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# Do's and Don'ts in Early Drug Development

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**Short Communication**

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## Abstract

Over the last decade, the health science landscape has been occupied by numerous biotech's and start-up companies. Most of the time, the scientific level of these companies is outstanding, the way new molecular entities have been developed has evolved with no doubt but despite this evolution changes it must be acknowledged that it still has certain limitations as to the way it functions. Drug development should be regarded as a drawer chest where each drawer represents a drug development step, such as preclinical, preformulation, formulation, regulatory affairs and clinical should be opened and closed at the same time.

This short communication will put the emphasis on the preclinical and the chemistry manufacturing and controls (CMC) phases since it has been noted that these sections are plus or less neglected in early drug development. This is confirmed by the fact that almost 50% of the new chemical entities are failing during the preclinical phase and the fact that new molecular entities are becoming more and more difficult to formulate (showing bad druggability profile), that has shown without a doubt that early drug development should be tailored around these two early drug development steps.

**Keywords:** Reliability and Reproducibility; Drug Development

**Abbreviations:** CMC: Chemistry Manufacturing and Controls; NME: New Molecular Entity; POCs: Proof-Of-Concepts; cGLPs: Current Good Laboratory Practices; PK: Pharmacokinetic; PD: Pharmacodynamy; IND: Investigational New Drug; CTA: Clinical Trial Application; ICH: International Conference on Harmonization.

## Introduction

### Why "Do's and Don'ts"?

a) Because the cost associated with drug development increases drastically after the discovery phase [1-3].

b) Gathering as much as possible information with regards to safety, efficacy and galenic aspects of the drug during early stages of drug development is often a challenge when faced with stresses of aggressive timelines, financial constraints and investor milestones.

c) Also, often under-appreciated is an understanding of the difficulties in bridging the gaps from the lab to the clinic.

### What is Early Drug Development?

a) Phase I drug development usually lasts around five to eight years [4].

b) Several steps are involved and any new molecular entity (NME) will have to go through each of them in order to obtain a drug status suitable for phase I clinical trials.
c) Scientists and clinicians will have to be sure of the reliability, the reproducibility, the safety, and the shelf-life of the drug product during the whole clinical development to get the insurance that the product will give the same performance throughout the different studies.
d) This presentation will briefly cover the different steps that should conducted in parallel(and not sequentially) in order for a NME to become a drug product that is a good candidate for phase I clinical trials.

## Steps involved in phase I drug development

### The preclinical phases:

a) Drug discovery-medicinal chemistry.
b) Lead compound (and back-ups) optimization.
c) Biological proof-of-concepts (POCs): in the quest of the nanomolar efficiency, few chemical entities are readily druggable; POCs are most of the time done with liquid solution/suspension…
d) Toxicology studies performed according to current good laboratory practices (cGLPs) that will support clinical protocols for phase I.
e) This step is the first drug development milestone which represents the discovery, the synthesis and the demonstration of the safety and the efficacy of NME (and its back-ups) in the animal.
f) The time allowed to this step could vary depending if the sponsor is licensing a molecule that has already demonstrated some safety and efficacy or if the sponsor is developing its own compounds from the beginning.
g) A good knowledge of the physiopathology is often a key element that helps in designing not only a good preclinical program but also to predict some Pharmacodynamic effects that will be seen during clinical phases.
h) To accelerate as much as possible the bioavailability prediction of an NME, a lot of IV/IVc equipments/tests are available but the best animal model for the human remains the human.

### Drug - Discovery – Chemistry

a) Thousands of molecules are discovered every year with the help of the combinatory chemistry and the high throughput screening. Far more drug candidates than ever have thus been generated for development. However, as a result of the preferred pharmacological activity process of drug discovery, biopharmaceutical properties of new drug candidates tend to suffer (e.g. water solubility).
b) The API does not only represent the beginning of development but remains the most important ingredient of a formulation.
c) For this reason, it should be characterized (as part of what is traditionally called “Preformulation”) as best as possible prior to being selected for “full development». Thorough preformulation work is the foundation of developing robust formulations. Preformulation must be considered as an interface between the drug substance and the drug product.

