Role of Regulatory Affairs in Clinical Drug Development

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PPD Scandinavia AB, Stockholm, Sweden

HELPING DELIVER LIFE
CHANGING THERAPIES

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Short self introduction

Current role:

Regulatory Affairs Specialist

Pharmaceutical Product Development (**PPD**), Stockholm, Sweden

Previous roles:

- Consultant Regulatory Operations Manager
- Consultant Regulatory Labelling Proofreader

AstraZeneca, Mölndal, Sweden

Education:

- Ph.D. in Neurobiology of Alzheimer's Disease, Karolinska Institutet, Sweden
- Masters in Medical Biosciences, Linköpings Universitet, Sweden

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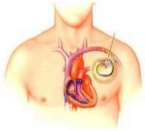
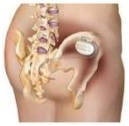
Pharmaceutical Drug

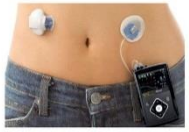
Devices/Implants



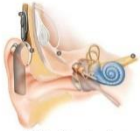
(a) Pacemaker



(b) Neurostimulator



(c) Insulin Pump



(d) Cochlear Implant

Pharmaceutical Drug

Devices/Implants

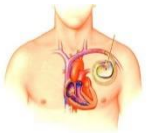
AI in Healthcare

Gene Editing in Humans??

Future

Pharmaceutical Drug

Devices/Implants



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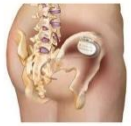

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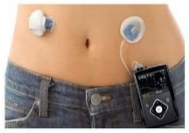

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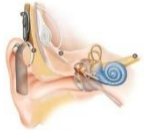

(d) Cochlear Implant

AI in Healthcare

Gene Editing in Humans??

Future

Pharmaceutical drug falls under the classification of a ”Medicinal Product”

Medicinal Product

A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action (**E**uropean **M**edicines **A**gency (**EMA**) definition)

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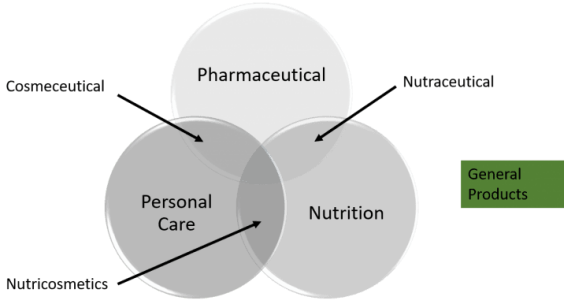


Borderline Products[1]

The regulatory status of products on the borderline between medicinal products and food supplements, biocides, cosmetic products, medical devices or 'general products may not be immediately obvious.

I. Regulations in Healthcare- A brief history

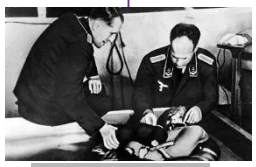
Drug Regulations- 20th Century

Nazi era- 1933-1945

Thalidomide- 1956-61

Tuskegee Syphilis Study- 1932-71

Drug Regulations- 20th Century



Nazi era- 1933-1945

Thalidomide- 1956-61

Tuskegee Syphilis Study- 1932-71

Vulnerable population and misled callous experimentalists

Drug Regulations- 20th Century

Nazi era- 1933-1945

Thalidomide- 1956-61

Tuskegee Syphilis Study- 1932-71

Nuremberg Code- 1947

WORLD MEDICAL ASSOCIATION

Declaration of Helsinki- 1964

Bellmont Report- 1979

USA- 1981

Nordics - 1989

World Health Organization

WHO-GCP 1992

ICH

ICH-GCP 1996

Declaration of Helsinki

Declaration of Helsinki

+ Cornerstone document on human research ethics

+ Categorically states that the interest, integrity, safety, informed/voluntary decision of a research participant surpasses the interest of research outcome, of the society or science

+ Revisions- 7 revisions till date with the last revision made in 2013

+ Each revision emboldens our understanding and acceptance of human rights/dignity

International Conference of Harmonisation - Good Clinical Practice (ICH-GCP)

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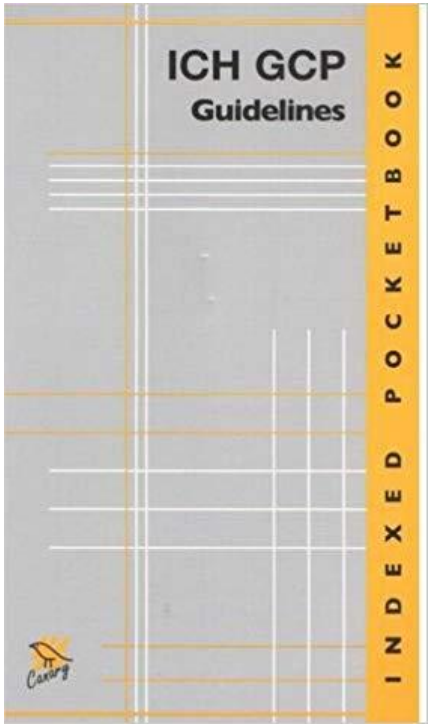


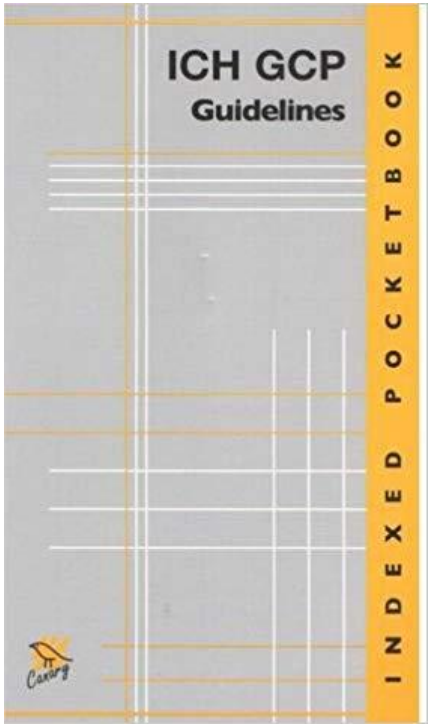
- To harmonise the GCP regulation in:

USA

European Union

JAPAN

International Conference of Harmonisation - Good Clinical Practice (ICH-GCP)



- To harmonise the GCP regulation in:
  - **USA**
  - **European Union**
  - **JAPAN**

+ In order to facilitate mutual acceptance of clinical data by the regulatory authorities in these jurisdictions

+ More than 95% of new medicines are worked out in ICH "regions" and follows ICH GCP guidelines

