Current regulatory framework : new legislation and relevance to stakeholders in medicines development

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EURORDIS Summer School
June 2, 2015

Overview

1. Regulatory affairs (RA) as an integral part of medicines development
2. Principles of GXP
3. What's new currently in Europe?

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3. What's new currently in Europe?

RA: the bridge between the company and health authorities

Role of RA

- To keep track of the ever changing legislative environment
- To register dossiers to the regulatory agencies
- To give strategic and technical advice to R&D, and other relevant functions such as Pharm. Dev, Preclinical..

Core competences

- RA professionals come from diverse backgrounds, eg pharmacist, physician
- Valuable skills include project management and organization, negotiation and communication, and the ability to learn from the experience of others, both inside and outside the organization
- RA professionals must keep up to date with regulatory policies, guidelines and procedures for one or more countries/regions, as well as maintain an understanding of the scientific and technical background of healthcare products
- Continuing education and professional development are critical
- Global aspects of regulatory affairs are taken up by organisations such as ICH, IMI

As a RA person, you have to know

- What is a dossier?
- What is a Drug Master File (DMF)?
- What is a eCTD?
- What is a NDA, IND, CTA, MAA?
- How to register a file, or a clinical trial?
- What are the legal, clinical/preclinical/CMC requirements?

What is a dossier?

- A collection or file of documents that contain all the technical data if a pharmaceutical to be reviewed, approved, registered and marketed in a country

- It is most commonly called as Registration dossier
  - In Europe, a Marketing Authorisation Application (MAA)
  - In the US, a New Drug Application (NDA)

- Or a Clinical Trial Application (CTA)

What is a EDMF?

- EU Drug Master File or Active Substance Master File contains detailed scientific information which the MAH has partly access to

- Objective is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the Applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product and the quality and quality control of the active substance

- To be assessed by Regulatory authorities

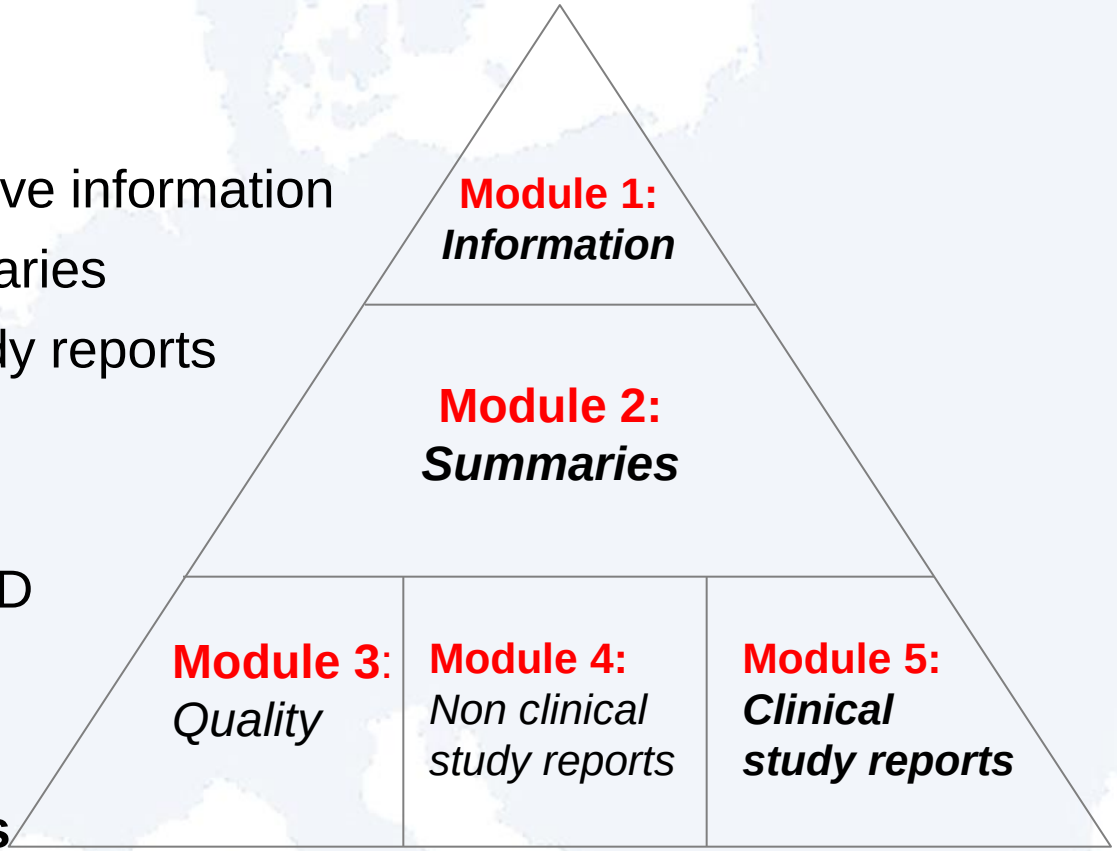
What is a eCTD?

