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# Drug Development and Clinical Trials

MBChB221B
Clinical Pharmacology and Therapeutics

Paula Lewis
Department of Molecular Medicine & Pathology
University of Auckland
New Zealand

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## Objectives

- Understand different classes of pharmaceutical drugs
- Appreciate the regulatory environment for bringing a drug from benchside to bedside
- Distinguish between drug discovery and drug development
- Understand the preclinical and clinical development process
- Be aware of the time, cost and attrition challenges

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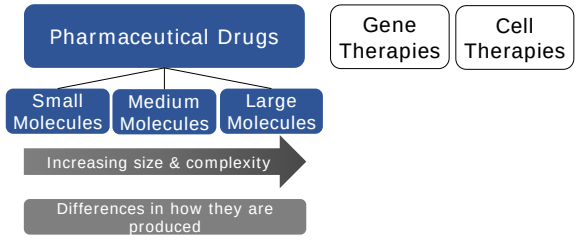
## Classes of Therapeutic Agents



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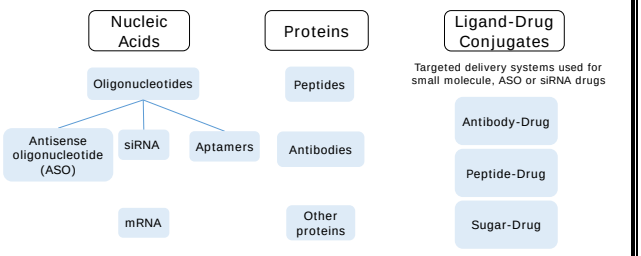
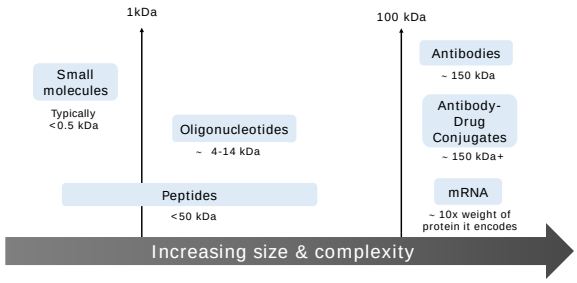
| Slide 4 | **Features of Pharmaceutical Drugs**<br><br>**Small Molecules**<br>• Low molecular weight (typically < 500 Da)<br>• Chemically synthesized<br>• Able to enter cells easily<br>• Most approved drugs fall into this class<br><br>**Medium-Large Molecules**<br>• Medium-high molecular weights<br>• Made by assembly of smaller monomer units<br>• May need assistance to enter a cell (delivery system) depending on site of action and chemical properties (size, charge, lipophilicity) | |
| Slide 5 | **Diversity of Medium-Large Molecule Drugs**<br><br>  <br> | |
| Slide 6 | **Size & Complexity**<br><br>  <br> | |

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## Different Ways Drugs Are Made

**Chemical Synthesis (chemical entities)**
- Small molecules
- Peptides
- Oligonucleotides

**In Vitro Transcription (IVT)**
- mRNA

**Living Cells (biologics)**
- Antibodies
- Other proteins

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## Delivery Systems That Help Drugs Reach Their Targets

**Non-Targeted Systems**
- Encapsulate drug (“cargo”)
- Allow drug to enter cell
- LNP used for siRNA & mRNA

Liposomes
Nanoparticles
↓
Lipid Nanoparticle (LNPs)

**Targeted Systems**
- Carry drug to specific cells or tissues
- Increase local drug concentration
- Reduce undesirable side-effects
- Ligand-drug conjugates used for small molecules, siRNA & ASO

Ligand-Drug Conjugates
Ligand-Nanoparticles (emerging)

Ligand can be a peptide, antibody or sugar

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## Top Selling Drugs In 2017

