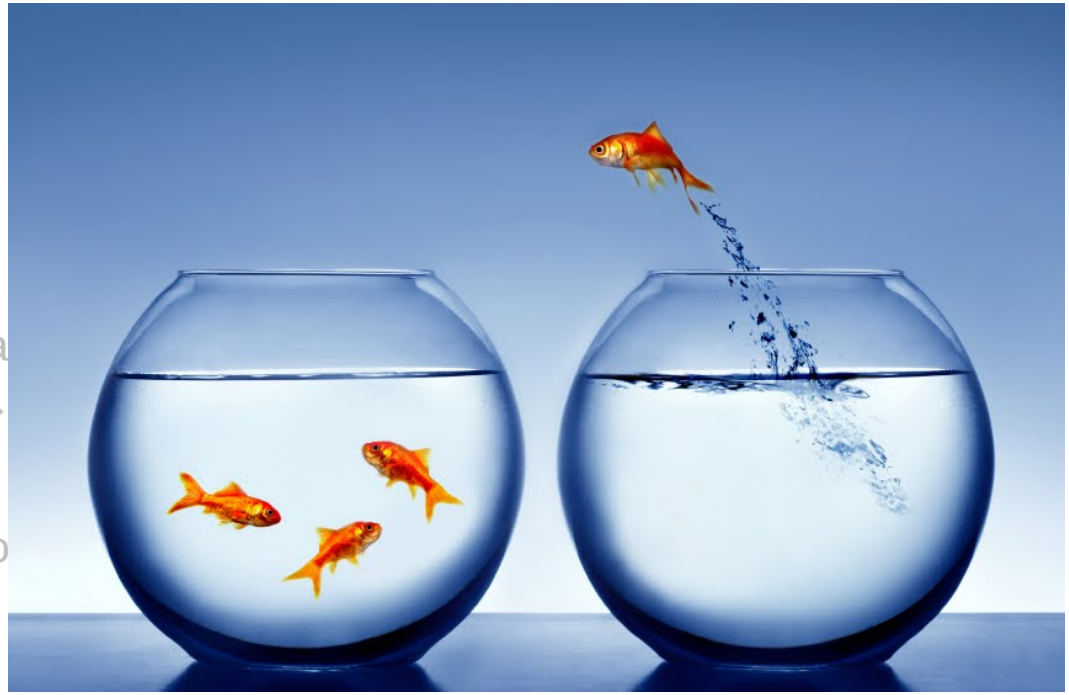
+ Small companies
  + Regulatory Intelligence pa
  + One person, many hats →
  + Reactive
  + Unstructured external info



How is Regulatory Intelligence used?

+ Development program optimization
+ Feasibility of clinical trials
+ Adaption of development program
+ Answering questions, regulatory requirement overview
+ Preparation for regulatory meetings
+ Bidding for research contracts
+ Education/training – company internal and external
+ Targeted alerts, Newsletter