- Electronic Common Technical Document
- A format set by ICH, which was agreed by the 3 main regulatory authorities, in Europe, Japan, and the US: EMA, PMDA and FDA
- Mandatory in Europe for submission at the EU medicines agency (EMA) via the e-gateway

The CTD triangle

- Prepare **Modules**:
  - **1:** Administrative information
  - **2:** CTD summaries
  - **5:** Clinical study reports (CSRs)

- Compile the whole CTD



Regulatory Authorities

- Submission to the EMA and/or FDA

CTD Modules

- Module 1: Administrative information, (region specific)
  - Application form
  - Labelling text and mock-ups
  - Environmental risk assessment
  - Description of the pharmacovigilance system
  - Information on Paediatric development
  - Risk Management Plan (RMP)
- Module 2: Summaries (efficacy, clinical safety..)
- Module 3: Quality (CMC)
- Module 4: Non-Clinical reports
- Module 5: Clinical Study Reports (CSRs)

EMA: focal point of the centralised procedure

ONE Marketing Authorisation application

Evaluation

Authorisation in all EU

Invented name

Product information

(Summary of Product Characteristics (SmPC), Labelling, Package Leaflet (PL))

ALL EU languages

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What are the medicines assessed at the EMA?

Assessment done on Efficacy/Safety/Quality

Mandatory Scope

- Rare diseases
- HIV, cancer, neurodegenerative disorders, diabetes
- Auto-immune diseases, viral diseases
- All biotech products
- Gene therapy
- Monoclonal antibodies + Other innovative products

Optional Scope

- New active substances
- Interest of patients at the EU community level
- Significant innovation (Therapeutic, and/or Scientific, and/or Technical)

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The CHMP at EMA

Committee for Medicinal Products for Human Use

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Good x Practices

'GxP' is defined as the series of laws, regulations and guidance governing the research, development, testing, manufacturing and distribution of pharmaceutical & bio-pharmaceutical products that constitute the 'Good x Practice' (i.e; **G**ood **L**aboratory **P**ractice, **G**ood **C**linical **P**ractice, **G**ood **M**anufacturing **P**ractice, **G**ood **D**istribution **P**ractice and **G**ood **P**harmacovigilance **P**ractice) of the business

Topics covered in this training

Starting point

"I know that this medicine is safe for me. But how is safety ensured?"

As a patient,

I expect this product to be **safe**, **effective** and of high **quality**

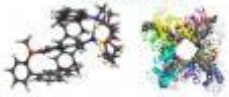
Flash-back…

…to when it all started !

Non-clinical

Drug discovery

Identification of candidate



Non-clinical testing

Safety and Efficacy tests

Clinical

Phase I

Phase II/III

Regulatory

Submission of marketing authorisation request

Approval after evaluation by authorities

Availability and pricing dependent upon individual country

Post-Marketing

Phase IV

How are medicines developed?

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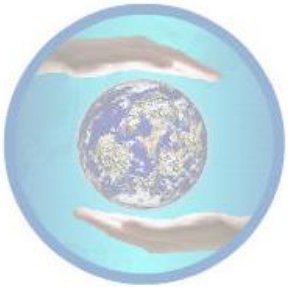
How can you guarantee that the product will be ***safe, effective*** *and of* ***good quality****?*

Research is the first step in the life of a medicine

During this important step, the researcher…

- Identifies potential candidates (i.e. molecules or products)
- Proceeds to a target screening (potential disease state)
- Takes out a patent (intellectual property)



Laboratory

Laboratory

Candidates that were identified during the research step are now investigated in the Laboratory

Good Laboratory Practices (GLP) are intended to guarantee that all results are reliable before going to the next step, i.e. ‘first-in-man’ (confidence in the results)

The studies under GLP encompass :

- studies on the efficacy of the product in *in-vitro* and animals models
- toxicology studies (i.e. carcinogenicity, lethal dose)
- studies on drug metabolism

Laboratory: exercise

And **you** ? Which practices would you ban in the laboratory?
to specify if this is a Good Laboratory Practice (GLP)