| Trade name | Drug | Type | | Main indications | Sponsor(s) | 2017 Sales (USD billions) |
|---|---|---|---|---|---|---|
| Humira | Adalimumab | Biologic | TNFα Ab | Immunology | AbbVie | 18.4 |
| Mabthera; Rituxan | Rituximab | Biologic | CD20 Ab | Oncology | Roche, Biogen | 9.2 |
| Revlimid | Lenalidomide | Small molecule | | Oncology | Celgene | 8.2 |
| Enbrel | Etanercept | Biologic | TNF receptor fusion protein | Immunology | Amgen, Pfzier | 7.9 |
| Herceptin | Trastuzumab | Biologic | HER2 Ab | Oncology | Roche | 7.4 |
| Eliquis | Apixaban | Small molecule | Factor Xa inhibitor | Stroke, thrombosis, pulmonary embolism | BMS, Pfzier | 7.4 |
| Remicade | Infliximab | Biologic | TNFα Ab | Immunology | J&J, Merc & Co. | 7.2 |
| Avastin | Bevacizumab | Biologic | VEGF-A Ab | Oncology | Roche | 7.1 |
| Xarelto | Rivaroxaban | Small molecule | Factor Xa inhibitor | Stroke, thrombosis, pulmonary embolism | Bayer, J&J | 6.6 |
| Eylea | Aflibersept | Biologic | VEGF fusion protein | Wet age-related macular degeneration | Regeneron, Bayer | 6 |

Data source: https://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2017/77901068?page=2

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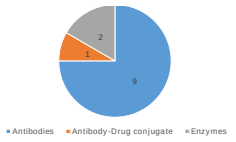
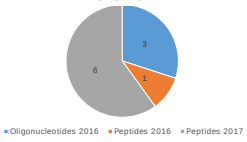
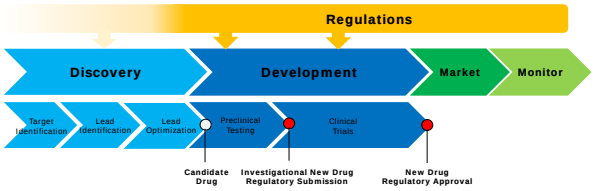
| Slide 10 | **New Molecule Drug Approvals**<br>• Record level of FDA approvals reached in 2017<br>• Majority of approved drugs are chemical entities<br>• Overall rise in biologics approvals over the last few years<br>  <br>de la Torre, B.G. and Albericio, F. The Pharmaceutical Industry in 2017. An Analysis of FDA Drug Approvals from the Perspective of Molecules. *Molecules* 2018, *23 (3)*, 533; https://doi.org/10.3390/molecules23030533 Open source | |
| Slide 11 | **Biologics, Oligonucleotide & Peptide Drug Approvals Are Rising**<br>12 biologics received FDA approval in 2017<br>  <br><br>7 peptides & 3 oligonucleotides received FDA approval in 2016-2017<br>  <br><br>Date source: de la Torre, B.G. and Albericio, F. The Pharmaceutical Industry in 2017. An Analysis of FDA Drug Approvals from the Perspective of Molecules. *Molecules* 2018, *23 (3)*, 533; https://doi.org/10.3390/molecules23030533 Open source | |
| Slide 12 | **Drug Discovery & Development**<br>Drug discovery & development occurs in a regulated environment<br>  <br> | |

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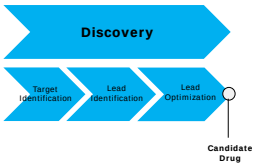
| Slide 13 | **Regulatory Process Is Staged To Ensure…**<br>• Good quality & safe products with potential to improve human health are progressed into the clinic<br>• Safety risks are minimized by conducting studies according to regulatory standards<br>  • Preclinical testing before first time in humans<br>  • Staged clinical trials before approval to market<br>• Governance of sale, marketing & manufacturing practices post-market approval<br>• Post-market monitoring | |
| Slide 14 | **Drug Discovery**<br>A preclinical research process that identifies new candidate drugs<br>  <br>• Identify the drug target and initiate validation<br>• Screen and identify leads<br>• Optimize leads<br>• Select a candidate drug | |
| Slide 15 | **Candidate Drug Selection**<br>Leads are optimized to identify a candidate drug that meets defined criteria, including<br>  • Chemical and physical properties<br>  • Activity<br>  • Potency<br>  • Mechanism of action<br>  • Selectivity<br>  • Efficacy, pharmacodynamic and pharmacokinetic relationships<br>  • Formulation<br>  • Drug metabolism & pharmacokinetic parameters<br>  • Initial toxicity risk assessments (in vitro)<br>  • Scope for large scale drug synthesis | |