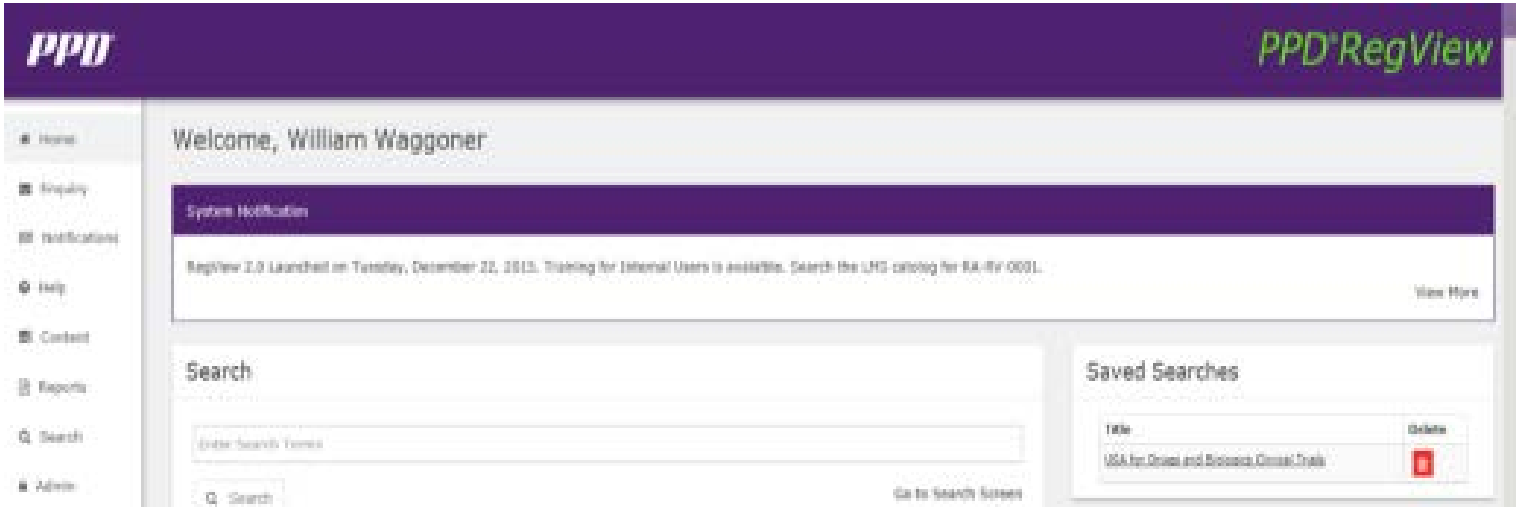
+ Sometimes as easy as checking if a certain medicine is available in various countries

Regulatory Intelligence Newsletter

+ Tool to keep employees up to date
+ Alert internal stakeholders to upcoming/possible changes
+ Lots of information – easy to digest