Lab flasks are not labeled

The same flask can be used for two different experiments

Raw data can be discarded after failure of experiment

Laboratory: exercise

And **you** ? Which practices would you ban in the laboratory?
to specify if this is a Good Laboratory Practice (GLP)

All answers are: NO

Lab flasks are not labeled

Correct. According to GLP, reagents should be labeled indicating identity (with concentration, if applicable), expiry date and storage conditions

The same flask can be used for two different experiments

What did the flask contain? If it is the test item, a new flask should be used for each study. If it is mobile phase/buffer solutions these may be used for different experiments but it should be documented in each study file

Raw data can be discarded after failure of experiment

Correct. All raw data should be maintained and if an experiment fails it should be mentioned on the data with reason why it failed, and the date and signature of responsible people

Eating and drinking in the lab

Involve QA only when study has been completed

All answers are: NO

Eating and drinking in the lab

Correct. Study personnel should take health precautions to minimise risk to themselves and to ensure integrity of the study

Involve QA only when study has been completed

Correct. QA is involved when receiving the draft study plan, in order to verify the phases that should be audited during the study (eventually perform vendor audits). QA checks if study plan is complete and verifies it is compliant to GLP and company's procedures. Finally QA also evaluates the coherence and the clarity/pertinence of the document


Clinical development

How do you demonstrate that the product is effective while being safe?

Clinical Development starts with the “first-in-man” (FIM) Phase

Pharma Industry/sponsor must demonstrate:

- **Positive Benefit/Risk**
  - **Safety**
  - **Efficacy**

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Clinical development

Driven by **Good Clinical Practice (GCP)** standards formulated by the International Conference on Harmonization (***ICH-GCP****), and consistent with the Declaration of Helsinki

Compliance with GCP provides public assurance

- **Protection** of Patients in Clinical Trials

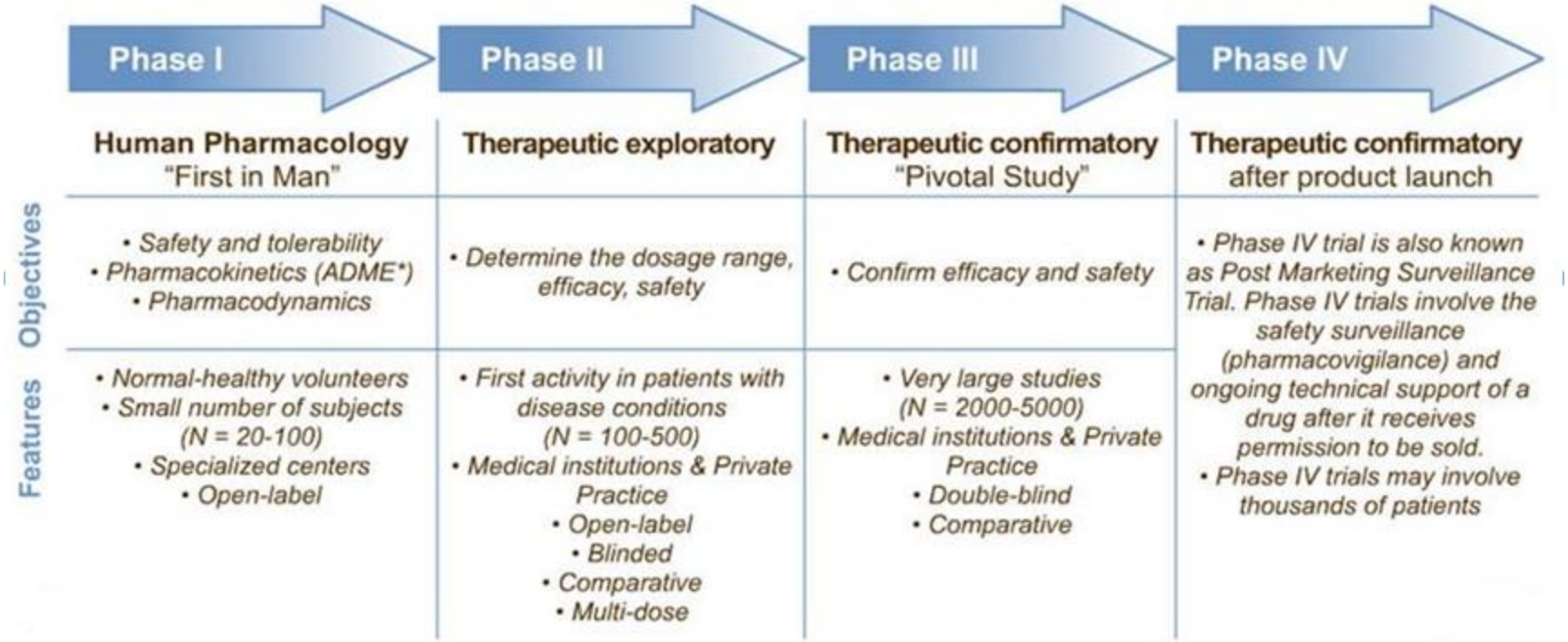
  Ensure that the rights, protection, integrity and confidentiality of the patient data are observed and respected