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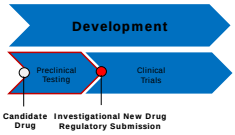
| Slide 16 | **Preclinical Development**<br>A phase of drug development where preclinical studies are completed to support the first critical regulatory submission for approval to conduct clinical trials of an Investigational New Drug (IND)<br>  <br><br>Drug must meet regulatory standards in these areas<br>• Pharmacology & Drug Disposition<br>› Pharmacological effects & mechanism of action in animals<br>› Absorption, distribution, metabolism & excretion (ADME)<br>• Safety (GLP)<br>› Toxicology in animals and in vitro<br>• Chemistry, Manufacturing & Controls (CMC, cGMP)<br>• Clinical Protocol & Investigators (cGCP) | GLP = Good Laboratory Practices<br>cGMP = current Good Manufacturing Practices<br>cGCP = current Good Clinical Practices |
| Slide 17 | **Preclinical Development Perspectives**<br>• Multi-discipline teams work together to complete preclinical data packages that guide decisions about whether a drug meets regulatory standards and warrants further investment to conduct clinical trials<br>• The outcome of pivotal safety studies in animals is an important milestone and will determine whether a candidate drug can progress any further<br>• Anything that can be done in Discovery to reduce the risk of delays or failure during preclinical development is critical as these studies are costly ($ and time) | |
| Slide 18 | **Role of Preclinical Safety Assessments**<br>Is the drug safe to administer to humans?<br>Need to demonstrate an acceptable safety margin<br>• Drugs assessed for specific toxicity risks using in vitro assays<br>• Kind, scope and duration of animal studies depends on the duration and nature of the proposed clinical investigations<br>• Need to determine if there is an acceptable safety margin above the human dose<br>• Based on reaching maximum tolerated or feasible dose (MTD/MFD) or defined exposure margins over the human dose and no-observed-adverse-effect-level (NOAEL) in animal studies<br>• Need to understand any potential toxicity risk | Examples of toxicity risks that are assessed using in vitro assays:<br>Interactions with other drugs (CYP)<br>Genotoxicity (Ames, chromosome aberration)<br>Heart failure from QT prolongation (hERG) |

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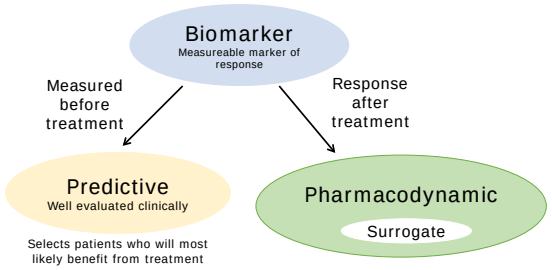
| Slide 19 | **Role Of Preclinical Pharmacology Studies**<br>Demonstrates activity-exposure relationships and mechanism<br>• Describes efficacy, pharmacodynamic (PD) & pharmacokinetic (PK) relationships in appropriate preclinical models<br>• Supports the proposed clinical investigations by<br>  • Demonstrating activity and mechanism in models representing features of the disease or intended patient population<br>  • Defining activity-exposure relationships that help guide<br>  • Route of administration<br>  • Dosing schedule<br>  • Drug combinations<br>  • Identifying PD biomarkers for further validation on clinical samples<br>• Informs risk assessments for achieving activity<br>  • Preclinical pharmacology data (including safety) is integrated into mathematical models to predict human PK and assess risks for achieving activity | |
| Slide 20 | **Biomarker Terms**<br>  <br> | |
| Slide 21 | **Biomarkers and Outcomes**<br>• Biomarker<br>  • Readily measurable marker of drug response<br>• Surrogate<br>  • A biomarker substitute for a clinical endpoint as although there maybe an association the relationship is not guaranteed<br>• Clinical Endpoint/Outcome<br>  • How the patient functions/feels/survives | |

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## Pharmacodynamic Biomarkers In Drug Development

- A measurable molecular, biochemical, cellular or physiological response caused by the drug
- May be the drug target itself, an associated downstream component of the signaling pathway or cellular consequence
- Measurable in an accessible disease tissue or a surrogate tissue
- Used to understand if sufficient drug exposure has been achieved to modulate the drug target
- Surrogate biomarkers provide increased confidence that the right dose and dosing schedule have been identified before a clinical outcome is observed

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## Clinical Development

Clinical development is a staged process for evaluating an Investigational New Drug in humans following regulatory approval to conduct clinical trials

| Phase | Purpose | Dose | Typical number of participants |
|---|---|---|---|
| **Phase 0** | PK | Sub-therapeutic | <10 healthy |
| **Phase 1** | Safety, PK | Ascending doses, starting low | 10-100 healthy (unless cancer) |
| **Phase 2** | Safety & Efficacy | Therapeutic dose | 100-300 disease |
| **Phase 3** | Safety, efficacy, & effectiveness | Therapeutic dose | 300-3000 disease |
| **Phase 4** | Post-market surveillance in public | Therapeutic dose | Anyone seeking treatment from physician |