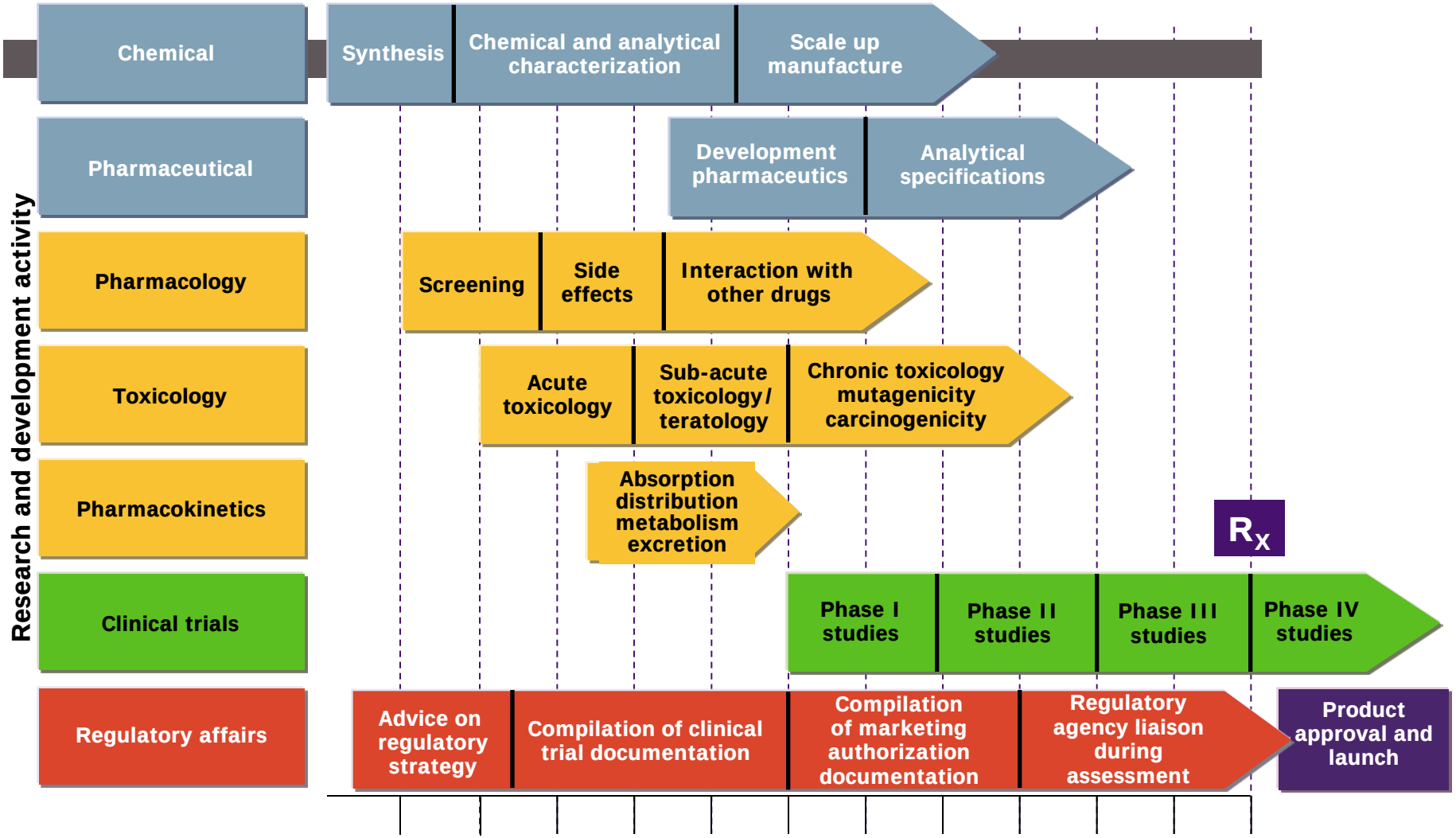
PPD® RegView

- Internal tool to keep employees up to date on country regulatory procedures and processes
- One stop source for regulatory and ethics regulations and requirements including PPD experience
- Customized country reports providing support material for client requirements



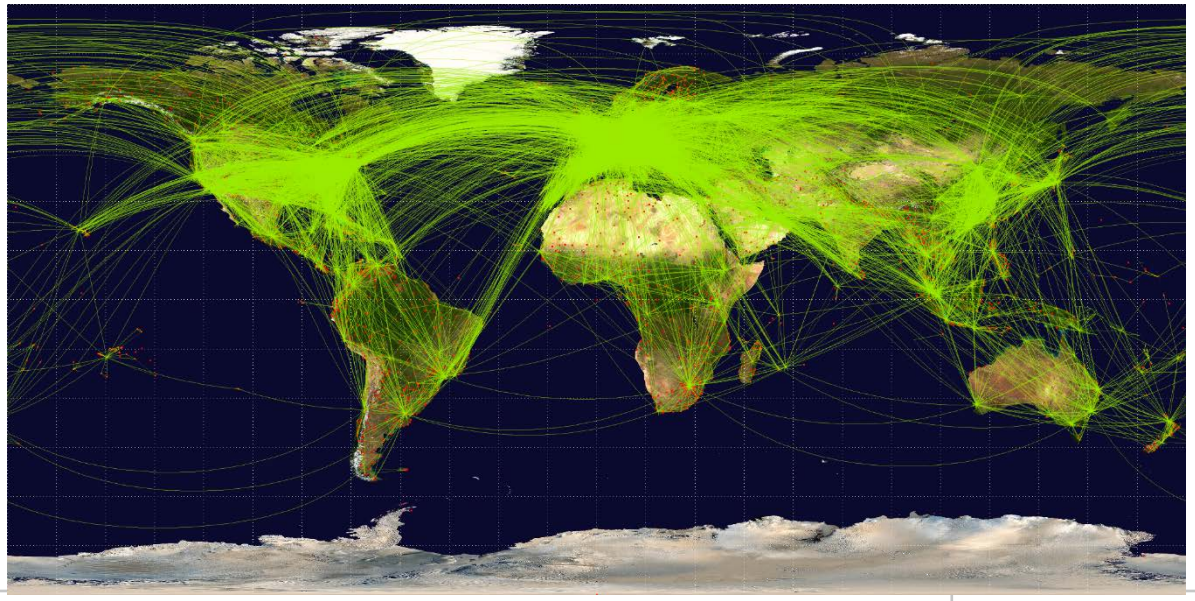
3 - Regulatory Intelligence in Drug Development