The patient’s integrity and safety

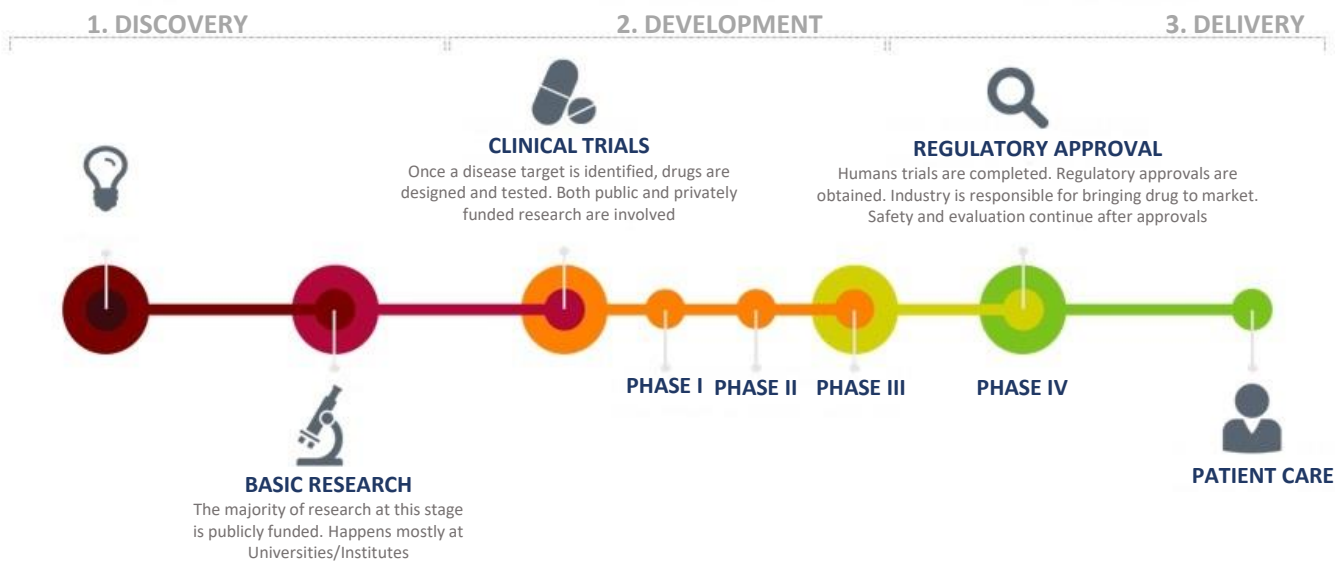
The integrity of data

Common practice and high standard

ICH-GCP

II. Overview of Drug Development

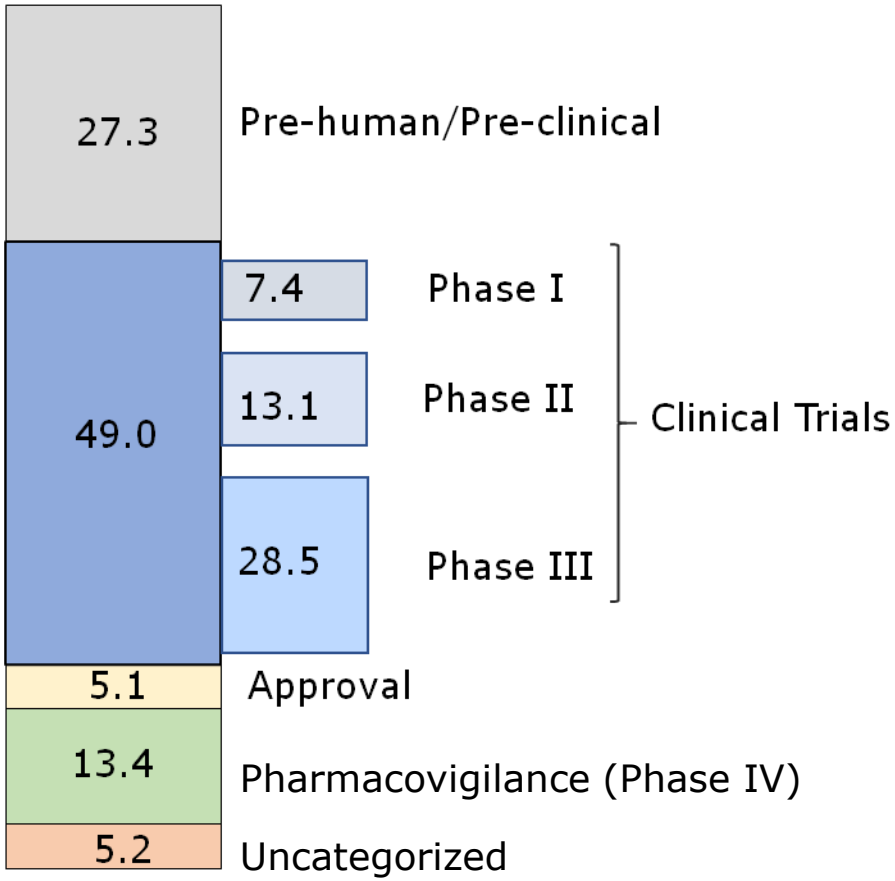
Drug discovery to delivery



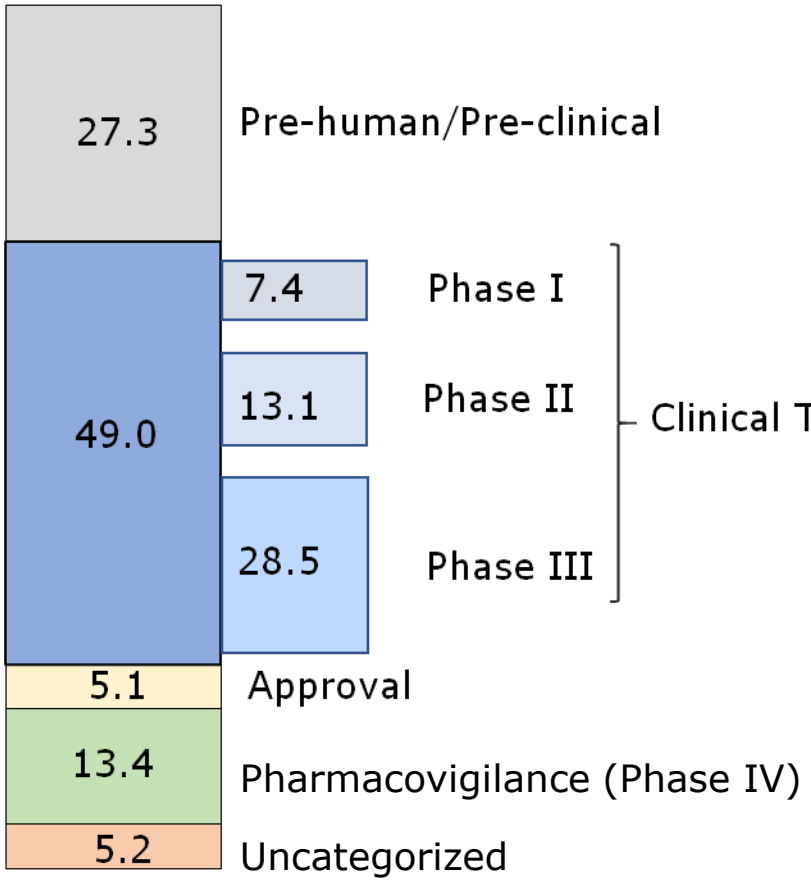
Clinical Trials- Different stages

Phase I	Phase II	Phase III	Phase IV
20-80 participants	**100-300 participants**	**1,000-3,000 participants**	**Thousands of participants**
Up to several months	Up to (2) years	One (1) - Four (4) years	One (1) year +
Studies the safety of medication/treatment	Studies the efficacy	Studies the safety, efficacy and dosing	Studies the long-term effectiveness; cost effectiveness
70% success rate	33% success rate	25-30% success rate	70-90% success rate

