A Pharmaceutical Translator's Guide to the Drug Discovery Industry

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Webinar objectives

- To provide a condensed overview of drug discovery by the biopharmaceutical industry
- To explain key technical jargon
- To provide resources for further reference
- To host a general discussion with participants

This webinar deals with English only

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Agenda

1) The products of the drug discovery industry

2) Some basic science

- To explain differences between drug types
- To explain how weights and measures are written out
- To explain drug nomenclature

3) The drug discovery pipeline

- Drug discovery
- Preclinical development of drug candidates
- Clinical trials
- Marketing authorization

4) Questions and discussion

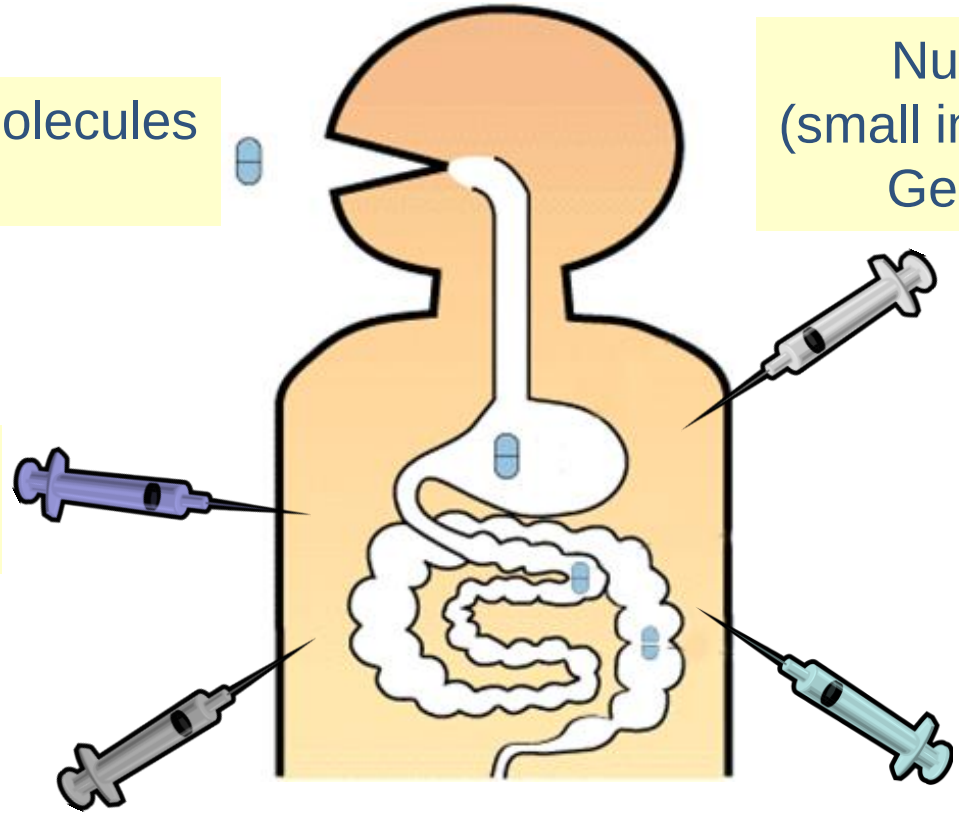
Drugs and drug targets

Drug molecules bind to a drug target to reduce or increase the activity of the target

Different types of drug molecule

Small chemical molecules
(aspirin)

Nucleic acids
(small interfering RNA)
Gene therapy



Proteins
(insulin)

Vaccines

Cell therapy
(stem cells)

Basic chemistry

To define some words commonly used in drug discovery:

Compounds

Small molecules

Large molecules

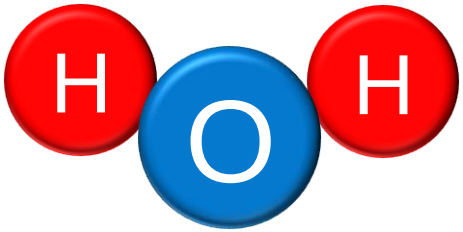
Molecular weight

Compounds

Two or more different elements bound together that have properties which are different from their component elements