Traditional Drug Development

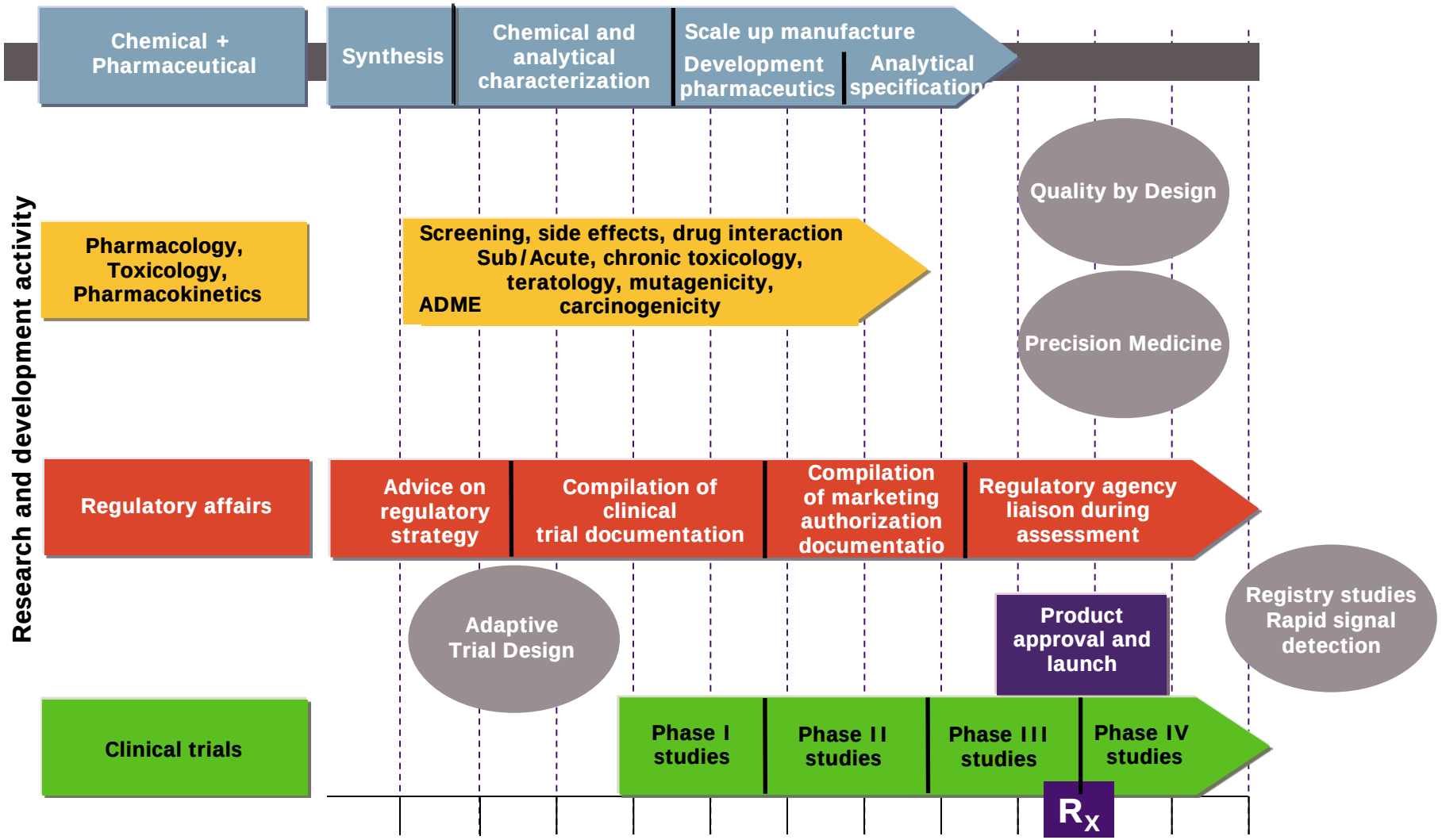


Paradigm Shift

+ Country level → Global, multinational
+ Retrospective data analysis → Regulatory consultation on prospective data generation
+ Regulation execution → Early discussions and collaboration
+ Dependence on clinical results → Relevance of the data in a real world setting