- **Quality** and **integrity** of the data collected
- **Reliability** of decision making regarding the approval of new medicines

*ICHE6(R1) guideline (under revision)

Clinical development

Clinical trial are commonly classified into 4 phases, developed over many years. When all Phases are successfully completed, the new medicine is evaluated by health authorities and approved for use in the population studied during clinical development



Clinical Development : Exercise

You have been invited to participate in a clinical trial …

Select what you expect from the informed consent process in accordance with Good Clinical Practice

I give my consent to participate

I am aware of the risks

I can take my dosage when I want

Clinical Development : Exercise

You have been invited to participate in a clinical trial …

Select what you expect from the informed consent process in accordance with Good Clinical Practice

Answers are: YES-YES-NO

I give my consent to participate

The trial participant is informed about her/his rights; emphasis is put on the participant's protection. The participant receives information on the study. The informed consent is documented and signatures are obtained

I am aware of the risks

The trial participant is fully informed about her/his rights, any foreseeable risks, expected benefits, and emergency contact information

I can take my dosage when I want

If the trial participant is not compliant regarding the intake of the Investigational Drug, he/she may not be included in the analyses

Clinical Development : Exercise

You have been invited to participate in a clinical trial …

Select what you expect from the informed consent process in accordance with Good Clinical Practice

I can stop whenever I want

I am informed of the latest news regarding the Investigational Product

Clinical Development : Exercise

You have been invited to participate in a clinical trial …

Select what you expect from the informed consent process in accordance with Good Clinical Practice

Answers are: YES-YES

I can stop whenever I want

It should be made clear that a participant may withdraw from a trial at any time without penalty

I am informed of the latest news regarding the Investigational Product

The informed consent must be updated if there are new developments that affect the safety and well-being of the participant or may affect his/her willingness to continue participation

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"How can I have the guarantee that each product will be of the same quality regardless of where or when it was manufactured?"

Here are some examples of manufacturing areas, where medicines are produced in large quantities:

The **quality** of the final product is guaranteed by the control of 5 critical parameters, **manpower, milieu, machines, methods** and **material**

This is the purpose of the **Good Manufacturing Practices (GMP)**

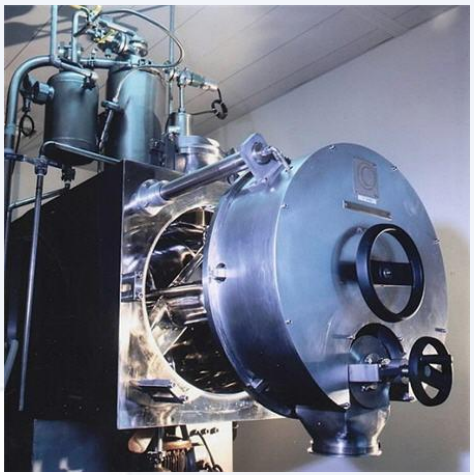
Learn more about these parameters:

t

1. People (**manpower**) must be competent for job, and trained accordingly

2. The **Milieu** (production environment) must not have an adverse impact on the quality of the product. Access to the manufacturing zone is restricted to authorised personnel.

3. Machines (any piece of equipment) that is used in the manufacturing or the control of the product must be calibrated and qualified in order to ensure that it will perform as expected and consistently produce reliable results



4. Methods encompass all the documentation (*Standard Operating Procedures, Manufacturing instructions, analytical methods*…) needed to ensure consistency. Records of activities are kept.

5. Materials must comply with their specifications and be correctly identified. Their consumption must be recorded and traceable

And you ?

If you want to visit a manufacturing plant, what should you pay attention to before entering the plant?

Identify the pictures where Good Manufacturing are followed:

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NO !

The cracks on the floor are a potential source of contamination

YES !