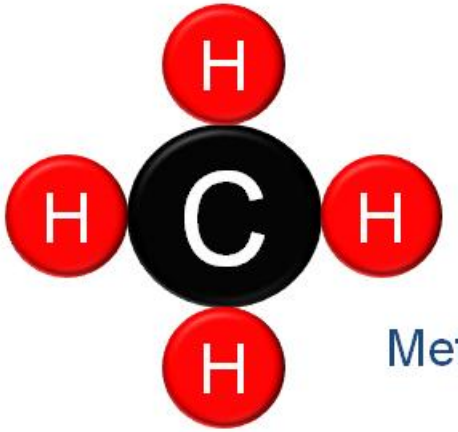
Hydrogen 

Oxygen

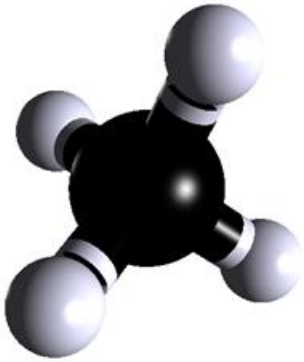


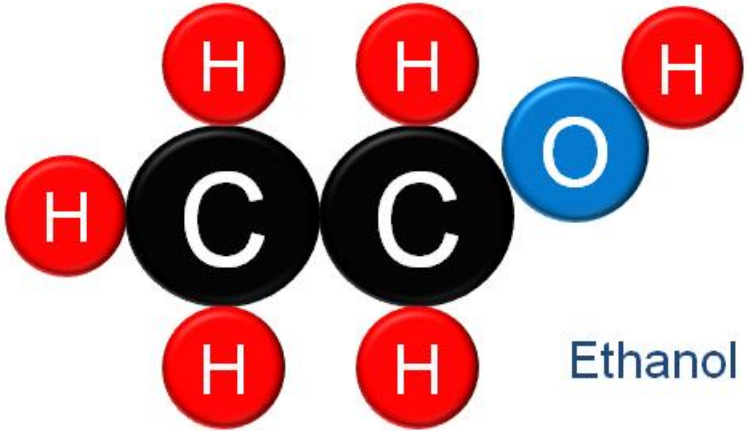
Water

Some small molecules

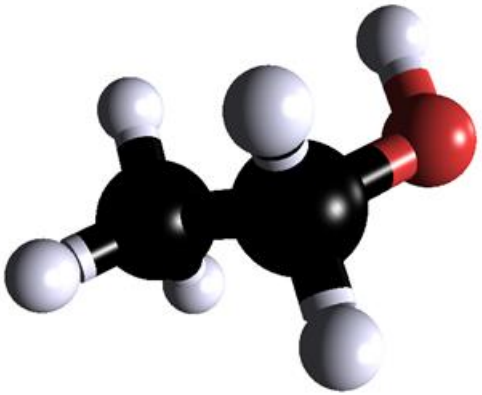


Methane

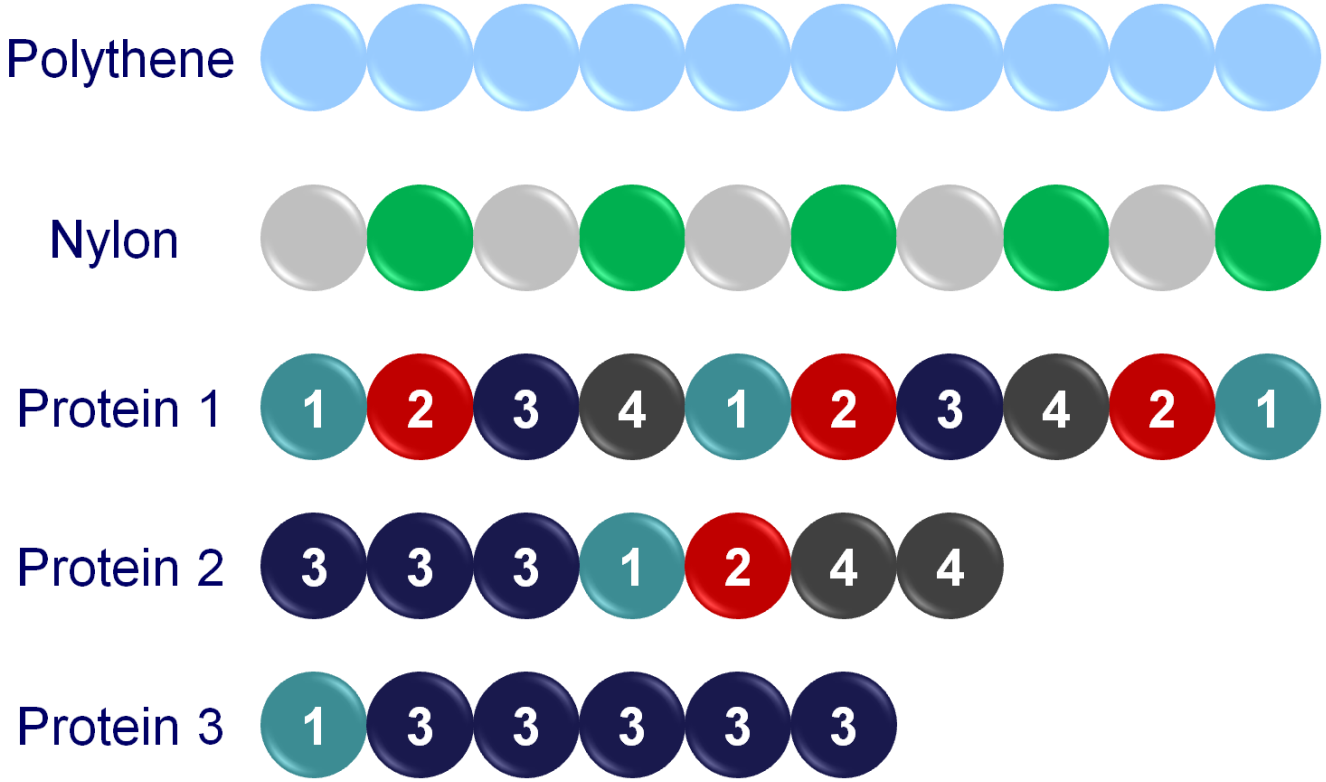




Ethanol



Large molecules - polymers



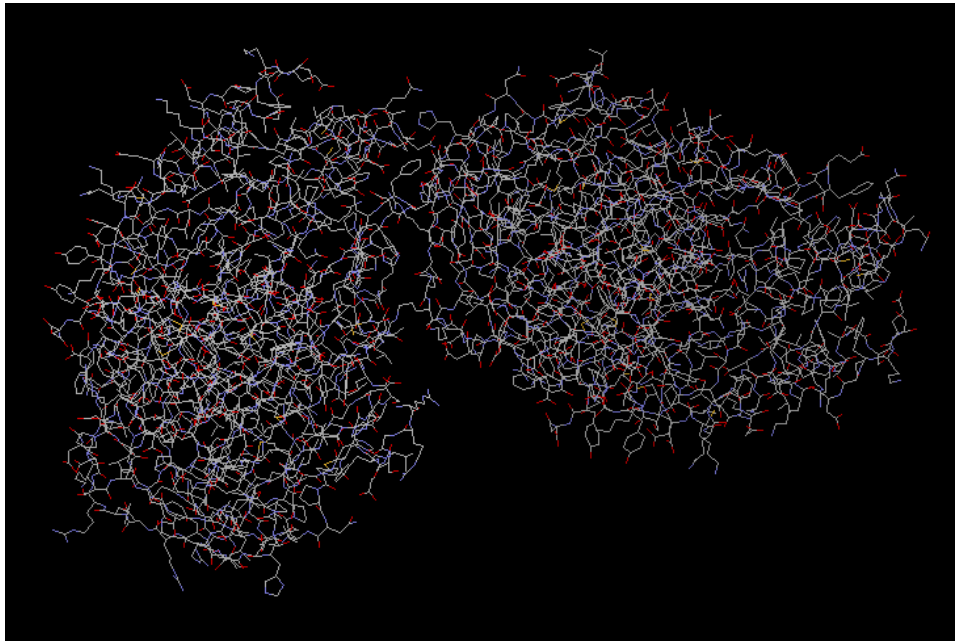
Terminology

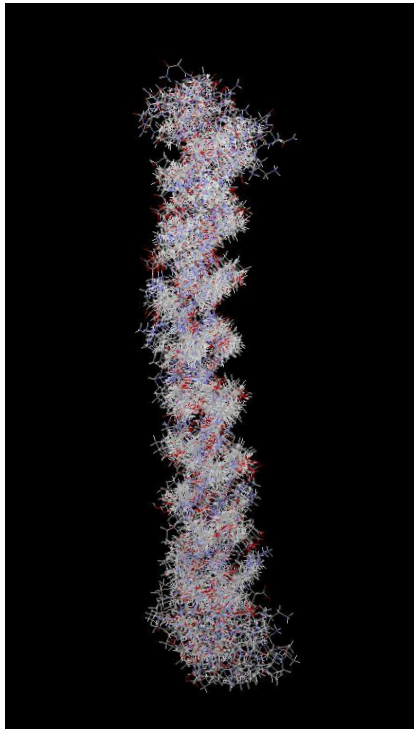
Peptide – 2 or more amino acids up to about 60 (dipeptide, tripeptide, tetrapeptide etc)

Polypeptide – approx 60 or more amino acids

Protein – same as polypeptide, up to 1000s amino acids

Proteins adopt different shapes





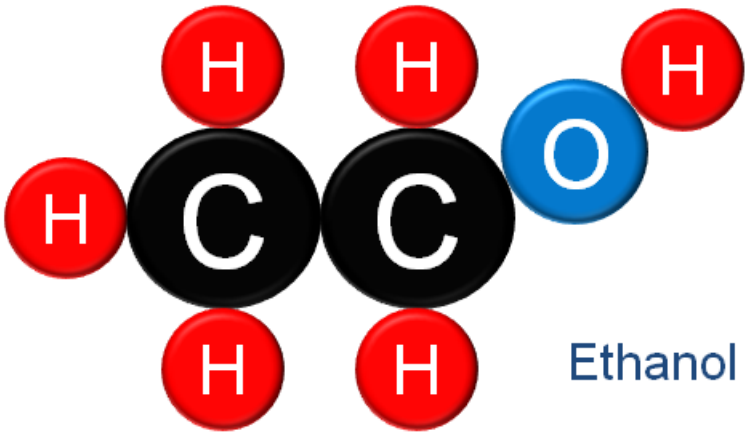
Most drug targets are proteins

Proteins can also be drugs

Biologicals
Biologics
Biotherapeutics

Protein therapeutics