Modern Drug Development

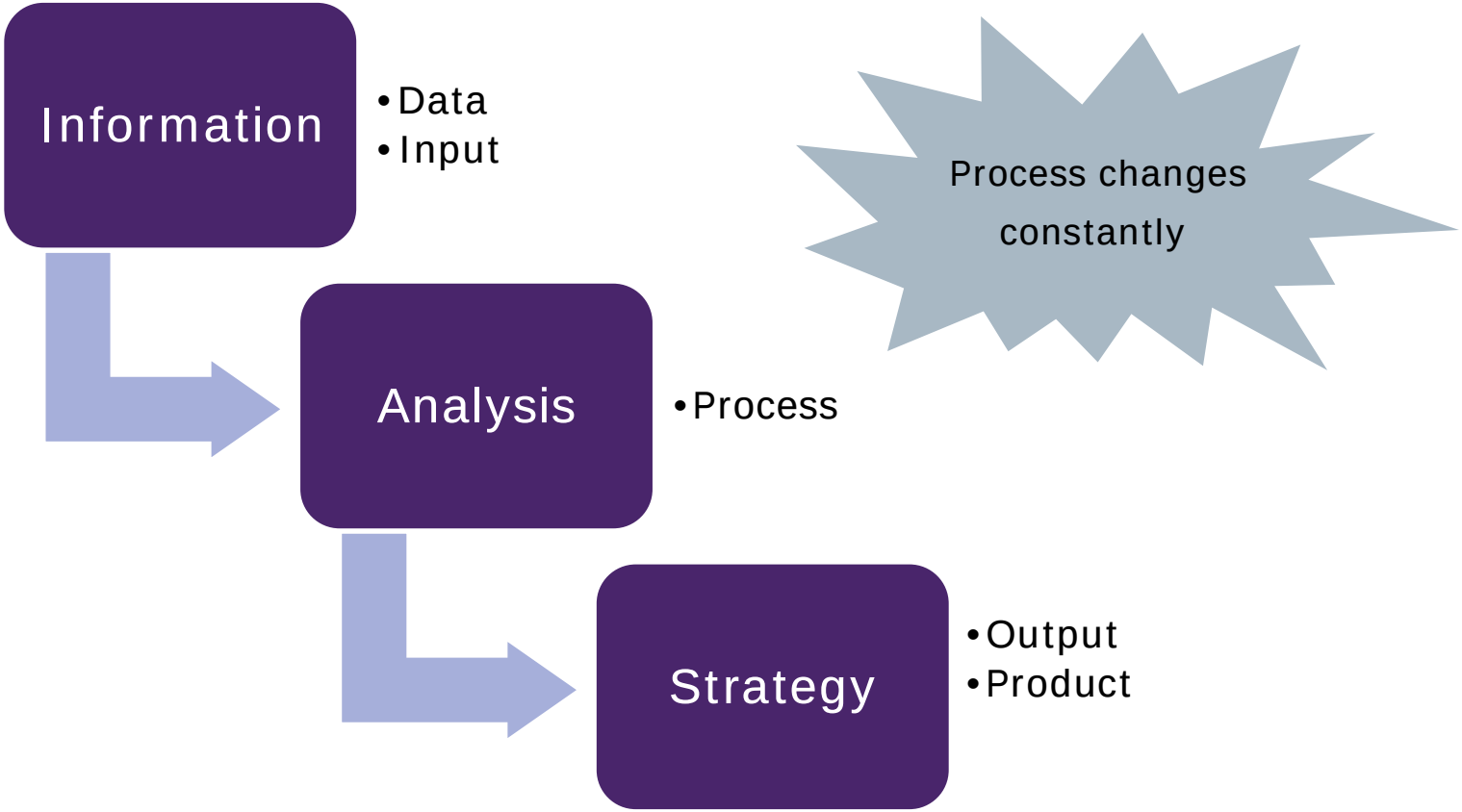


Importance of Regulatory Intelligence

- Regulatory are constantly changing – at a faster pace
  - Need to be 'on the ball' all the time
- New technologies and products – e.g. 1st 3D printed drug recently approved
  - May not fit completely in current regulatory landscape requiring intelligent adaptation
- Expansion and Harmonization
  - Australia is adapting new EU regulations continuously
  - New countries may join the EU
- Increased transparency means also increased scrutiny
  - Recent push in EU and USA for transparency – e.g. trial registers
  - More information becomes public information
- Information overload