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## Phase 0

Pharmacokinetics

- Not often used (optional)
- Used when there is a sufficient degree of uncertainty about the predicted human PK
- Primary purpose: human PK parameters
- Small number of healthy volunteers (<10)
- Low dose, sub-therapeutic

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| Slide 25 | **Phase 1**<br>Is it Safe?<br>• Primary purpose: Evaluate safety<br>• Small number of healthy volunteers unless cancer (~10-100)<br>• Ascending dose, starting low (often sub-therapeutic)<br>  • Gradual, step-wise increase<br>  • Stop if any adverse events<br>• Learn:<br>  • Single and multiple dose PK<br>  • Might include biomarkers | |
| Slide 26 | **Phase 2**<br>Is it safe and will it have efficacy?<br>• Primary purposes: Confirm safety & evaluate biological activity or effect<br>• Patients with specific disease (~100-300)<br>• Therapeutic dose<br>• Learn adverse effects in target population<br>• Phase 2A<br>  • Establish "Proof of Concept"<br>  • YES/NO decision point<br>• Phase 2B<br>  • Dose finding for optimal active dose with minimal side-effects<br>  • Learn effective dose range | |
| Slide 27 | **Phase 3**<br>Is there therapeutic benefit?<br>• Primary purposes: Confirm safety, efficacy, & effectiveness<br>• Larger number of patients with specific disease (~300-3000)<br>• Therapeutic dose<br>• Learn adverse effects in larger target population<br>• Confirm effective dose(s)<br>• Learn PD of surrogate/outcome<br>• Learn PK & PD covariates<br>  • Age, gender, other drugs | |

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| Slide 28 | **Phase 4**<br><br>What are the long-term effects?<br><br>• Primary purpose: Post-market surveillance in the public (anyone seeking treatment from physician)<br>• Safety monitoring<br>  • Confirms common adverse events<br>  • Learn uncommon adverse events<br>• Confirm therapeutic benefit | |
| Slide 29 | **Clinical Trial Design**<br>***ABCS***<br><br>• Assignment<br>• Blinding<br>• Comparison<br>• Sequence<br><br>Slide courtesy of Professor Nick Holford, University of Auckland | There are 4 major elements in the design of a clinical trial. Each has an effect on the way trials are designed and interpreted. |
| Slide 30 | **Assignment**<br><br>• First Come, First Served<br><br>• Randomized<br>  • Balanced<br>  • Stratified<br>  E.g. Sex, Previous Stroke<br><br>Slide courtesy of Professor Nick Holford, University of Auckland | The assignment process is used to determine which subjects get which treatment.<br><br>The “First Come, First Served” assignment process covers a range of possibilities that will typically introduce bias e.g. giving active treatment to subjects seen in the morning and placebo to those seen in the afternoon, or alternating between active and placebo treatment. The main source of bias from this process is the loss of blinding. The investigator can guess which subjects are getting different treatments even if he/she is blinded to the actual assignment.<br><br>A randomized assignment process is considered the best method of deciding which subjects get which treatment. A list of random numbers is used to decided on treatments e.g. if a random number is drawn from a uniform distribution between 0 and 1 then active treatment might be assigned if the number is <0.5 and placebo if it is >=0.5.<br><br>In order to ensure balanced allocation of treatments the number of subjects to be randomized is decided ahead of time and a balanced list of treatments is drawn up. This list is then randomly permuted and subjects drawn in turn from the permuted list. This |