The operator wears appropriate clothes and accessories to protect the product from contamination

NO !

Trace of product and/or dust on the lid can cause cross-contamination between products.


Distribution

"I understand you take the necessary precautions during the manufacturing of the products, but what about the distribution? Can it also have an impact on the quality?"

Good Distribution Practices (GDP) are the guarantee that the **distribution** process has no negative impact on product from the Plant to the Patient

Some examples of domains that GDP cover :

- Cold chain
- Cross contamination
- Traceability

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The Pharma company's **responsibility is also engaged in the delivery** of the product to the patient

Therefore the Pharma company must ensure that the **storage conditions** are monitored during the distribution process to ensure they do not have an adverse effect on the product. This is particularly critical when the product must be stored under specific conditions of temperature and/or relative humidity.

Traceability is important to ensure a quick response in case of recall.

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"Can I **trust the information** I received from my physician or pharmacist about your product?"

Physicians are encouraged to prescribe the products in line with their **approved label/indication(s).**

Information provided by Pharma companies to healthcare professionals **must comply with strict regulations**

Prescription-only medicines may only be promoted to healthcare professionals and **not directly to patients** unless permitted by local laws (e.g. USA)

The information provided to physicians must be fair and **balanced**, which means reflecting both efficacy (clinical effects) and safety (side effects)

Promotion: exercise

What would you consider as acceptable practice ?

You have been asked if one of our products can be used for an indication that is not listed on the label. *Would you suggest they try it?*

In the USA I have seen a TV advertisement for the new antiepileptic product of a pharmaceutical company. *Could I see this in Europe?*

Promotion: exercise

What would you consider as acceptable practice ?

Answers are: NO-NO

You have been asked if one of our products can be used for an indication that is not listed on the label. *Would you suggest they try it?*

It is required that the pharmaceutical company only promotes its products according to the approved label indication(s)

In the USA I have seen a TV advertisement for the new antiepileptic product of a pharmaceutical company. *Could I see this in Europe?*

Direct to patient promotion of prescription-only medicine is not allowed in Europe

To support the development and manufacture of pharmaceutical drug substances (i.e., active pharmaceutical ingredients) and drug products, including biotechnology and biological products, throughout the product lifecycle

Standards included in ICH Q10 guideline

Quality system

"I understand everything you have explained so far…

What other safeguards do I have to ensure that I receive a high quality medication?"

Pharma companies have a **Quality System** in place

- Right the first time
- Continuous improvement, thanks to established and follow-up of Corrective Action & Preventive Actions (CAPA)
- Change control
- Internal Audit
- Quality Unit is independent and ensures Quality is built into systems
- Handling of product complaints

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"Everything you have told me so far is clear to me but can you prove that you have everything under control?"

Pharma companies have a Good Documentation system in place:

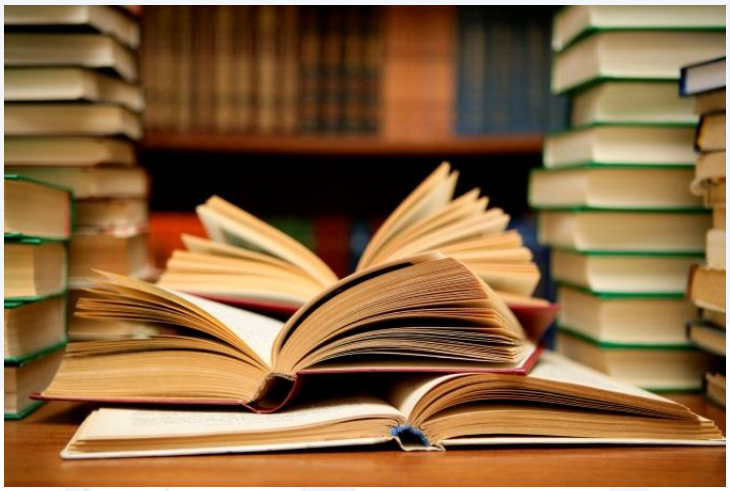
- Documents that can have an impact on the quality of the product are controlled, clearly identified, versioned, and copies/distribution are manage
- People understand the meaning of their signature
- The date format used is not ambiguous

These are the foundations of **Good Documentation Practices** together with records

Records demonstrating that activities were performed according to regulations must be kept. These are called “**raw data**”