4 - Regulatory Intelligence Process

Regulatory Intelligence Process



Step 1 - Sources of Regulatory Intelligence

External

- Rules, regulations, directives, laws → generally published by the agencies and available on their website
- Guidances, past approval documents, warning letter, FOIA and review documents → generally on agency websites
- Press releases, news sections, news feeds, e-mail alerts, organization newsletters
  - FDA, EMA news on regulations, guidances, initiatives, meetings etc.
  - RAPS – Regulatory Recon
  - Biopharma Dive, Fierce, RegLink News
  - Commercial (pay for): Scrip, Cortellis, Pink/Grey Sheet
- Business intelligence websites, newspaper, industry events
- Professional, scientific publications, presentations, webinars

Step 1 - Sources of Regulatory Intelligence - continued

Internal

+ Personal past experience
+ Experience of your colleagues or your connections
+ Corporate experience of your company → proprietary databases
  + Preclarus: Summarizing PPD Clinical Trial experience
  + RegView: Summarizing regulatory information and experience
+ Generally, as a regulatory intelligence professional you are not alone but collect information from all these different sources to feed into the process.

Step 2 - Intelligence Analysis

- Digest the information to form an assessment
  - Filter, compare, refine
  - Review, sort, context
  - Interpret, precedents, trends

- Regulatory Intelligence Solutions (RIS) team
  - Compile all information gathered from countries into a spreadsheet
  - Mark any ‘red flags’
  - Group countries with common requirements

Step 3 - Output/Presentation of Regulatory Intelligence

- It depends…
  - Well formulated answer to a question
  - All data presented in a well organized spreadsheet
  - Gap analysis
  - Slide presentation
  - Full regulatory Strategy Report

- Sponsor and sometimes data determine format
  - Sponsor will ask for a specific output
  - Request is structured in a certain way
  - Data determines best format to present
  - Sometimes format changes

5 - Case Study 1 - Biosimilar

Case Study 1 – Biosimilar Program

- Development of Biosimilar monoclonal antibody
  - Approved indications: Oncology
  - Off-label use: prevent inappropriate neovascularization after injury
  - Application includes colorectal and NSCLC but also knee cartilage regeneration

Case Study 1 – Biosimilar program – continued

- Development of a Biosimilar protein for the global market to the blockbuster product
  - Sound product – similar in CMC characteristics
    - Stability study requirements for the target countries
  - General development considerations
    - EU and US requirements may cover 90% of the global requirements
    - Comparator approval in indication (if not may be additional IP)
    - Hurdles and Extras
      - Very specific country requirements
      - Import restrictions (e.g. Cambodia – no IP import)
      - Export restrictions for e.g. biological samples
  - Clinical similarity to comparator
    - Controls and comparator – regional differences in comparator approval
    - Availability of comparators and standard of care
    - Need to provide all comparators, adjunct, add on therapies
    - Bridging Studies
    - Bioequivalence and comparability studies

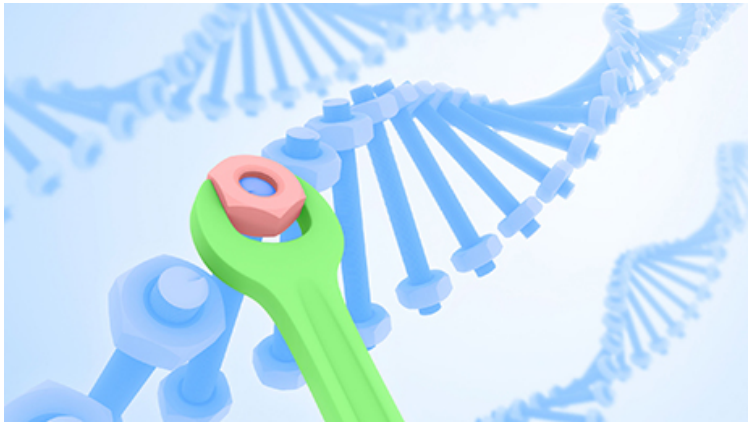
6 - Case Study 2 – Advanced Therapy

Case Study 2 – Advanced Therapy

- Gene therapy to treat Duchene Muscular Dystrophy
  - Adenoviral vector based – replace dystrophin
  - Quality and non-clinical studies complete
  - Study:
    - Single center in Italy
    - Patient recruitment global
  - Follow-up plan to be determined