### Drug - Discovery – Chemistry: Physical and chemical characterization of an active pharmaceutical ingredient (API)

a) Solubility: APIs are becoming less and less soluble and permeable!
b) Amorphous and crystalline states (polymorphism)
c) Solvated and hydrated states
d) Hygroscopicity
e) Particle size and particle size distribution: Almost always an issue for poorly or not soluble APIs!
f) Salts versus parent molecule: Rational for salt selection!
g) Chirality.
h) All these characteristics are closely connected with the API’s activity and will deeply influence the formulation and the process development strategy.
i) Lipinski mentioned that 35 to 40% of compounds have aqueous solubility less than 10 micromolar at pH 7 (sample size of 90 000 compounds screened at Pfizer in Groton since 1995) [5,6].

### Conclusion

a) a free moiety should not be killed because it is insoluble
b) Bad druggability is then expected. Preformulation/formulation steps has become a crucial step in early drug development

## Drug - Discovery – Chemistry: lead compounds and back-up optimization [7]

### Objective

a) To demonstrate the reliability of both the chemical (yield, purity) and the physical characteristics (polymorphism) of the API irrespective of the batch size.

b) The success of the feasibility or proof-of-concept studies does not mean that the API is stable!
c) Be sure that the same polymorphic form/particle size distribution will be used for preclinical and clinical phases. Each of these forms will have their own behaviour that could jeopardize the reliability of the overall drug product performance (differences between the preclinical and the clinic).
d) This should lead to better reproducibility of the pharmacokinetics (PK) and the pharmacodynamics (PD) of the drug substance from the bench to the phase I scale.
e) Once crystal shape selected, a robust crystallization process should be developed and be reliable and scalable.
f) Polymorphism could occur during formulation development, during stability studies, and after marketing (Ex: ritonavir (Norvir®, HIV protease inhibitor, Abbott): new much less soluble crystal form after 2 years; had to recall the original formulation from the market.

### Some of the properties of the API dependant on the solid-state [8]

a) Dissolution rate
b) Chemical stability
c) Melting point
d) Particle size/Shape
e) Hygroscopicity
f) Filterability
g) Suspension viscosity
h) Bioavailability
i) Flowability
j) Compressibility
k) Bulk and Tap Density
l) Tablet hardness
m) Color
n) Solubility rate

Drug release from the product (and sometimes absorption) can be significantly affected by these above variables!

## The Chemistry Manufacturing and Controls (CMC) development [9]

a) Preformulation/formulation of the drug substance and the drug product.
b) Chemistry, formulation, manufacturing, packaging and stability studies performed according to the current good manufacturing practices (cGMPs).
c) These processes occur in a simultaneous fashion as the preclinical activities.

### Objective

a) Flexibility in the formulation and the manufacturing of phase I clinical supplies because doses are still not defined in phase I.
b) This flexibility should not change the PK profile!

### Other Considerations to Keep in Mind

a) Excipients are not necessarily inactive and should be selected carefully.
b) The dosage form and route of administration intended to be used in clinic should be determined as soon as possible and should be feasible and transferable from the pre-clinical/pilot steps to the clinical/pivotal studies.
c) A correlation between the formulation used in toxicology and clinical studies should exist (often neglected…).
d) Packaging is extremely important (neglected!).

Good results obtained at the beginning might not be reliable because of the packaging.

### The Regulatory Submissions

The regulatory submissions needed to carry out clinical studies, such as Investigational New Drug and Clinical Trial Application (IND for the United States and CTA for Europe and Canada), as per cGMP, cGLP, cGCP, and the International Conference on Harmonization (ICH) guidelines.

### The Clinical Studies

The clinical studies (safety and PK) carried out according to the current good clinical practices (cGCPs).

## Conclusions and Final Thoughts

a) Phase I drug development should be tailored around the CMC.
b) Solid-state chemistry should ultimately drive the API selection:
c) Which crystal form and particle size should be selected after preclinical and early clinical development.
d) Decision based on the best physico-chemical characteristics (best candidate may often be the best compromise).
e) Each scientific discipline (i.e. pre-clinical, pharmaceutical R&D, clinical, etc.) should work very closely, not sequentially, in order to minimize risk of failure or costly delays.

**It should be aware that**

a) Few chemical entities that are readily druggable (POC are most the time done with liquid solution/suspension).
b) Often dose forms used in phase I/bioequivalence will not be the commercial formulation.
c) Formulation scientists will depend on clinical scientists to provide dosing information in order to fine tune formulation.
d) Formulation affects toxicology support
e) A correlation between the formulation used in toxicology and clinic should exist (often neglected).

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