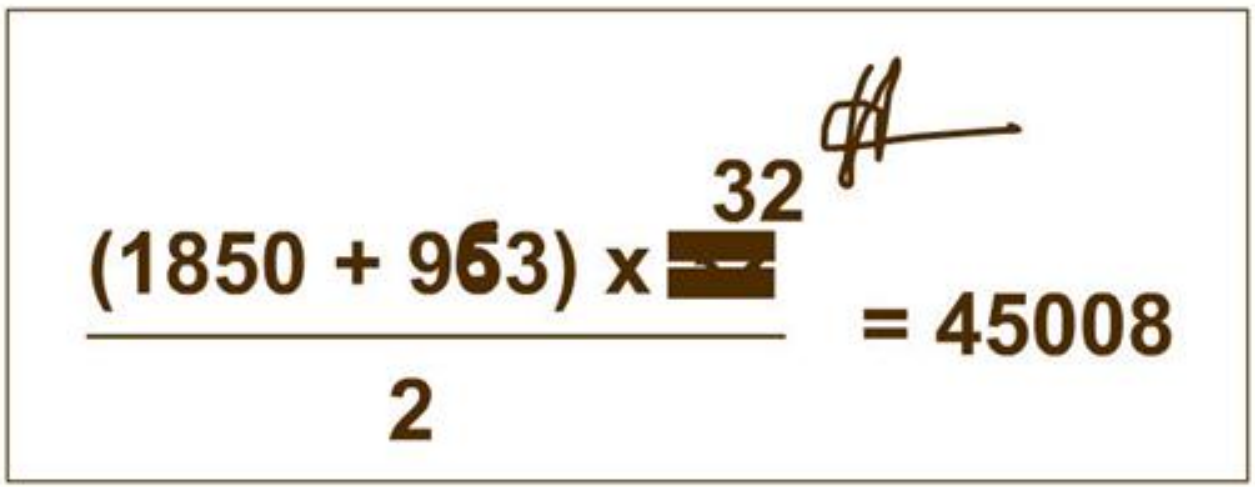
Raw data must be recorded with **indelible ink** at the time the task is performed

If an error is made, the **correction should be signed and dated**. The alteration should permit the reading of the original entry. Where appropriate, the alteration should be justified



Documentation: Exercise

What is wrong on this record? (how many errors?)



Answer:

Original data not legible anymore

Date missing

$$\frac{(1850 + 963) \times 32}{2} = 45008$$

Original data overwritten

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*"What happens if I experience a **side effect**?"*

- All patients have the potential to experience side effects also known as adverse events, through their use of pharmaceutical products
- All known adverse events associated with a medicine are collected by pharmaceutical companies
- Adverse event reporting is done through the lifecycle of the product and has to be reported to regulatory authorities
- If you become aware of an adverse event (side effect), you may want to report it to your general physician, your pharmacist or directly to your national reporting system

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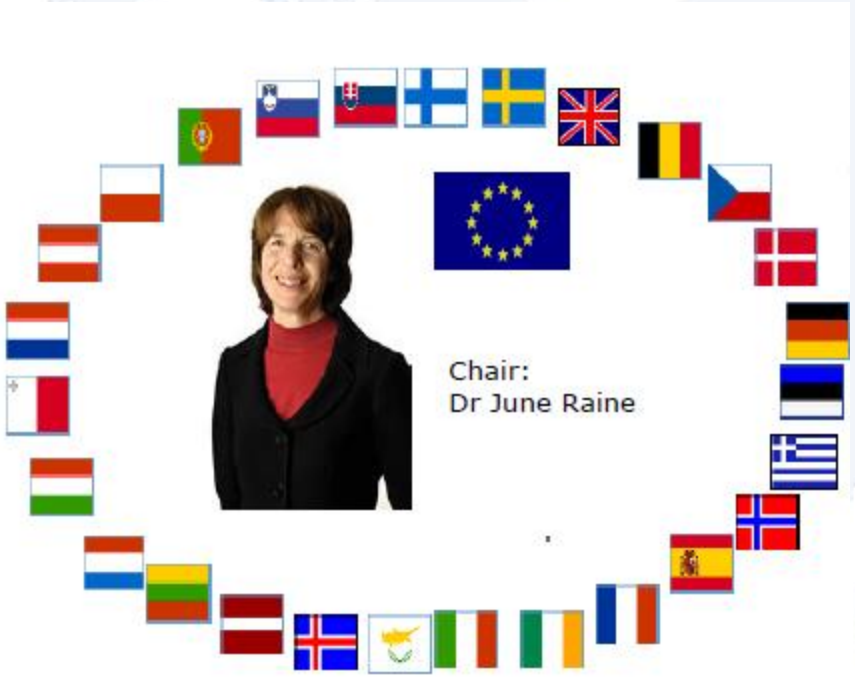
The PRAC at EMA