Major costs during drug development



Major costs during drug development



- **Internal (Sponsor's in-house) or operational**
  - Trial monitors, study/project managers, data managers, regulatory affairs
  - Medical doctors
  - Data management (can be external)
  - Statisticians
  - Trial report (medical) writers
  - Study materials
  - Drug production
- **External**
  - Investigator fees
  - Subject fees
  - Clinical Research Organization (CRO monitoring: but can perform many tasks)
  - Test procedure costs
  - Meetings & Travel

III. Clinical Trials and Reg Affairs

+ Clinical Trials is the centerpiece in drug development and is governed by Good Clinical Practice (GCP) principles & other regulatory requirements

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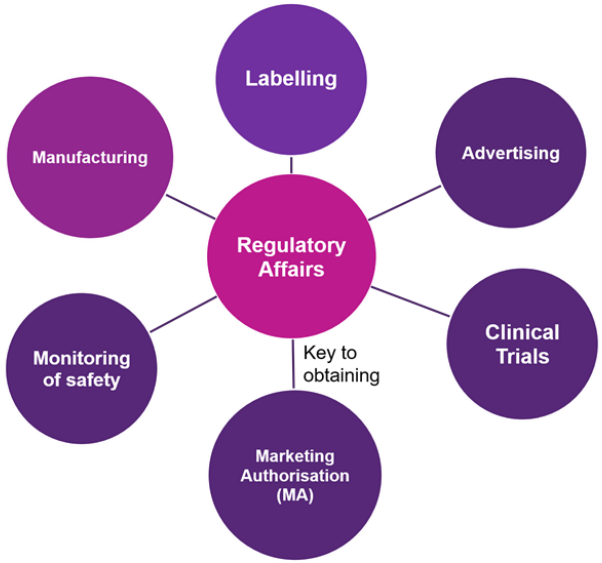
+ Regulatory Affairs is an intermediate field between the pharmaceutical industry and health authorities that assesses quality, safety & efficacy of medicinal products throughout their lifespan



What do regulatory agencies do – Clinical Trials

Regulatory Agency (RA)

Also referred to as Competent Authority (CA), Health Authority (HA), Ministry of Health (MoH) in some countries

Review essential documents and give decisions

Perform GCP inspections and end of trials

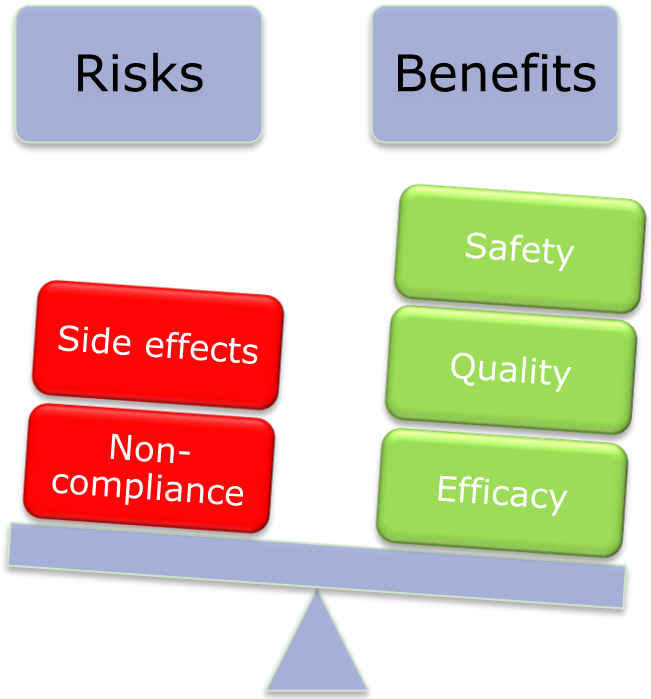
Assess robustness of evidence and safety all throughout

Before clinical trials

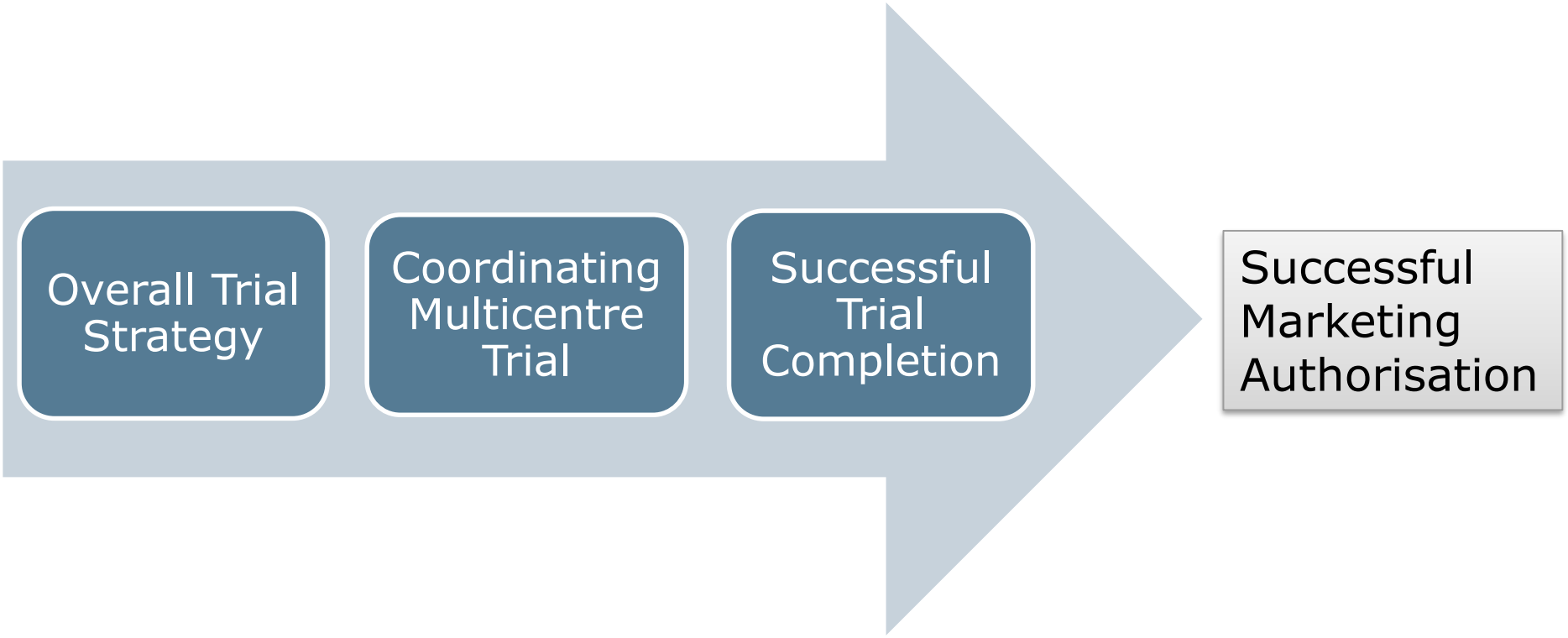
During clinical trials

After clinical trials

What do regulatory professionals ensure



Why do you need regulatory support



I. Clinical Trials in Europe

Directive 2001/20/EC

+ The current directive governs rules around clinical trials in the EU and applies to all clinical studies on humans

+ Came into force in 2004 as a first step to harmonize processes and requirements for clinical trial authorizations in EU member states