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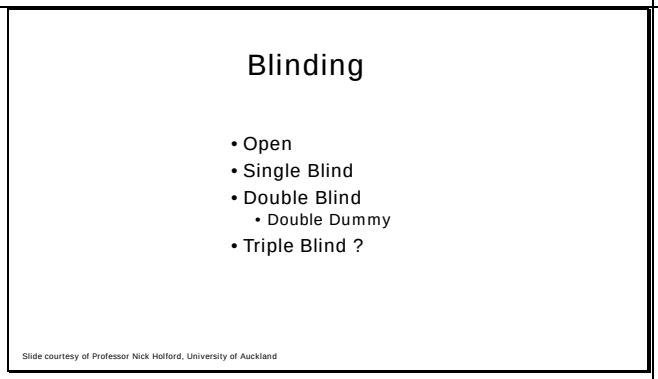
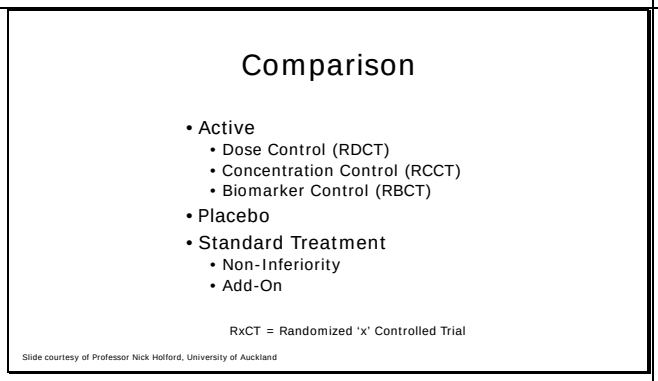
| | | ensures that the desired balance e.g. 50% in each of two treatment groups, is not affected by the randomization process.<br><br>If different sub-groups might have different responses it is common to stratify the randomization sequence. Separate sequences are drawn up for each sub-group e.g. one list for males and one for females. |
| Slide 31 |  | Blinding is used to reduce bias. Bias can arise from both the investigator's and subject's expectation of the treatment effect.<br><br>Open trials are unblinded. They are still commonly used for marketing purposes but have little scientific merit.<br>Single blind trials mean the investigator will know the treatment but the subject does not.<br>Double blind trials mean both the investigator and subject are not aware of the treatment.<br>Double dummy trials are used when two physically different treatments are compared e.g. tablet and inhaler treatments for asthma.<br>Triple blind trials may occur if the randomization sequence is lost or misinterpreted – this means that nobody ever knows what treatment was given.<br>Blinded trials often become unblinded if the treatment has very prominent beneficial effects or adverse effects. This is very hard to prevent or adjust for in the analysis. |
| Slide 32 |  | Good experimental science uses a control group to account for factors that might influence the outcome that are not experimentally assigned.<br><br>Within an active treatment arm it is usually desirable to learn about the relationship between intensity of treatment and outcome. The within active treatment control that is most widely used is the dose control i.e. there are two or more different doses arms in the active treatment group e.g. 100 mg, 200mg, 300mg.<br>Concentration control can be used to reduce the influence of random between subject differences in pharmacokinetics. By measuring concentration and individualizing the dose to reach desired target concentrations e.g. 10 mg/L, 20 mg/L, 30 mg/L, then the concentration effect relationship can be discovered.<br>Finally, if there is a biomarker (e.g. cholesterol concentration) that reflects the effect of the drug it can be used to control the intensity of treatment and reduce both pharmacokinetic and pharmacodynamic |

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| | | variability. Subjects are randomize to one or more target biomarker levels and the dose is adjusted to reach the target biomarker effect.<br><br>From a scientific perspective the best treatment control is to use a placebo i.e. an inactive substance. If there is genuine uncertainty about the effect of the active treatment then it is usually considered ethical to randomize to placebo (the ethical principle of 'equipoise').<br><br>However, if there is a standard treatment that would always be used because it is known to be effective then investigation of a new treatment may be in comparison with the standard treatment. This kind of trial is sometimes designed to show that the new treatment is no worse than the standard treatment – a non-inferiority trial.<br><br>If the standard treatment is given to all subjects then this would be considered an add-on trial design i.e. it looks for the effect of the new treatment in addition to the standard treatment. A placebo control group would receive the standard treatment. |
| Slide 33 | The Placebo Effect<br><br>• Placebo is an inert treatment (such as a sugar pill or saline injection) that has no active therapeutic ingredient<br><br>• Placebo effect can be a measureable positive health response attributed to the brain's role in physical health<br><br>• Placebo is an important control in a clinical trial<br><br>  <br>Is this a genuine advertisement?<br><br>Adapted slide from Professor Nick Holford, University of Auckland | Is this a genuine advertisement?<br>http://www.theonion.com/article/fda-approves-sale-of-prescription-placebo-1606<br><br>Placebo is an important control in a clinical trial<br>If there is genuine uncertainty about the active treatment effect<br>If no standard treatment exists, placebo alone control used<br>May be added to standard treatment |
| Slide 34 | Sequence<br><br>• Parallel<br>• Crossover<br>• Titration<br>  • Forced<br>  • Flexible<br><br>Slide courtesy of Professor Nick Holford, University of Auckland | The sequence of treatments can influence what is learned from a trial and the kind of bias that can arise.<br><br>The parallel design has different treatments assigned to different groups of sujects. It is a good design for finding out the answer to the simple 'Does the drug work?' question but gives unclear answers to learning questions that ask about the shape of the dose response relationship of what dose is needed to achieve a particular effect.<br><br>A crossover design uses two or more treatments in each subject. This allows individual dose response curves to be observed and the true shape of the dose response relationship can be determined.<br><br>The crossover design may also have an advantage in terms of statistical power. If it assumed that within subject variability is |