Pharmacovigilance Risk Assessment Committee

To assess and monitor safety issues of human medicines



- 1 member (+ 1 alternate) per Member State, plus Norway & Iceland
- 6 experts nominated by EC
- 1 member (+ 1 alternate) healthcare professionals
- 1 member (+ 1 alternate) patients organisations

Summary

The pharmaceutical industry is highly regulated

All employees are knowledgeable about GxP & Regulatory requirements

They know that they have to fulfil these requirements and all relevant procedures when performing their tasks to develop new medicines

Remember …

Patients are at the heart of the activities of the pharmaceutical industry.

Throughout their activity, chain from early research through manufacturing, to sales force activities, every employee is contributing to the improvement of the lives of people living with diseases

Overview

1. Regulatory affairs (RA) as an integral part of medicines development
2. Principles of GXP
3. What's new currently in Europe?
   - Earlier access to market
   - Data sharing/transparency
   - Paediatric development

Authorisation to Market: the legal framework

- **Full approval** based on a comprehensive set of data allowing appropriate Benefit/risk assessment
- **Approval under exceptional circumstances**
  - Must meet criteria to be met: rarity, medical ethics, state of scientific knowledge
  - Comprehensive data not available and cannot be provided
- **Conditional approval**
  - Comprehensive data not available; to be provided after approval
  - Must fulfil scope (orphan drugs, emergency threats, serious and life-threatening diseases)
  - Approval valid for 1 year, renewable

