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
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)

Proteins (insulin)

Nucleic acids (small interfering RNA)
Gene therapy

Cell therapy (stem cells)

Vaccines
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 $\text{H}$  
Oxygen $\text{O}$  
Water $\text{H}_2\text{O}$
Some small molecules

Methane

Ethanol
Large molecules - polymers

Polythene

Nylon

Protein 1

Protein 2

Protein 3
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

\[ \begin{align*}
H &= 1 \\
C &= 12 \\
O &= 16 \quad \text{MW} = 46
\end{align*} \]

46g of ethanol contains $6.023 \times 10^{23}$ 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

<table>
<thead>
<tr>
<th>Weight of drug</th>
<th>Unit</th>
<th>Description</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>milligrams</td>
<td>mg</td>
<td>1 thousandth gram</td>
<td>$10^{-3}$ g</td>
</tr>
<tr>
<td>micrograms</td>
<td>μg</td>
<td>1 millionth gram</td>
<td>$10^{-6}$ g</td>
</tr>
<tr>
<td>nanograms</td>
<td>ng</td>
<td>1 billionth gram</td>
<td>$10^{-9}$ g</td>
</tr>
<tr>
<td>picograms</td>
<td>pg</td>
<td>1 trillionth gram</td>
<td>$10^{-12}$ g</td>
</tr>
</tbody>
</table>
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

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

Amount of experimental drug added

IC$_{50}$
The drug discovery pipeline

**RESEARCH DISCOVERY**

- Laboratory studies
  - *In vitro* studies
  - *In vivo* studies
  - Toxicology
  - Pharmacokinetics
- Formulation development

**PRECLINICAL TESTING**

- 20-100 healthy volunteers
- Assess safety and dosage

**PHASE I**

- 100-500 patient volunteers
- Observe effectiveness and side effects

**PHASE II**

- 1,000-5,000 patient volunteers
- Confirm effectiveness, monitor adverse reactions from long-term use

**PHASE III**

- Additional testing if required by FDA

**PHASE IV**

- FDA review
- Market

**IND**

**NDA**

**REMS**

Review process and approval

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From discovery to development candidate

Small molecules → Drug target protein → Biologicals

Choose most potent and selective inhibitors

Cell studies (in vitro)

Animal studies (in vivo)

Development candidate
Development candidate to first time in humans

1. Development candidate
2. Manufacturing and formulation of drug
3. Animal studies for pharmacokinetics/metabolism
4. Safety pharmacology and toxicology
5. Dose estimation for FTIH
6. IND (or CTA) application
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

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

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

Chemistry and nomenclature
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
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/
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
National Institute of General Medical Sciences (NIGMS)
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/
EudraVigilance (European Union Drug Regulating Authorities Pharmacovigilance)
And finally ---

*The Science and Business of Drug Discovery: Demystifying the Jargon*

by Edward D. Zanders, Springer, New York


www.pharmaguide.co.uk