Monoclonal antibodies
Recombinant antibodies

Molecular weights



Ethanol

H=1
C=12
O=16

MW=46

46g of ethanol contains 6.023×10^{23} molecules

- Small molecule drugs have MW<500-600

- Large molecules such as proteins and nucleic acids have MW from thousands to millions

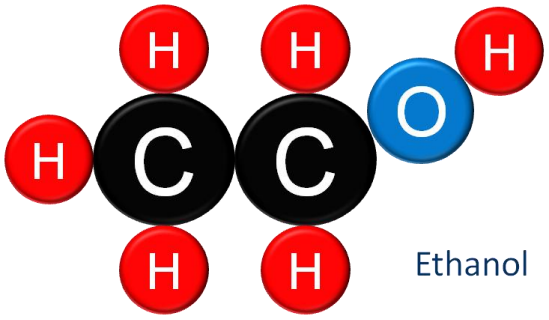
Weights and measures -1

Weight of drug

milligrams	mg	1 thousandth gram	10^{-3} g
micrograms	μg	1millionth gram	10^{-6} g
nanograms	ng	1 billionth gram	10^{-9} g
picograms	pg	1 trillionth gram	10^{-12} g

Weights and measures -2

Molarity of drug



Ethanol

H=1
C=12
O=16

MW=46

1 **mol** ethanol = 46 grams
1 **molar (M)** ethanol = 46 grams/liter

Measurements of drug concentration

By weight:
milligrams/milliliter* (mg/ml)
micrograms/milliliter (μg/ml)
nanograms/milliliter (ng/ml)