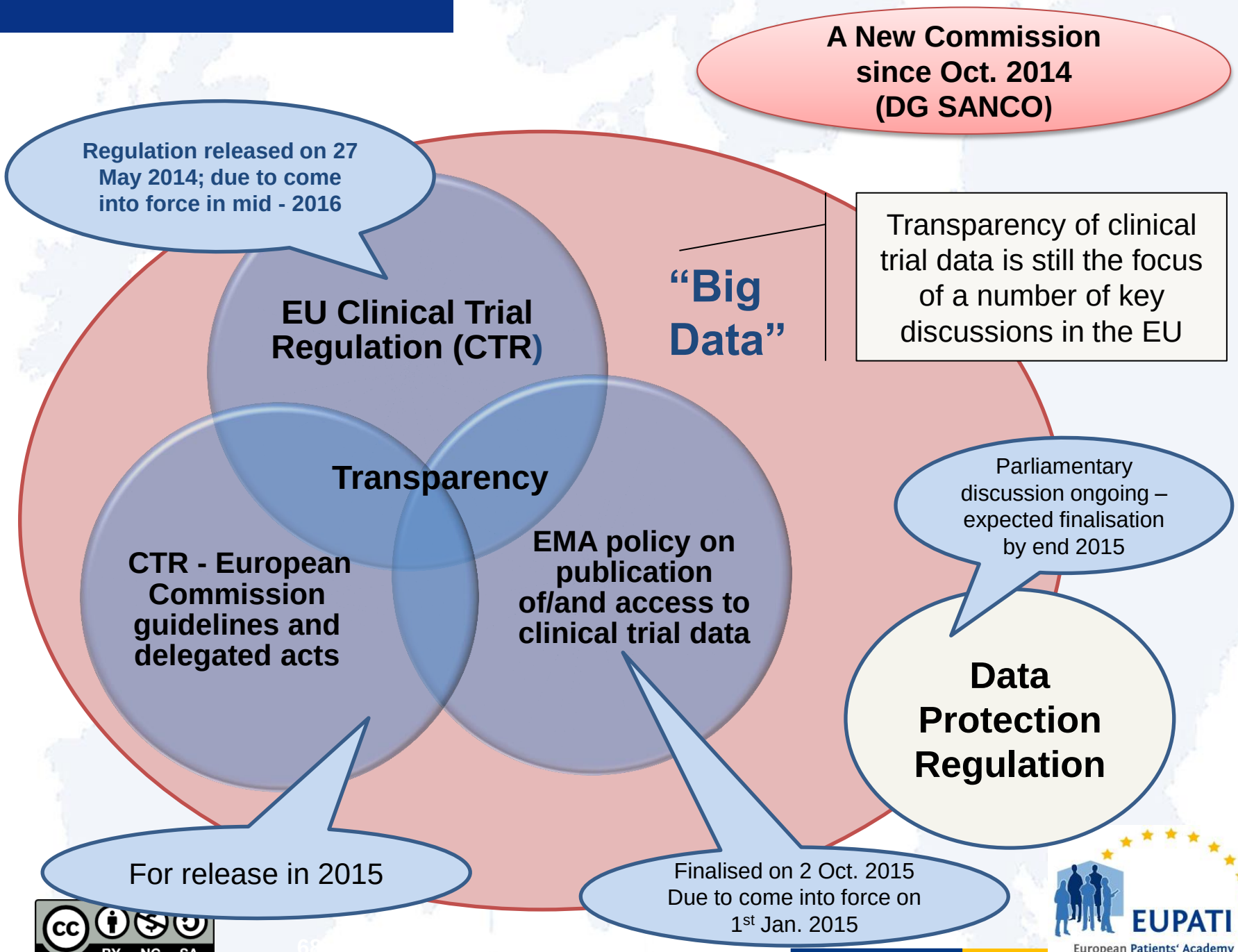
Some EU initiatives

Earlier access to market initiatives

- Compassionate use opinion granted by EMA
- French ATU system
- UK MHRA Early access Scheme
- EMA Adaptive Pathways Pilot

Innovative Medicines Initiatives (IMI) – public private partnerships

- EUPATI
- ADAPT-SMART
- Benefit/risk – patient elicitation



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TRANSPARENCY IN EUROPE

The CT Regulation

Scope:

- Interventional CTs conducted in the EU

Implementation:

- Implementation linked to the availability of new EU portal/database – mid 2016
- Stepwise transition from CT Dir. to Reg.
- CTR is binding in its entirety and directly applicable in all MSs

Annexes to the Regulation:

- Application dossier
- Safety reporting
- Labelling
- Summary & lay summary of results
- Review clause – every 5 years

The EMA Policy on publication of clinical data

Scope:

- Clinical data submitted via the CP
- Out of scope: clinical data held by the EMA
  - for applications received before 1 Jan. 2015
  - for extension of indication (EoI) and line extension (LE) applications submitted before 1 July 2015

Implementation - by phases:

- 1st phase starts on 1 Jan. 2015, when EMA will publish CRs supporting MAAs submitted after this date
- Data will only start to become accessible once the final decision has been reached by the EC, i.e. ~ 18 months
- 2nd phase starts on 1 July 2015 - for Line Extension and Extension of Indication of already approved medicines

Both are complementary…

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Clinical data and public disclosure

- Summary results of CTs conducted in Europe must be submitted to EudraCT database within one year (6 months for paediatrics) after CT completion (LPLV), and disclose to the public via the EU Registry

- Summary results of CTs in Lay language

- Clinical data (some part of CTD including CSRs) will be publicly disclosed after approval

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Paediatric Regulation

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 December 2006

on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

THE EUROPEAN PARLIAMENT AND T
PEAN UNION,

Having regard to the Treaty estal
munity, and in particular Article 95

Having regard to the proposal from

s to facilitate the development and
cinal products for use in the paedia-
sure that medicinal products used to
population are subject to ethical
lity and are appropriately authorised
tric population, and to improve the
on the use of medicinal products in

EU Paediatric Regulation – the 3 Pilars

- Obligation : Paediatric Investigation Plan [PIP] (agreed and compliant in its conduct)

- Reward [incentives] for studies conducted (6 months patent extension, only once)

- Paediatric Committee [PDCO] at the EMEA (advisory body to EMA in its executive role)

Key objectives of the Regulation

- **To improve the health of the children of Europe, by:**
  - increasing high quality research for medicinal products for children
  - promoting the development and authorization of such medicines at the EU level
  - improving the information on medicines designed for children
- **While *avoiding unnecessary studies* in children and not delaying the authorization of medicines for adults**

Key elements of the regulation

- Mandatory paediatric development for new products according to a PIP agreed upon by the PDCO (possible deferrals or waivers)
- Mandatory submission of paediatric data when filing new applications unless waiver or deferral approved by the PDCO
- New Marketing Authorisation Procedure for off-patent products (PUMA)

Acronyms

CHMP	Committee for Medicinal Products for Human Use
CP	Centralised Procedure
eCTD	electronic Common Technical Document
DMF	Drug Master File
EMA	European Medicines Agency
FDA	Food and Drug Administration - USA
IMI	Innovative Medicines Initiative
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Health Care Products Agency
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PMDA	Pharmaceuticals and Medical Devices Agency - Japan
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan