An Introduction to Drug Development

Duncan Richards
MA DM MRCP MFPM FBPharmacolS
Head, Academic DPU GSK
What is drug development?

Molecular pharmacology

Cell pharmacology

Cell physiology

Tissue physiology

Organ Physiology

Clinical effect

Agonist at β₂ adrenoceptor, activates adenylate cyclase

Increase in cyclic AMP

Relaxation of smooth muscle

Bronchodilatation

Improved lung dynamics

Breathing better
There is a process but it’s much more than that........

<table>
<thead>
<tr>
<th>Drug discovery</th>
<th>Pre-clinical testing</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Submission for approval</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-80 healthy volunteers</td>
<td>100-300 patient volunteers</td>
<td>1000-3000 patient volunteers</td>
<td></td>
<td></td>
<td>2000-1000 patient volunteers</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound patent for 17 years</th>
<th>12 years in development</th>
<th>5 years exclusive marketing</th>
</tr>
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<tbody>
<tr>
<td>4 years</td>
<td>1 year</td>
<td>2 years</td>
</tr>
<tr>
<td>5000 compounds</td>
<td>5 enter trials</td>
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</table>
Where to start - vision for your medicine

- What are the potential indications and what is the optimal sequence to investigate them?
  - How does the science link to clinical benefit?
- Which patient segment will receive the most benefit and how will this develop?
  - Which group has the optimal risk /benefit profile?
- In each target segment, which treatment option(s) will be displaced?
  - Is this really offering something that is of value?
- What is the medicine's differentiating Scientific Advantage?
  - Is there clear differentiation that everyone can understand and agree with?
- What differentiates this medicine for the prescriber, payer and patient?
  - Why should I prescribe/pay/take for this?
- What is the “Value Proposition” to the payer/policy maker?
Where do drugs come from?

- Natural Products
- Mimicry of endogenous substrates
- Serendipity
- Systems biology
  - Rational drug design
Devising an early clinical plan

- What you know before you start
  - Chemical information about the drug and its formulation
  - Pharmacology in vitro and in vivo
  - Toxicology (28 days) in 2 species
  - Information on ADME in animal species

- What you want to know by the end of the early phase
  - Is the drug sufficiently safe and tolerable that you can give enough of it for long enough to have a chance of showing a beneficial clinical effect?
  - Does the drug engage its target at sufficient concentration for long enough to have the potential clinical benefit?
Start with the end in mind
1- the disease

• What is the nature of the disease I am trying to treat?
  – Acute vs Chronic
  – Natural history

• What is the profile of the patient population I wish to treat?
  – Young vs elderly
  – Single disease or many co-morbidities
  – Drug interactions

Proof of concept study
Start with the end in mind
2- the drug

• Pharmacokinetics
  – How can it be given?
  – How long does it last?
  – How is it eliminated?

• Pharmacodynamics
  – What dose?
  – How long to treat?

• Safety
  – What are the likely adverse effects?
  – Are there any critical interactions?
    • Drug/Disease
A traditional approach to early drug development

First into Man

Repeat dose study

Safety study in patients

Drug interaction studies

ADME study

Formulation study

Food effect study

PD study with dose ranging in patients

Safety and tolerability in target patient population

Proof of concept study
The traditional approach

- Delivers a comprehensive package of information at POC
- Ability to explore a wide dose range
- Suitable for precededented mechanisms (high probability of success)
- Potentially slow to POC
- Expensive
- Not very suitable for novel mechanisms
The targets are changing

Molecular biology has delivered new types of Target
eg pluripotent modulators of second messenger systems

Huge potential but which disease represents the best target to show PoC?
Drug development priorities for new targets

• Does the drug hit the target?
• Does the target contribute significantly to the pathophysiology of the disease?
How early drug development is changing

First into Man
With PD marker

Repeat dose safety and tolerability in target patient population (with PD marker)

Proof of concept study
The new approach

- Quickly establishes whether have a developable drug
- Good for novel mechanisms- clinical role may not be known
- Complex (expensive) studies
- Scarce resource
- Relies on PD markers (how useful are they?)
- Carry safety risks later into development
Why do drugs fail?

Only 20% of drugs are successful in phase II

Nature Reviews Drug Discovery 10, 328-329
Full development - traditional approach

- Learning
  - Dose Ranging Phase IIB study
    - e.g. H2 antagonist
    - 4-6 week endoscopic studies
    - 80-90% healed on drug
    - 30-40% healed on placebo

- Confirming
  - Replicate placebo-controlled phase III studies
    - e.g. H2 antagonist
    - Similar design, similar endpoint
Full development - new targets, new challenges

Phase IIb

- Plaque volume
- Plaque stability
- Presence of thrombus
- Glycaemic control

Phase III

- MI/Stroke/mortality
- MI/Stroke/mortality
- Pulmonary embolus
- Microvascular complications

Globalization
Different standards of care
Risk management plans
Full development—changing paradigm

Inlicensed following positive POC study

Phase IIb  Phase III

Clinical Pharmacology package
The evolving regulatory framework

Clinical Development Package

FDA EMA review and approval

Marketing

Additional indications
New formulations

Focussed development package

FDA EMA early review and level of approval

Limited Marketing

More comprehensive safety data
Longer term efficacy data

Broader label
Wider reimbursement
GCP and clinical development
Purpose of GCP

- To provide a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.
- May also be applied to other clinical investigation that may have an impact on the safety and well-being of human subjects.
ICH
(International Conference on Harmonization)

A joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.

- European Commission - European Union (EU)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Ministry of Health, Labor and Welfare, Japan (MHLW)
- Japan Pharmaceutical Manufacturers Association (JPMA)
- US Food and Drug Administration (FDA)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
ICH Guidelines

- **"Quality" Topics**, i.e., those relating to chemical and pharmaceutical Quality Assurance.
  - Examples: Q1 Stability Testing, Q3 Impurity Testing

- **"Safety" Topics**, i.e., those relating to in vitro and in vivo pre-clinical studies.
  - Examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing

- **"Efficacy" Topics**, i.e., those relating to clinical studies in human subject.
  - Examples: E4 Dose Response Studies, Carcinogenicity Testing, **E6 Good Clinical Practice**.

- **Multidisciplinary Topics**, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories.
  - M1: Medical Terminology (MedDRA)
This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the attached notes. If you have doubts about the answer to any of the questions contact the clinical trials unit at MHRA ☎ 0207 084 2327

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is it a medicinal product?</strong></td>
<td><strong>Is it not a medicinal product?</strong></td>
<td><strong>What effects of the medicine are you looking for?</strong></td>
<td><strong>Why are you looking for those effects?</strong></td>
<td><strong>How are you looking for those effects?</strong></td>
</tr>
<tr>
<td>Are you administering a substance to a human subject?</td>
<td>Are you only administering any of the following substances? - Human whole blood; - Human blood cells; - Human plasma; - Tissues except a somatic cell therapy medicinal product; - A food product (including dietary supplements) not presented as a medicine; - A cosmetic product; - A medical device</td>
<td>To discover its clinical effects?</td>
<td>To ascertain the efficacy(^\text{\textsuperscript{a}}) of the medicine?</td>
<td>Is the prescription of the medicine linked to the decision to include the patient in the study?</td>
</tr>
<tr>
<td>Is the substance presented as a medicine? i.e. for preventing or treating disease</td>
<td>To discover its pharmacological effects?</td>
<td>To ascertain the safety of the medicine?</td>
<td>Is the medicine prescribed in a manner outside the terms of the marketing authorisation?</td>
<td></td>
</tr>
<tr>
<td>Does the substance function as a medicine? i.e. can it be administered, with a view to making a medical diagnosis, to restore, correct or modify physiological functions in human beings or is otherwise administered for a medicinal purpose?</td>
<td>To discover its pharmacodynamic effects?</td>
<td></td>
<td>Does the protocol specify when the patient will take the medicine</td>
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<tr>
<td>Is it an active substance in a pharmaceutical form?</td>
<td>To identify its adverse reactions?</td>
<td></td>
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<tr>
<td>Is the substance an ingredient in the preparation of a combination of substances administered for a medicinal purpose?</td>
<td>To study its absorption, distribution, metabolism or excretion?</td>
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<tr>
<td>Is it being used for a medicinal purpose?</td>
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Summary

• Drug development should aim to answer critical questions about how what a medicine offers and how it should be used
  – It’s not just a set of programmed procedural steps
• Line of sight is critical to successful drug development
  – Make sure you know what constitutes success and what does not
• The regulatory framework is evolving
• ICH GCP describes the responsibilities and expectations of all participants in the conduct of clinical trials