By molarity:
millimolar (mM)
micromolar (μM)
nanomolar (nM)

* UK spelling: litre

Drug nomenclature

1) **Formal chemical name** using IUPAC system (International Union of Pure and Applied Chemistry)

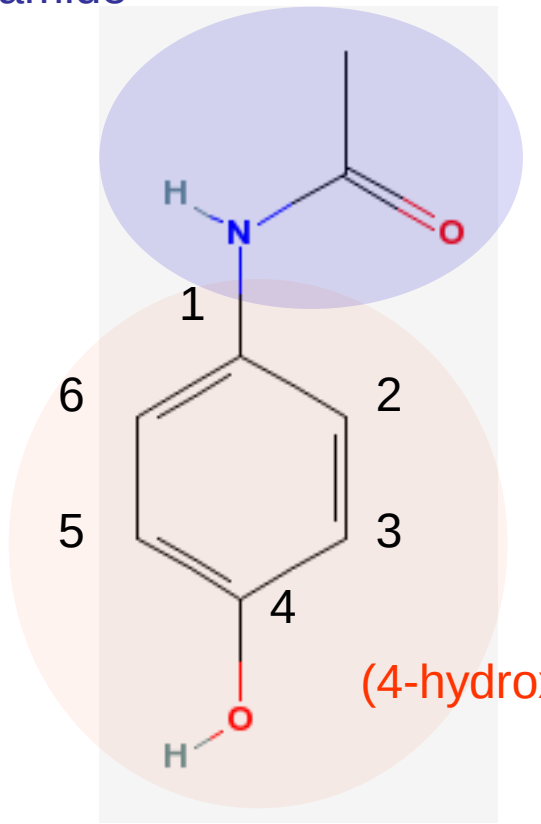
2) **Generic name**
International Nonproprietary Name (INN)
or the United States Adopted Name (USAN)

3) **Proprietary** or **trade name**

4) **ATC Code** (Anatomical Therapeutic Chemical Classification System)

Nomenclature example

acetamide



(4-hydroxyphenyl)

IUPAC name:

N- (4-hydroxyphenyl) acetamide

Drug name: Acetaminophen

Trade name: Paracetamol, Tylenol *etc*

Salt forms and hydrates

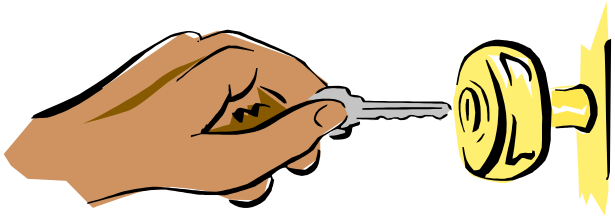
Base (alkali) + **Acid** ⟶ **Salt**

Ranitidine	hydrochloric acid	ranitidine hydrochloride
Imatinib	mesylic acid	imatinib mesylate
Sildenafil	citric acid	sildenafil citrate