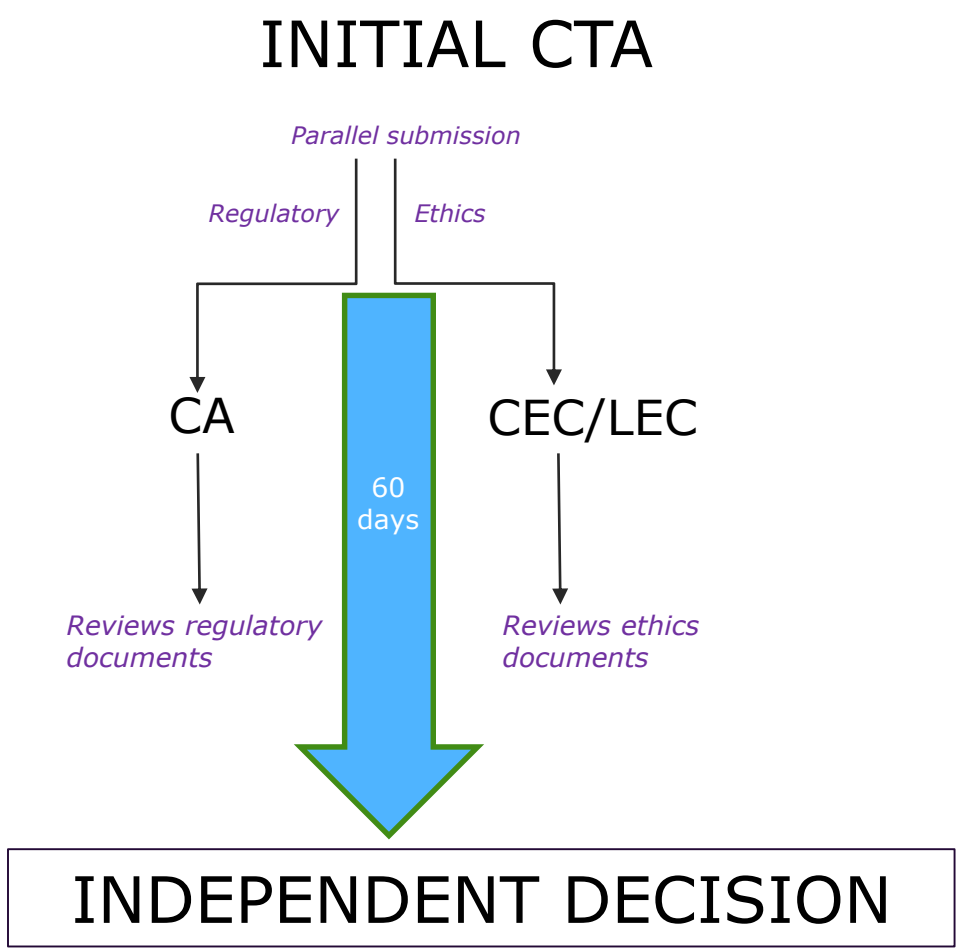
+ Is implemented into national laws of EU member states by their respective Competent Authorities (**CA**) and Ethics Committees (**EC**)

Clinical Trials Regulation (EC) No. 536/2014

Clinical Trials Regulation (EC) No. 536/2014

- Shall overwrite the existing directive and expected to be implemented by 2019 – but delayed – 2021?
- Objective: Make EU attractive for R&D
- Features[2]
  - *Single e-submission to all Concerned Member States (CMS)*
  - *Harmonised electronic submission and assessment process for clinical trials conducted in multiple Member States; (covering both regulatory and EC approval requests)*
  - *Improved collaboration, information-sharing and decision-making between and within Member States;*
  - *Increased transparency of information on clinical trials;*
  - *Highest standards of safety for all participants in EU clinical trials*

Initial Clinical Trial Application (CTA) process in the EU



Types of submissions to a Regulatory Agency - In relation to Clinical Trials

Clinical Trial Application (CTA)

Permission to start a clinical trial

Types of submissions to a Regulatory Agency - In relation to Clinical Trials

Clinical Trial Application (CTA)

Permission to start a clinical trial

During a Clinical Trial

Substantial/Non substantial amendments

Annual Safety Report

Types of submissions to a Regulatory Agency - In relation to Clinical Trials

Clinical Trial Application (CTA)

Permission to start a clinical trial

During a Clinical Trial

Substantial/Non substantial amendments

Annual Safety Report

At the end of a Clinical Trial

End of Trial Form

Clinical Trial Application (CTA)

Clinical Trial Application (CTA)

+ Cover letter with EudraCT number and Study Protocol number
+ Application form as pdf signed by the sponsor
+ XML-file
+ Protocol with current amendment, signed by sponsor and investigator
+ Investigator's Brochure (IB) and/or Summary of Product Characteristics (SmPC)

Clinical Trial Application (CTA) - continuation

+ Investigational Medicinal Product Dossier (IMPD)
  - *Quality data/ Manufacture / Control*
  - *Non-clinical pharmacology and toxicology data*
  - *Previous clinical trial and human experience*
  - *Overall Risk Benefit Assessment*

Clinical Trial Application (CTA) - continuation

+ Investigational Medicinal Product Dossier (IMPD)
  - *Quality data/ Manufacture / Control*
  - *Non-clinical pharmacology and toxicology data*
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  - *Overall Risk Benefit Assessment*

+ Labelling
  - *Sponsor contact details*
  - *Name of the drug, strength, dosage form, route of administration, quantity etc*
  - *Trial reference code, patient number, investigator's name*
  - *Batch number, expiry date, directions for use, storage conditions*
  - *Warnings: "Only for Clinical trial" and "Out of reach of children"*

Clinical Trial Application (CTA) - continuation

- Investigational Medicinal Product Dossier (IMPD)
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- GMP certificates and EC opinion if available

During a Clinical Trial - Amendments

During a Clinical Trial - Amendments

+ If there are substantial amendments done, then it has to be submitted to the concerned CA

+ Substantial/Non-substantial ? Sponsor decision based on safety and integrity of trial participants

+ All amendments has to be recorded and archived properly. Should be produced on request at the time of GCP inspection

During a Clinical Trial - Annual Safety Report

+ For ongoing trials, an annual safety up-date needs to be provided to CAs

+ Includes summary of all SAEs and SUSARs

End of Trial

+ Notify the respective CA and EudraCT with the ”End of Trial” form

+ If the trial ended prematurely, there need to be a justification, information on the number of patients receiving treatment at the time of termination, and other relevant information

+ When the trial has ended globally, no special need to notify the CA again

GCP inspection - Things to keep in mind

+ Declaration of Helsinki
+ GCP (ICH, WHO or other)
+ Essential documents and TMF
+ Local laws and regulations
  * *Clinical trials*
  * *Ethics*
  * *Medical care and records*
  * *Secrecy and confidentiality*