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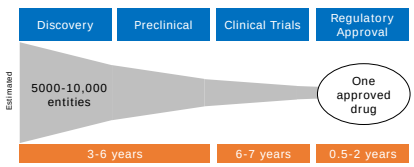
| | | small then fewer subjects need to be studied to detect a treatment effect.<br><br>There are several disadvantages of the crossover design. There may be a treatment carryover effect e.g. due to a drug with a long half-life. This would bias the response seen in a placebo treatment period that followed an active treatment period. If there is some systematic difference between periods e.g. the first treatment is given in the winter and the second treatment is given in the summer, then there may be a period effect that influences the response. Because each subject is asked to take several treatments there is a higher risk of dropout and loss of information from that subject.<br><br>Titration designs are a special kind of crossover design. These may involve giving a fixed sequence of doses ('forced titration') to each subject to learn about the dose response relationship. A more realistic titration design ('flexible titration') involves starting with a low dose and if the subject responds the dose is kept constant. The dose is only increased if the desired response is not reached. |
| Slide 35 | **Adaptive Trial Designs**<br><br>• Innovative design<br>• Allows for adaptations or modifications on a pre-specified schedule as the trial progresses without compromising the validity or integrity of the trial<br>• Aim is to more quickly identify<br>  • Drugs with therapeutic benefit<br>  • Appropriate patient population | Adaptive designs are an innovation that allow for adaptations or modifications to trial design after it has initiated without compromising the validity or integrity of the trial. Patient outcomes are monitored and adaptations made as the trial progresses on a pre-specified schedule and process. Modifications may include dose, sample size, drug, patient selection criteria or "cocktail" mix. |
| Slide 36 | **It's A Long, Costly & Risky Road**<br><br>The process of bringing a drug from idea stage to market<br>• Can take approximately 15 years<br>• Cost is approaching $3B*<br>• Has high attrition rates<br><br>  <br><br><br>* DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016 May;47:20-33. https://www-sciencedirect-com.ezproxy.auckland.ac.nz/science/article/pii/S0167629616000291 | |

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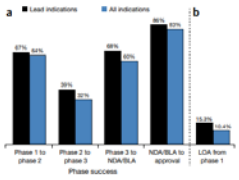
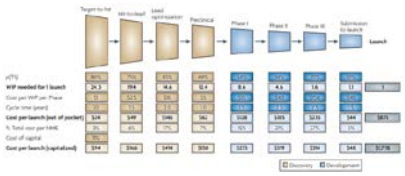
| Slide 37 | **Causes Of High Attrition Rates**<br>• Poor drug-like properties<br>• Poor pharmacokinetics<br>• Lack of efficacy<br>• Safety issues<br>• Commercial interests<br>• Market competition<br>• Patent protection expiry | |
| Slide 38 | **Clinical Trial Attritions**<br>• Only 10-15% of drugs tested in humans are approved<br>• Failure usually due to poor pharmacokinetics, safety issues or unable to meet primary endpoint<br>• Success rate is lowest in Phase 2<br>  • Larger number of patients than Phase 1<br>  • Evaluating both safety & efficacy<br>  <br><br>Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nature Biotechnol. 2014 Jan; 32(1):40-51.<br>http://www.nature.com.ezproxy.auckland.ac.nz/nbt/index.html | |
| Slide 39 | **Drug Discovery & Development Productivity Model**<br>Predicts that at least 9 molecular entities need to enter clinical development every year to yield 1 new molecular entity launch per year<br>  <br>Model based on industry performance assumptions<br>Calculates the number of assets (work in progress, WIP) to achieve one new molecular entity launch<br>Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discovery. 2010 Mar;9(3):203-14. http://dx.doi.org.ezproxy.auckland.ac.nz/10.1038/nrd3078 | |