Compound + **Water** ⟶ **Hydrate**

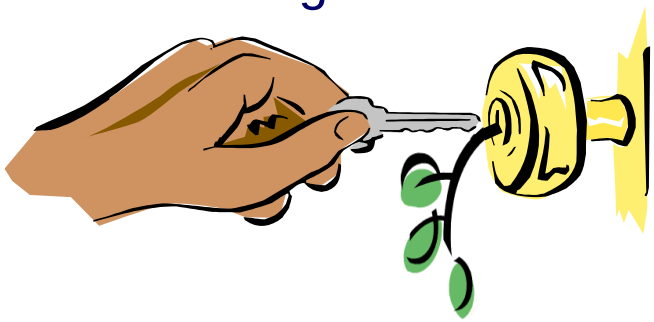
doxycycline hydrate

Pharmacology



Natural ligand

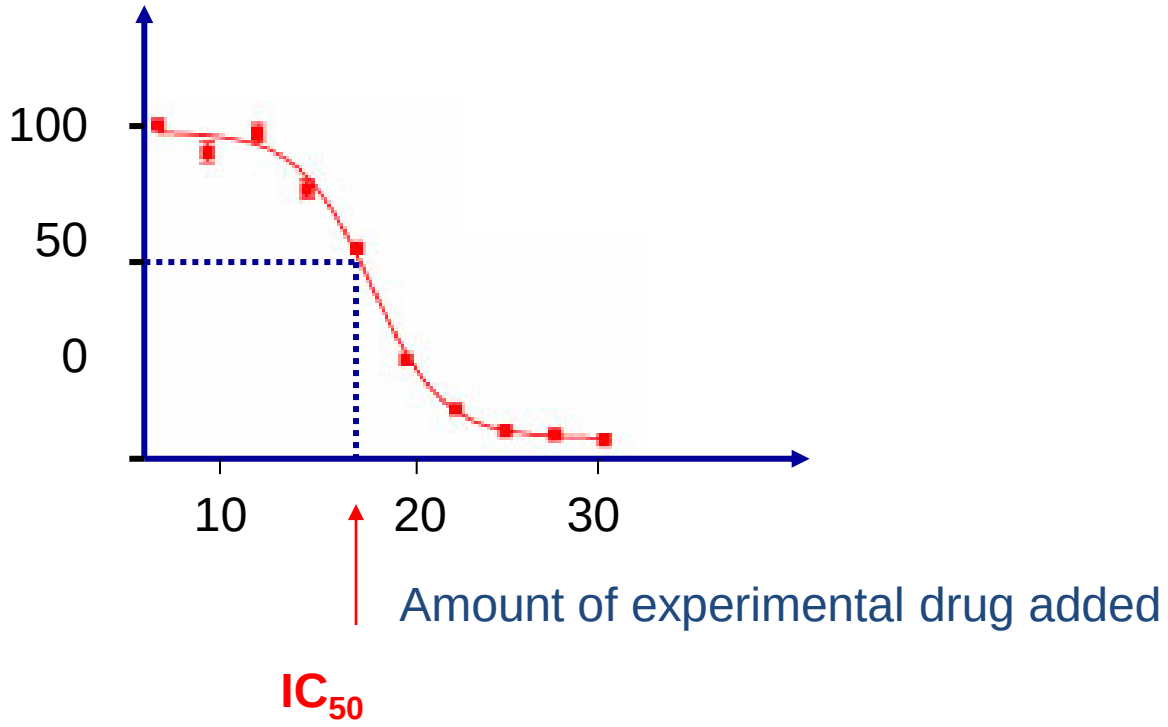
Agonist



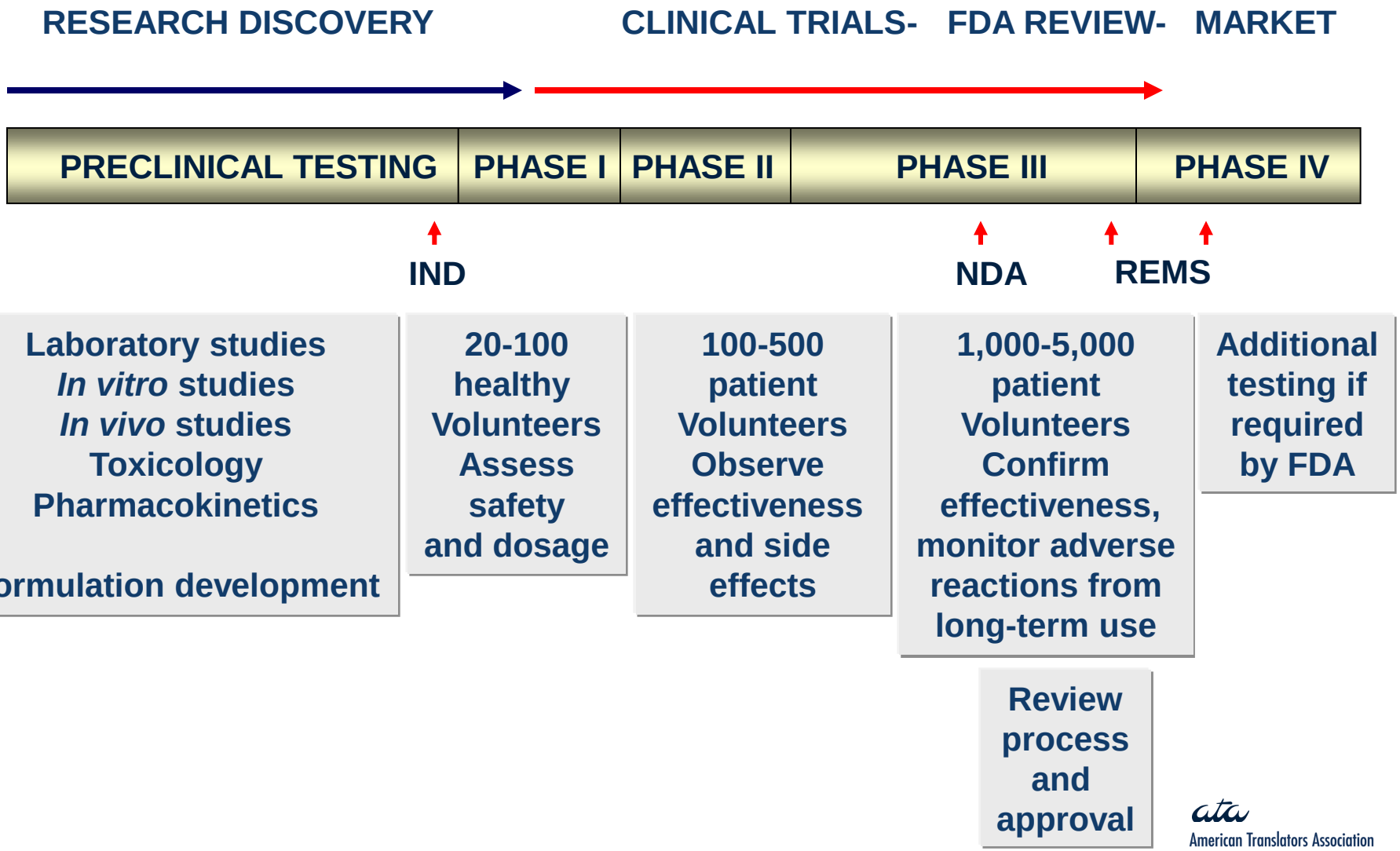
Antagonist

Drug potency – the IC_{50}