GCP inspection - Things to keep in mind

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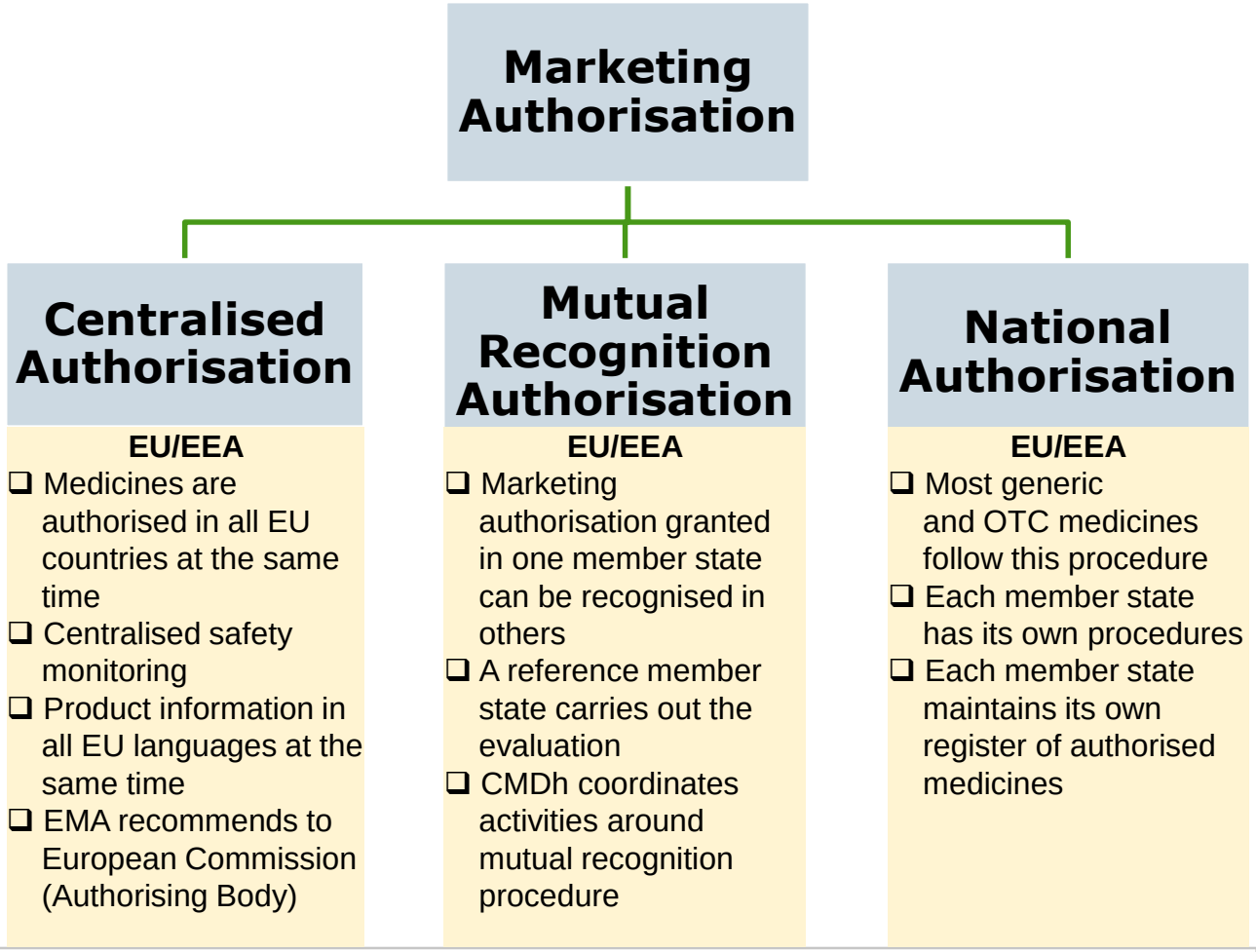
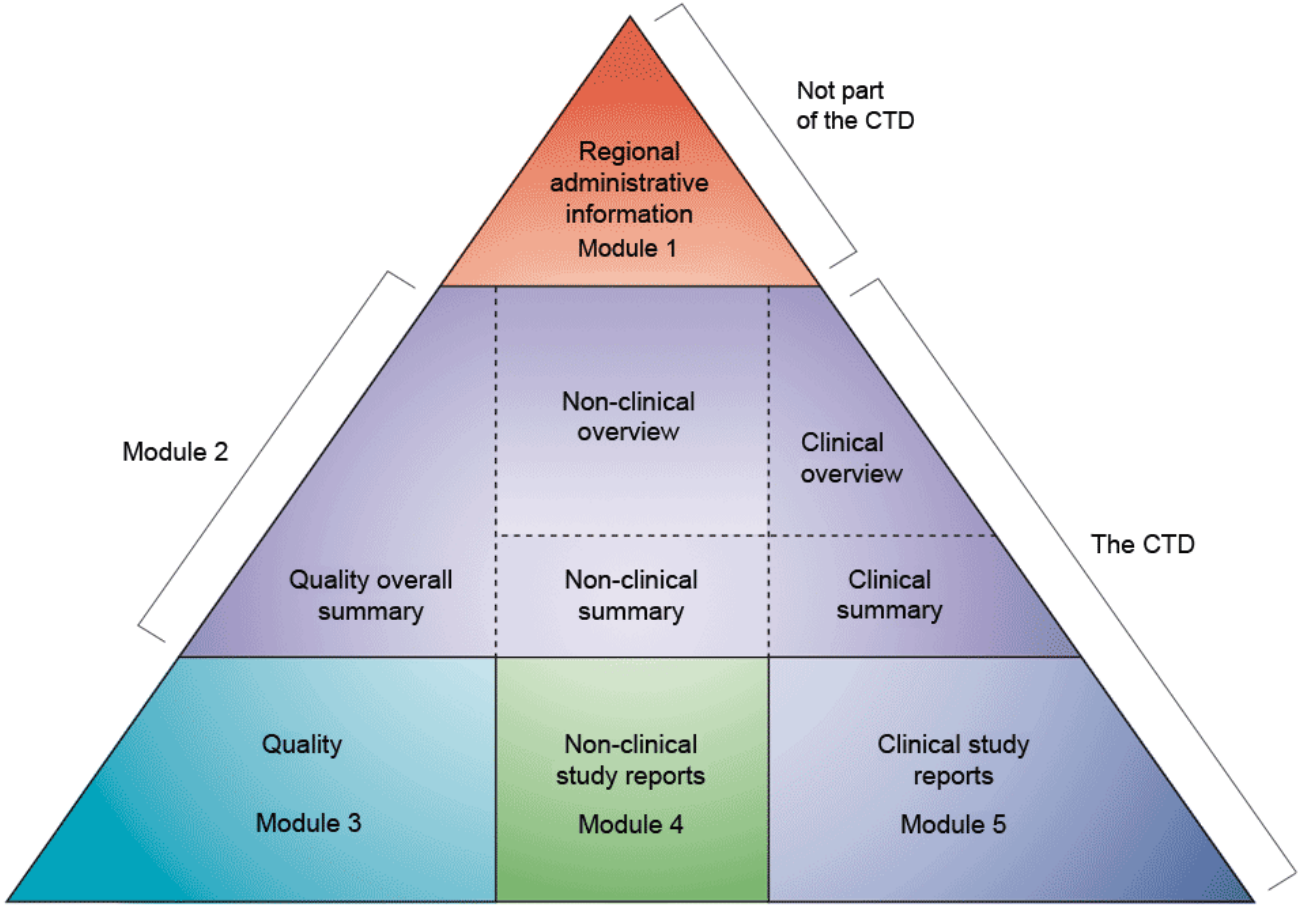
  * *Ethics*
  * *Medical care and records*
  * *Secrecy and confidentiality*

+ Sponsor site
+ Investigation site
+ CRO
+ Manufacturing sites
+ Biobanks/Sample storage sites

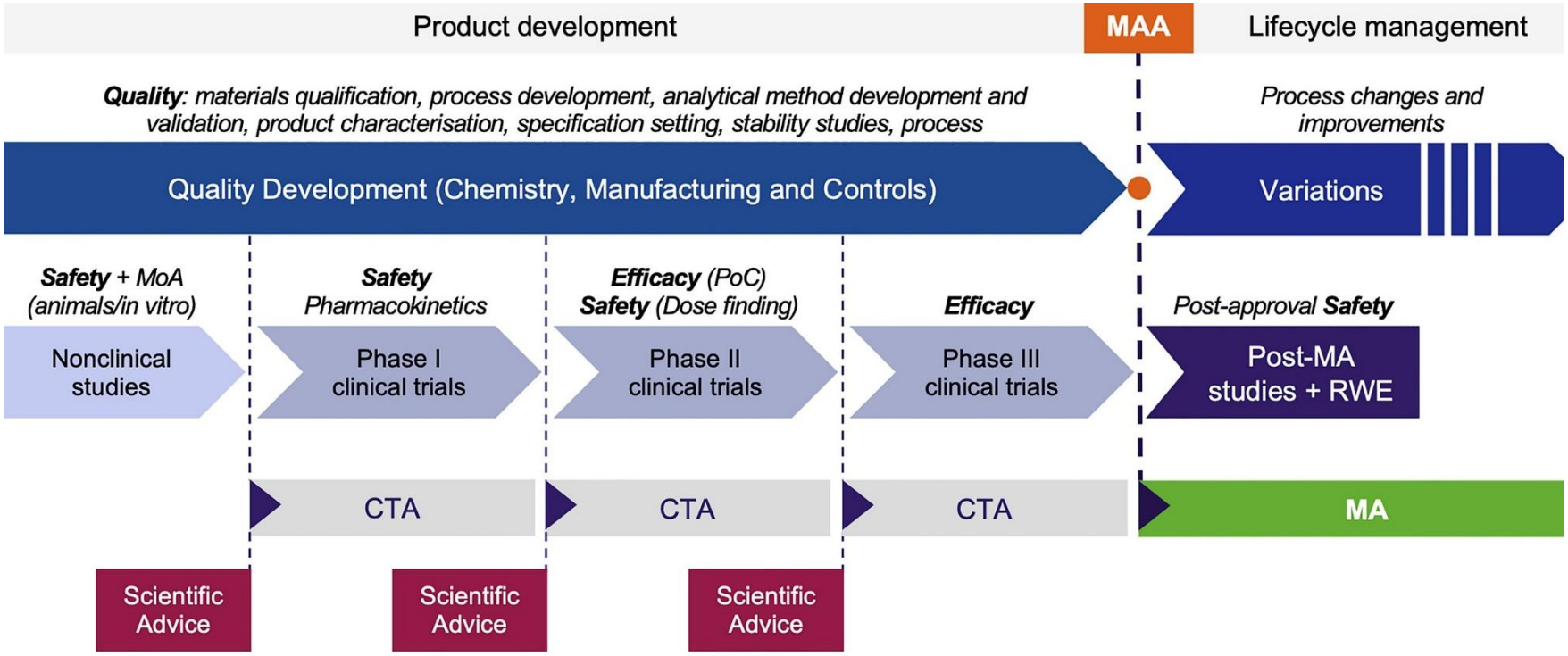
What happens when Clinical Trials are succesfully completed – EU/EEA



Marketing Authorisation Application – Common Technical Document (CTD)



Summary - Product Development to Marketing-EU



II. Clinical Trials in the USA

Clinical Trials in the US

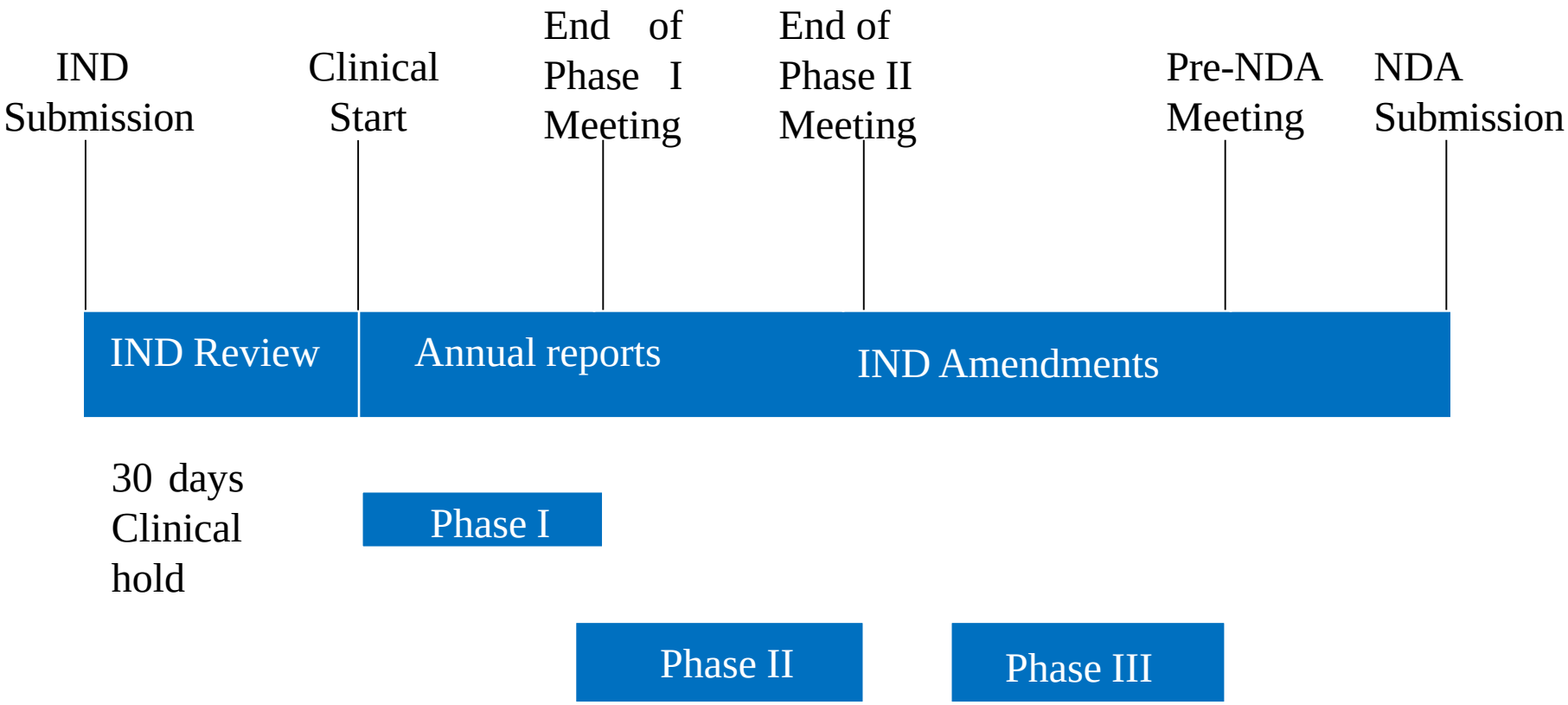
- An Investigative New Drug (IND) Application is required to be submitted to the FDA prior to start of a Clinical Trial
- FDA and OHRP are two regulatory agencies monitoring CTs
- IND Application contains
  - *Preclinical Testing section that includes animal studies pharmacology and toxicology*
  - *Manufacturing Information incl. CMC details*
  - *Investigator Information*
  - *Clinical Trials Protocols*
  - *Other essential documents incl. IRB review and opinion*

Clinical Trials in the US- Continuation

- Pre-IND meeting- highly recommended by the FDA
  - *Discuss drug development plan- gain FDA support*
  - *Discuss topics not clearly covered by FDA guidance documents*

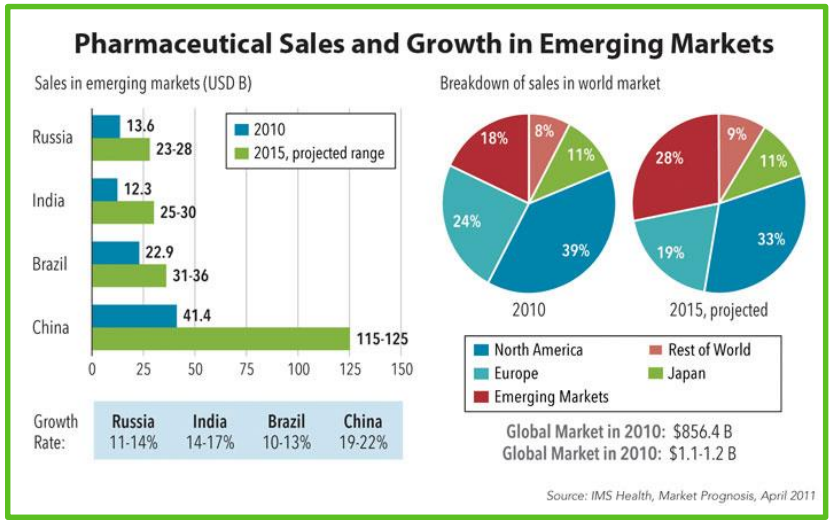
- End of Phase 1 /EOP1) meeting – not very common
  - *Review and agree Phase 2 study designs*
  - *FDA recommends only requesting EOP1 meetings for life-threatening/debilitating indications, especially if approval based on Phase trials or accelerated approval*

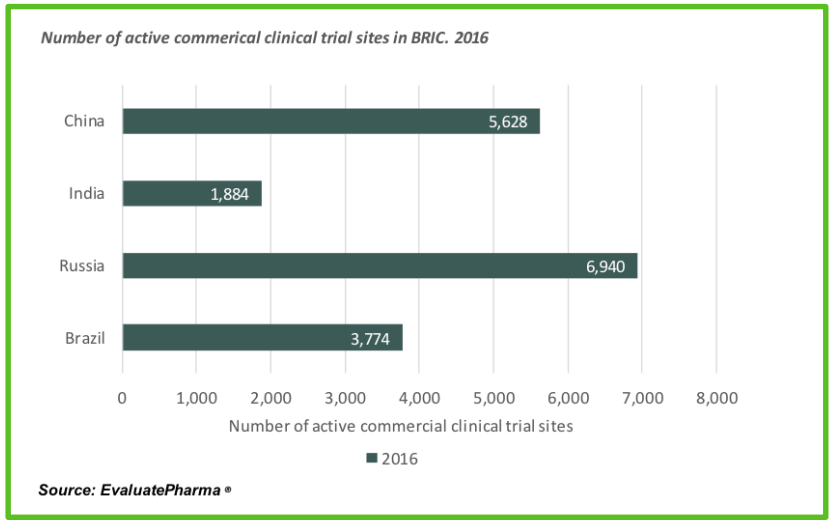
Summary - Product Development to Marketing- US



Clinical Trials in Emerging Markets

Clinical Trials in Emerging Markets





+ In 2006, commercial Clinical Trials were coducted in 92 countries, which jumped to 140 countries in 2016[3]

Clinical Trials in Emerging Markets- Continuation

+ Offer advantages such as broader population base to work with

+ Regulatory considerations vary among countries and choosing an emerging market for Clinical Trials can depend on various factors

+ Countries such as China, Taiwan, Russia, India, Vietnam require local clinical data as a part of MAA[4]

+ Key challenges: Non-compliance with ICH-GCP, GMP, bureaucracy, corruption among others

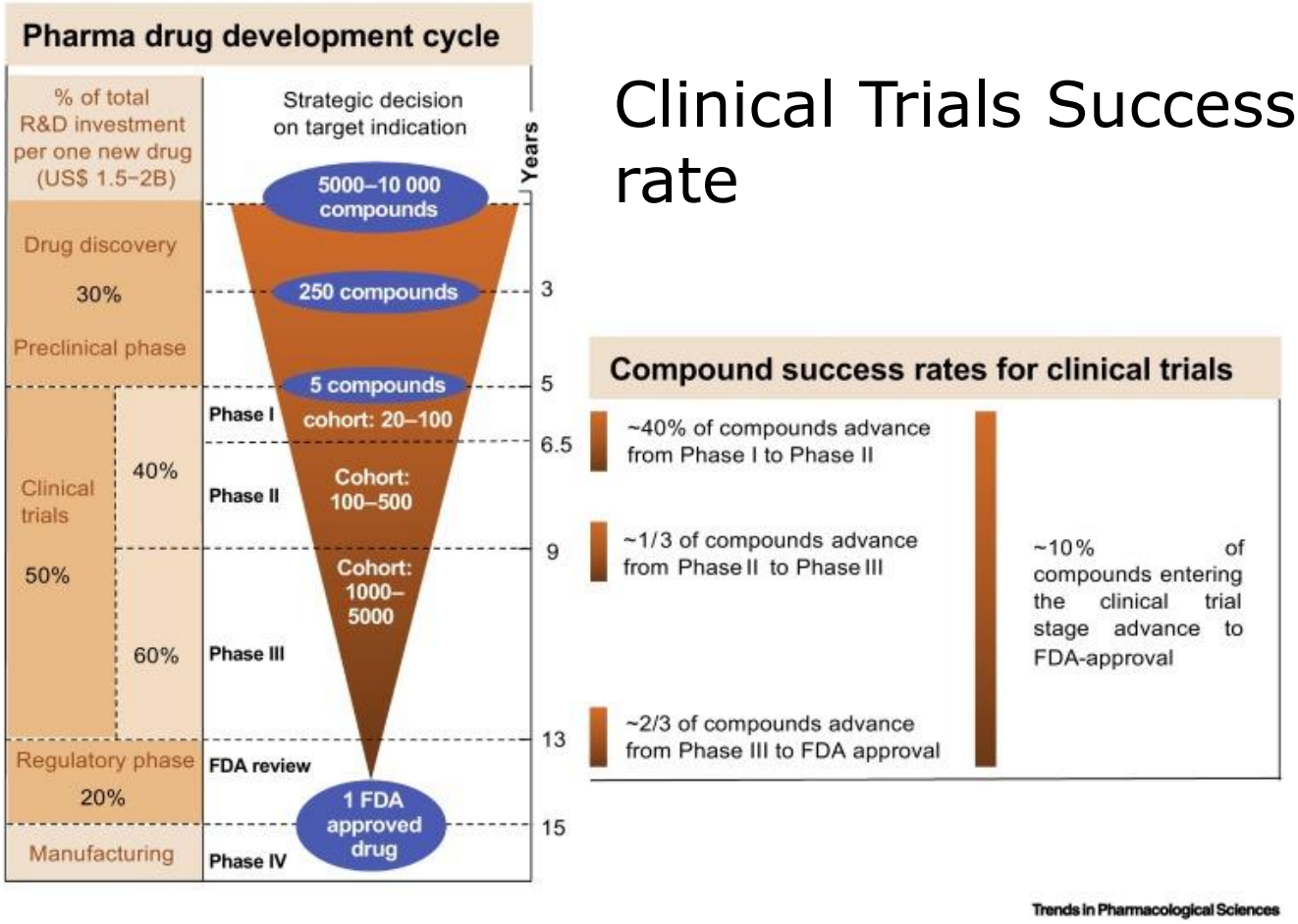
Comparison of CTA requirements in some Emerging Markets[4]

