# **Steps from discovery to market**

**Drug discovery and development**

* Zone of inhibition on agar plate
* Isolate producer, purify, identify organism – molecule
* Confirm activity on bacteria, (relevant bacteria / pathogens / ESKAPE pathogens)
* Check resistance
* Identify gene or protein responsible for producing antibiotic
* Clone gene and express compound
* manufacturing/synthesis/purification issues – large scale production

**Preclinical studies** – is it safe? - does it work in relevant model before testing in humans?

* In vitro – characterise toxicity testing - mammalian cell lines
* animal testing (in vivo)
* Home office licence and ethical approval / ethical approval for animal testing – toxicity
* Safety in at least two animal models
* Maximum dose
* Route of administration
* infection models
* pharmacokinetics – how long does it stay around for – ADME (absorption, distribution, metabolism, excretion) in animal models

Now we’ve finished animal studies, and everything is fine what’s next?

**Clinical trials** – what are the phases?

* Phase 0 – ADME and PK in humans (very small study)  
  Phase I - testing for toxicity in **small number** of healthy people  
  Phase II – small trial (100 or so) with infected patients  
  Phase III – large trial (thousands) with infected patients – expensive, what people do we recruit – wide variance of people to make sure it works across population
* How do we conduct these studies? Things to consider for clinical trials (controls)
* randomised
* placebo controlled – how do we pick groups
* double blind – neither doctor or patient knows if they giving or receiving a placebo/current best treatment or new drug.
* large sample size, range of ethnicities
* => good evidence that drug is non-toxic & effective AND know its pharmacokinetics

**Regulatory Approval and Marketing**

* Market approval (eg FDA in America or EMRA - European Medicines Regulatory Agency).
* What are the challenges now that your drug is approved.
* Marketing / advertising
* Sell it to hospital trust
* Now it’s being used in a large group of people in the open market what responsibilities do we have?

**Phase IV (success on market and monitoring)**

* Post market surveillance – watching market
* Any side effects in population?
* Someone makes another product that outcompetes yours
* The worst hurdle – what could happen now if our drug fails due to antibiotic - resistance occurring?

Excellent job of naming all the challenges – gives you a good overview of the effort, money, challenges to bring a drug to market and even then, it may fail when on the market due to resistance occurring!

**Potential hurdles – These are the lists students might use for their board game**

**Pre-clinical trials:**

* Too toxic in cell line
* Too toxic in animals
* Rubbish half life
* Poor bioavailability
* Doesn’t reach target
* Doesn’t cure in animal infection
* Creates a second disease in animals (off target effects)
* Can’t be given by preferred route

**Phase 0/1**

* ADME/PK in humans is rubbish compared to animals – could not be used as drug – go back and modify?
* Toxic / Non-toxic – could break it down into subgroups of people

**Phase 2:**

* Only cures certain subgroup – roll again
* Cures everyone – proceed
* Cures no-one go back
* Makes another disease worse
* Only works on certain strains
* No better than placebo

**Phase 3:**

* Effective
* Not effective
* Side effects – roll again
* No better than current drug – roll again?

**Regulatory approval and marketing – applying for FDA approval**

* Drug not approved
* Drug approved
* Bad marketing / press
* Production costs too high
* Physicians prefer other alternatives

**Success on market / MONITORING**

* Someone creates a better antibiotic
* Bugs develop resistance
* Company goes bust
* Long term side effects discovered
* Manufacturing facilities shut down on inspection