% “natural” hormone etc bound to receptor



The drug discovery pipeline



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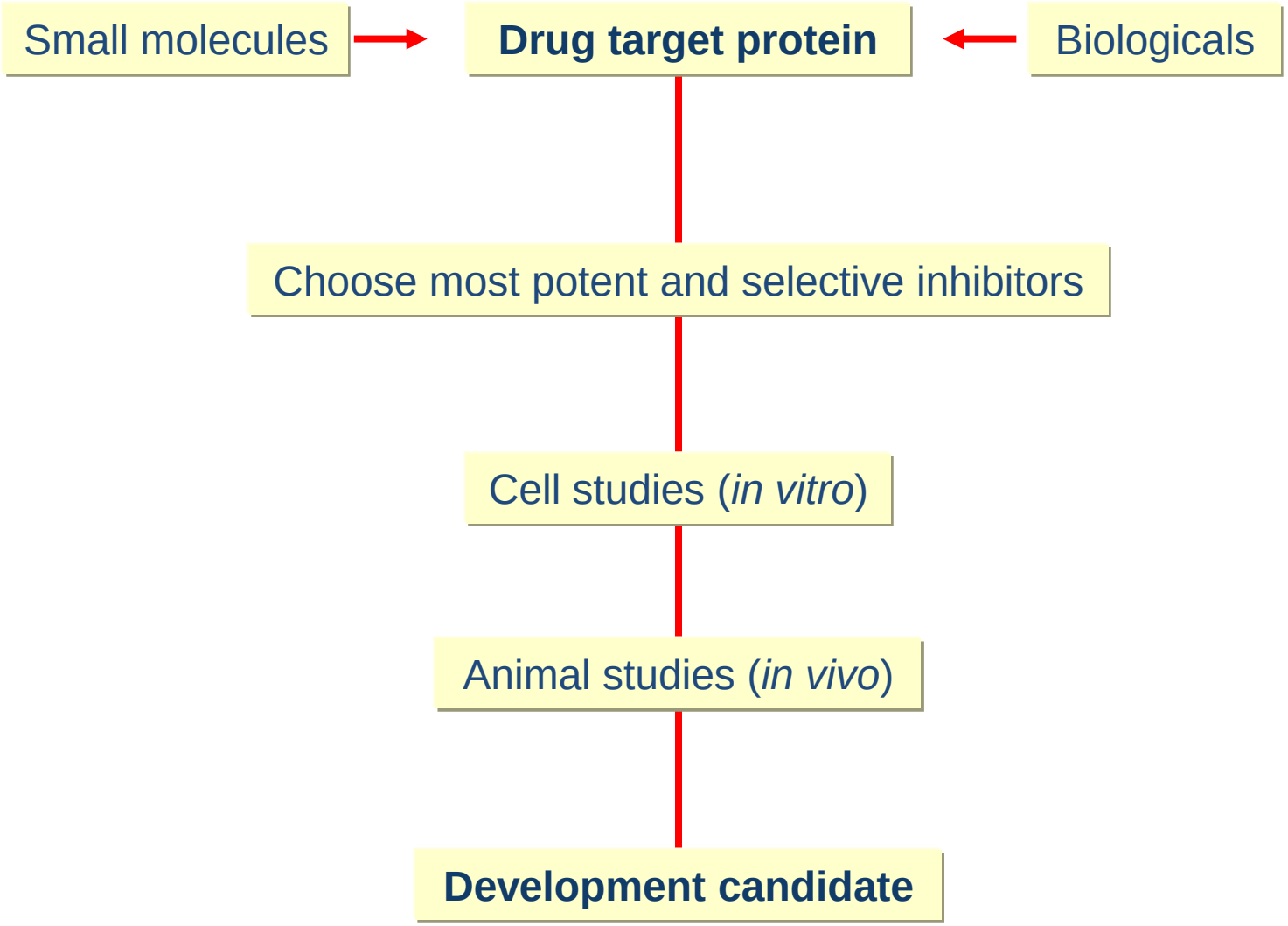
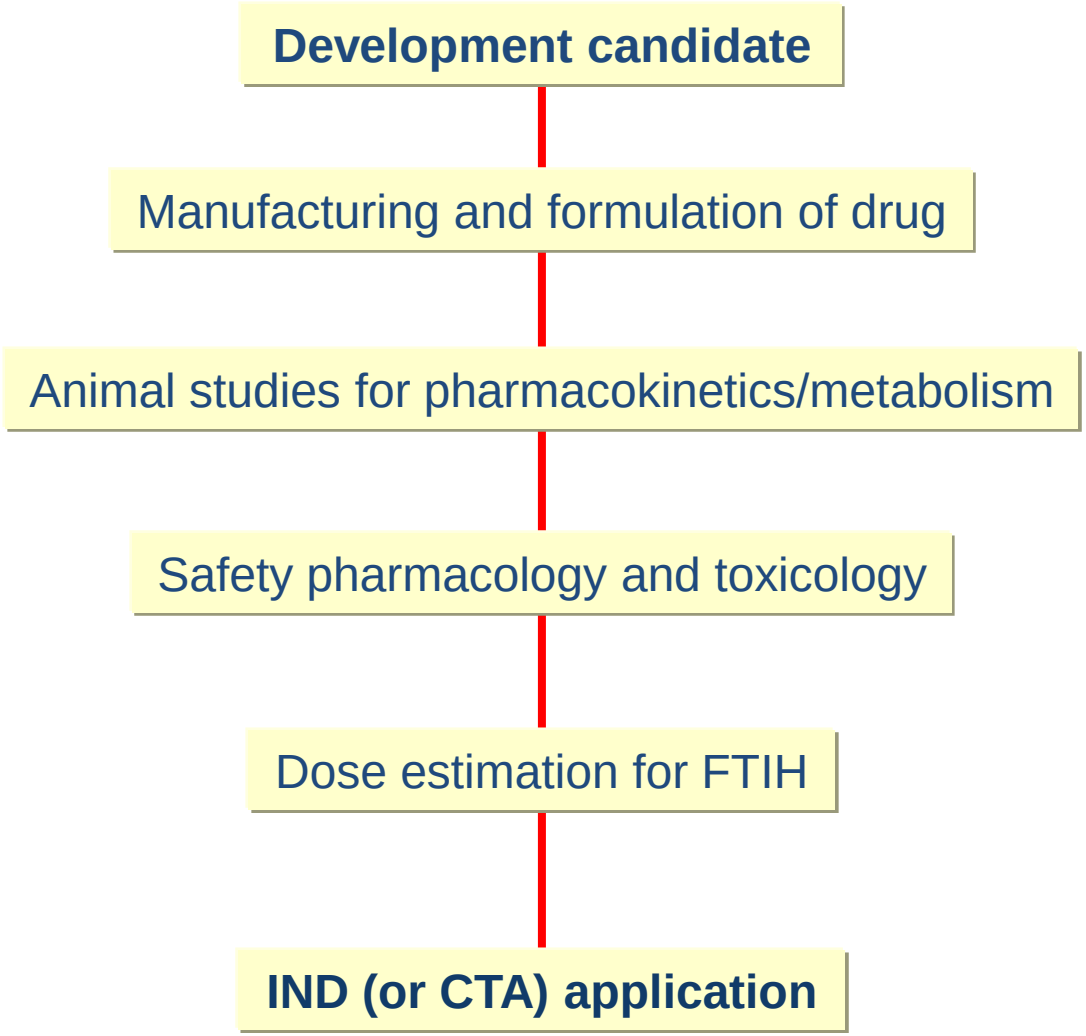
From discovery to development candidate