Country	Estimated number of patients for stand-alone registration studies*	Estimated number of patients if participated in phase 2 to phase 3	Regulatory approval time for CTA (months)	Comments, special requirements
China	100–chemical 300–biologics	Variable depending on number of Chinese in global studies	16–22	Extensive CMC section; CTA similar to full MAA; extensive quality testing upfront as part of CTA approval process (see Notes a–c, e–f); EC approval after agency approval
India	100–200	0–100	9–12	New CMC regulations require more information than before (see Notes d–f); EC approval in parallel with agency approval
S. Korea	100	0–50	2–6	Straightforward CTA approval process; EC approval in parallel with agency approval
Taiwan	0–50	0–20	4–6	Straightforward CTA approval process; EC approval in parallel with agency approval
Russia	No guidance	No guidance	2–4	Inclusion Russian sites in global development program exempt from mandatory local pre–registration inspection; EC same application as CTA
Brazil	Not required	–	6–8	Straight forward CTA approval process; Sequential review process, Local EC first, then National EC (CONEP) and agency (ANVISA) in parallel.
Mexico	Not required	–	3–4	Straightforward CTA approval process Sequential process, EC first, then agency (COFEPRIS)
Argentina	Not required	–	4–5	Straightforward CTA approval process Sequential review process, EC first, then agency (ANMAT).
S. Africa	Not required	–	4–6	Straight forward CTA approval process; Pre–defined submission deadlines to MCC, typically 6 review cycles per year. EC approval in parallel with agency approval
Israel	Not required	–	3–4	Straight forward CTA approval process; Sequential review process,EC first and agency review second IF EC decides agency review is required.

Singh and Wang. Elsevier 2013

IV. Regulatory challenges

Regulatory challenges- Sponsor perspective



Clinical Trials Success rate

Regulatory challenges- Sponsor perspective

Reasons for failure

+ Failure to demonstrate efficacy and safety
+ Financial impact- Unplanned costs
+ Eligibility criteria
+ Patient recruitment
+ Respecting the patient’s concern
+ Poor recruitment, dropout and underpowered trials
+ Employing quantitative measures
+ Patient time investment

Regulatory challenges- Patient/User perspective

+ Political decisons impact regulations- Pricing, safety monitoring etc

Regulatory Focus™ > News Articles > Major Deregulation? FDA Withdraws Several Rules and Regulations Related to Medical Products

Major Deregulation? FDA Withdraws Several Rules and Regulations Related to Medical Products

Posted 29 November 2017 | By Zachary Brennan

Almost a year ago, President Donald Trump told pharmaceutical executives that his administration would cut 75% to 80% of FDA regulations, "at a level no one has ever seen before."

Since those comments last January, the US Food and Drug Administration (FDA) has withdrawn the most rulemakings of any Department of Health and Human Services (HHS) agency, though only a handful are related to medical products (the others are tobacco related) and it's unclear how the withdrawal of these proposals and regulations so far in 2017 will impact patient safety or industry burdens.

What are Brexit contingency plans for pharmaceutical industry?

With fears over manufacturing costs and future investment, here's what firms are doing

+ Advancements in Science and Technology

POINT/COUNTERPOINT

Point: Should AI Technology Be Regulated?: Yes, and Here's How

By Oren Etzioni
Communications of the ACM, December 2018, Vol. 61 No. 12, Pages 30-32
10.1145/3197382
Comments

VIEW AS: SHARE:

Government regulation is necessary to prevent harm. But regulation is also a blunt and slow-moving instrument that is easily subject to political interference and distortion. When

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The Legal and Regulatory Context for Human Gene Editing

BY R. ALTA CHARO

The potential use of human gene editing is stimulating discussions and responses in every country. I will attempt to provide an overview of legal and regulatory initiatives around the globe. But I need to note that we are talking not only about government when we talk about law, regulation, and biotechnology. We are really talking essentially about an ecosystem that is made up of government, the public, and private industry, which produces innovative products based on the basic science and applied research coming out of our universities.

Sources: 6, 7, 8 and 9 (References)

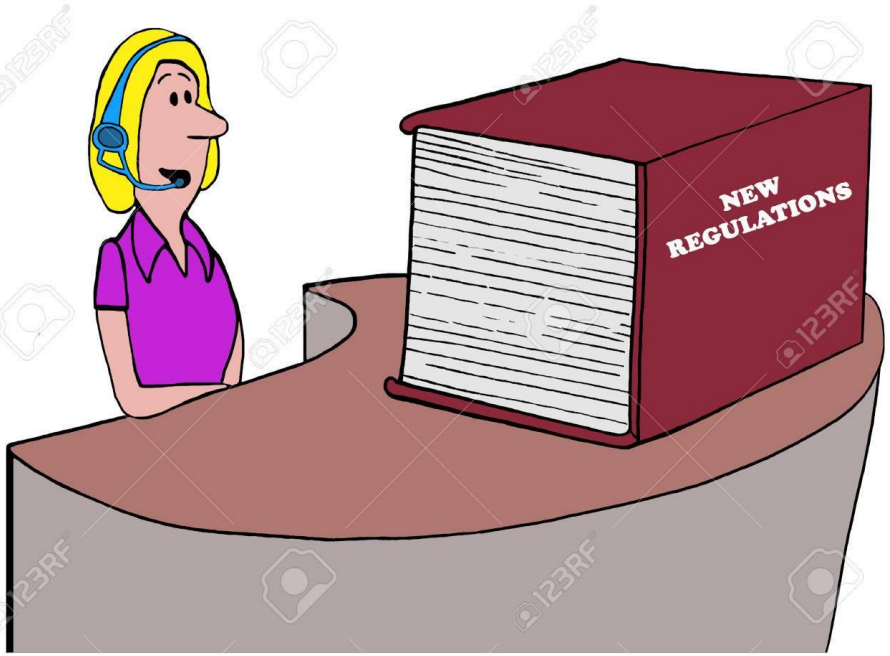
If you like learn more about regulatory affairs

+ Organizations
  i. TOPRA, UK
  ii. RAPS, USA
  iii. Läkemedelsakademin, Sweden
  iv. Legemiddelverket, Norway

+ Courses
  i. Essentials of European Pharma Reg Affairs, 27 Feb 2020, TOPRA, London, UK
  ii. GMP meets Regulatory Affairs- 28/29 May 2020, ECA Academy, Hamburg, Germany
  iii. Regulatory Affairs Cetificate: Pharmaceuticals, RAPS- Online
  iv. Whitehall training: Online

Thank you

Regulatory affairs



"Give me a couple years, and I can answer your simple question about the new regulations."

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