Case Study 2 – Advanced Therapy continued

- Regulatory requirements in addition to standard requirements
  - Testing during development and for CMC
  - Facility requirements, inspections
  - Approvals by specialized bodies (e.g. for GMO in gene therapy)
  - Features in clinical trial and safety restrictions
  - Genetic disclosure requirements as applicable, data storage
- Post-approval registry Study
  - EU mandatory
  - May still be regarded as interventional study (e.g. Belgium, Brazil, Germany)
  - Vector persistence, insertion, mutagenesis, shedding



7 - Case Study 3 – Pediatric Development Program

Case Study 3 – Pediatric Development Program

+ US pediatric exclusivity program
+ Epilepsy
+ Pediatric population
+ Pediatric formulation
+ Global enrollment

Case Study 3 – Pediatric Development Program - continued

- Time of the essence
- Understand and plan for country-specific requirements
  - Selection process
    - Great sites but longer regulatory process
    - Technological differences
    - Shipping and logistics
  - Patient population concerns
    - Adequate provision of safety data
  - Specific quality management plans to manage studies in countries and sites that are deemed “risky”

- Relevant assent, parental and adult consent
  - 3 types: young adolescent, older adolescent, adolescent reaching majority
  - Additional assents/consents for genetic testing and sub-studies

Case Study 3 – Pediatric Development Program - continued

- Data management
  - Rating scales/tools - validation and familiarity
  - Less complex the CRF the better
- Other considerations for success
  - Site visits
    - Duration and frequency
    - Consider option of Saturday clinics
    - Transportation
    - Accommodation if hospitalization is required
  - Inform parents of side effects particularly those that could cause distress or embarrassment for school age children
  - Ensure site staff are experienced and confident with pediatric trials
  - Training and education of patients and parents/guardians on any tools such as diary

Resources

- ***Agency websites:***
- FDA news: Drugs: http://www.fda.gov/Drugs/NewsEvents/default.htm
- Biologics: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WhatsNewforBiologics/default.htm
- EMA news: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/whats_new.jsp&mid=WC0b01ac058004d5c4
- Links to global regulatory agencies: http://www.pharmweb.net/pwmirror/pwk/
-
- ***Access to assessment/approval documents:***
- EMA: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124
- FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- Use search function to find your drug of interest and assessment/approval documents available.

Resources - continued

- ***FREE public regulatory newsfeeds (with subscription to daily/weekly news):***
- RAPS – Regulatory Recon: http://www.raps.org/regulatory-focus/news/research-resources/regulatory-recon/
- Fierce Biotech: http://www.fiercebiotech.com/ part of FierceMarkets. Fierce Biotech has many sister sites – check out which ones are of interest
- BioPharma Dive: http://www.biopharmadive.com/
- RegLink News: http://reglinknews.com/
-
- ***Pay-for public regulatory newsfeeds:***
- Scrip Regulatory Affairs/RajPharma: http://www.rajpharma.com/home/
- Pink Sheet (Drugs): https://www.pharmamedtechbi.com/publications/the-pink-sheet
- Grey Sheet (Devices): https://www.pharmamedtechbi.com/publications/the-gray-sheet
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- ***Subscription databases:***
- Cortellis (Thomas Reuters): https://cortellis.thomsonreuterslifesciences.com/ngg/login.do?session=nosso
- Pharmaprojects (Informa): https://ppd-pipeline.citeline.com/CpAccount.aspx
- Adis (Springer): http://bi.adisinsight.com/Login/Login.aspx

Resources - continued

+ ***Industry Association websites:***
+ RAPS: http://www.raps.org/news-trends/
+ DIA: http://www.diaglobal.org/en/resources/topics-of-interest/ra
+ TOPRA: https://www.topra.org/
+ BIO: https://www.bio.org/
+
+ ***Clinical Trial Registries:***
+ NIH: www.clinicaltrials.gov
+ EudraCT: https://eudract.ema.europa.eu/
+ WHO International Clinical Trial Registry Portal: http://apps.who.int/trialsearch/

Questions?

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