Development candidate to first time in humans



Some key terms

Formulation
Active pharmaceutical ingredient (API)
Excipient

ADME
Adsorption Distribution Metabolism Excretion
(Sometimes DMPK -distribution metabolism pharmacokinetics)

Pharmacokinetics – action of body on drug
Pharmacodynamics – action of drug on body

Safety pharmacology
NOAEL – no observable adverse effect level

Regulated procedures
Good laboratory practice GLP
Good manufacturing practice GMP
Good clinical practice GCP

Regulatory affairs

Standardisation and monitoring of procedures to ensure drug safety, efficacy and value for money

FDA - Food and Drug Administration (USA)

EMEA - European Medicines Agency (EU)

MHLW - Ministry of Health, Labour and Welfare – (Japan)

ICH - The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Clinical trial objectives

Assess safety and effectiveness of:

- Single medicine in specified disease
- Altered dose of medicine
- Marketed medicine for new indication
- New drug compared with “gold standard” medicine
- Two or more different medicines

Clinical trial terminology

Sponsor

Investigator

Placebo

Active comparator

Randomization

Stratification

Open label study

Blinded trial (single and double)

Crossover trial

Washout period

Phase II and III trials

Different effectiveness measurements

Primary variable

Secondary variable

Global assessment variable

Categorised variable

Composite variable

Surrogate variable

Biostatistics

Quantitative estimate of whether treatment has worked

Power of the study
The more subjects, the more significant the results

Statistical tests include
Chi squared, or $\chi 2$ test
ANOVA – Analysis of Variance

Results reported
P-values, type I and type II errors

Pharmacovigilance

Detection, assessment, understanding and prevention of adverse effects

Adverse event (AE)
An untoward symptom or laboratory finding that occurs after drug administration and which may not necessarily be caused by the treatment

Adverse Drug Reaction (ADR)
All unintended and noxious responses to a drug administered at any dose. A Serious ADR may result in death or major disability

Marketing applications

Submitted during phase III

Depends upon two **pivotal clinical trials**

USA -New Drug Application (NDA)

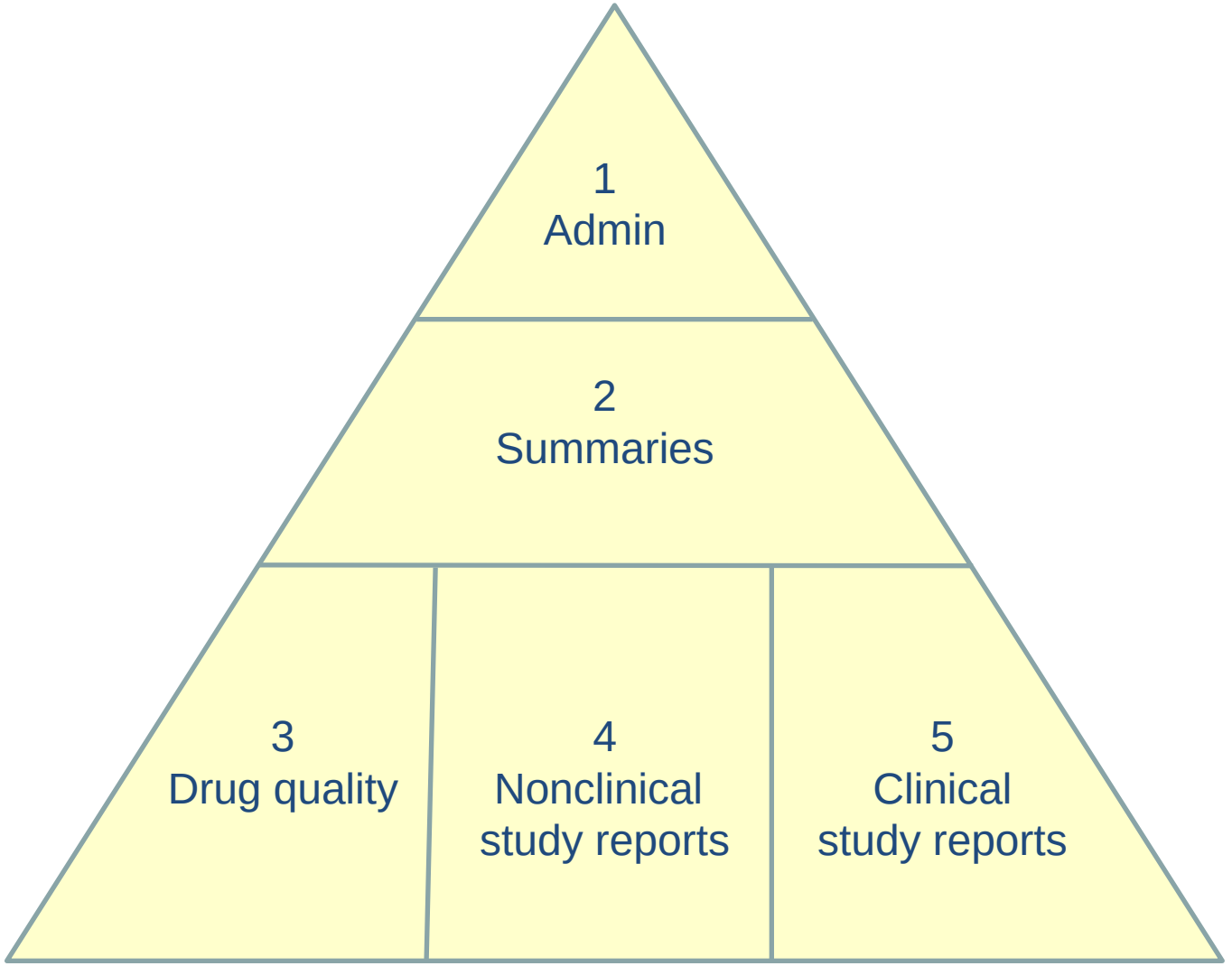
EU - Marketing Authorisation Application (MAA)

Physical end product is the paperwork supplied with the medicine

USA - **Package insert** (or **label**) USA

EU- **Patient information leaflet** (PIL) an abbreviated form of the **Summary of Product Characteristics** (SPC) document

The Common Technical Document (CTD)*



*may be over 100,000 pages

Once the medicine is on the market

Phase IV post-marketing studies

Post authorisation safety studies (PASS)

or compare with established medicine (active comparator)

or special populations – e.g. pregnant women

Phase V post-marketing surveillance

Several high profile product withdrawals

Summary of clinical and regulatory phases

Clinical phase	Comment	Timescale
Phase 0	Preclinical pharmacokinetics using humans instead of animals	Weeks
Phase I	Dose ranging study in human volunteers	Weeks
Phase II	Testing drug in up to approx 100 patients for proof of concept	Months
Phase III	Testing drug in 100s to 1000s of patients over longer period	Years
Phase IV	Post-marketing studies	Years
Phase V	Post marketing surveillance	Years
Application		
IND	Investigational New Drug - FDA	Pre phase I
CTA	Clinical Trial Application - EMA	Pre phase I
NDA	New Drug Application - FDA	During phase III
MAA	Marketing Authorisation Application - EMA	During phase III
REMS	Risk Evaluation and Mitigation Strategy - FDA	During Phase III

Resources

Organizations

The Pharmaceutical Research and Manufacturers of America (PhRMA)
http://www.phrma.org/
EMA http://www.ema.europa.eu/ema/index
FDA http://www.fda.gov/
ICH http://www.ich.org/home.html

Chemistry and nomenclature

ICH M5 EWG list of approved measures (This ICH guideline downloadable from EMA website, not ICH)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002731.pdf
Royal Society of Chemistry (RSC) Educational resources http://www.rsc.org/Education/
American Chemical Society (ACS) Education links on main website http://www.acs.org
International Union of Pure and Applied Chemistry (IUPAC) http://www.iupac.org/
Compendium of chemical terminology http://old.iupac.org/publications/compendium/A.html
Queen Mary College London compilation http://www.chem.qmul.ac.uk/iupac/
Glossary of medicinal chemistry terms http://www.chem.qmul.ac.uk/iupac/medchem/
WHO Guidelines for INNs http://apps.who.int/medicinedocs/pdf/h1806e/h1806e.pdf
ATC Classification system http://www.whocc.no/atc/structure_and_principles/
United States Adopted Names Council http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/adopted-names.shtml

Resources

Biotechnology

All about the Human Genome Project. National Human Genome Research Institute (NHGRI) http://www.genome.gov/10001772
The Sanger Centre: Educational resources http://www.yourgenome.org/
Pharmacogenetics/genomics. NHGRI http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml
National Institute of General Medical Sciences (NIGMS) http://publications.nigms.nih.gov/cjs/2007/narr_discover.html
SNPs http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml

Clinical Trials

WHO International Clinical Trials Registry Platform (ICTRP) http://www.who.int/ictrp/en/
US database of clinical trials http://www.clinicaltrials.gov/
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/
The Medical Dictionary for Regulatory Activities (MedDRA) A standard reference for describing adverse events http://www.meddramsso.com/
EudraVigilance (European Union Drug Regulating Authorities Pharmacovigilance) http://eudravigilance.emea.europa.eu/human/index.asp

And finally ---

The Science and Business of Drug Discovery: Demystifying the Jargon

by Edward D. Zanders, Springer, New York

http://www.springer.com/biomed/pharmaceutical+science/book/978-1-4419-9901-6

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