Chapter 12
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Addressing Gaps in Early Drug Development: A Focus on Preclinical and CMC Phases

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ABSTRACT

This present study serves as an indispensable guide for researchers, offering valuable insights to navigate the complexities of drug discovery. Over the last decade, the health science landscape has been occupied by numerous biotech and start-up companies. Most drug development policies in developing countries are enacted without achieving the desired results. Minimizing the uncertainties associated with drug development by strengthening the aforementioned factors is a major catalyst that can encourage pharmaceutical industries to invest more money in drug development. The scientific caliber of these companies is typically excellent; there is no doubt that the development of new molecular entities has changed over time, but it is still necessary to recognize that these developments have constraints on how they may be used. Drug development should be regarded as a drawer chest where each drawer represents a drug development step, such as preclinical, pre-formulation, formulation, regulatory affairs and clinical should be opened and closed at the same time. However, it should be kept in mind that early drug development should rely on seasoned people showing proven track records in development; prior to relying on science, most research scientists think that scientific degrees give all the answers and the ability to succeed.

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 more 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 a bad druggability profile). This shows

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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

1. INTRODUCTION

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

1. Because the cost associated with drug development increases drastically after the discovery phase [1-3].
2. Gathering as much as possible information available in regard to safety, efficacy and galenic aspects of the drug during the early stages of drug development is often a challenge when faced with stresses of aggressive timelines, financial constraints and investor milestones [3a].
3. Also, and often under-appreciated is an understanding of the difficulties in bridging the gaps from the lab to the clinic.
4. These above points have become more and more important during the COVID-19 event, where translational research was demonstrated to be the crux of the matter, trying to accelerate the development of safety assessment technologies from the bench to the clinic
5. No one of the above points could be done without the help of seasoned executive people who have a proven track record in early drug development, irrespective of the pharmaceutical technology (small molecules, biologics, CART cells, ….)

1.2 What is Early Drug Development?

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

a) 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. This last point is very important and highly neglected since a lot of people think that their technology will be better than regulatory requirements. Regulatory agencies do not care about the science, they will

assess the clinical drug application by “ticking” the boxes, irrespective of their potential to cure cancer or any life-threatening conditions.

b) Scientists and clinicians will have to be sure about the reliability, reproducibility, safety, and shelf-life of the drug product during the whole clinical development to ensure that the product will give the same performance throughout the different studies [3a]. Again, this step is neglected, with scientists focusing much on the “at a glance” results rather than their reliability and reproducibility over time.

c) This presentation will briefly cover the different steps that should be conducted in parallel (and not sequentially) in order for an NME to become a drug product that is a good candidate for phase I clinical trials [3a].

2. STEPS INVOLVED IN PHASE I DRUG DEVELOPMENT

2.1 The Preclinical Phases

a) Drug discovery-medicinal chemistry.
b) Lead compound (and back-ups) optimization.
c) Biological proof-of-concepts (POCs): in the quest for nanomolar efficiency, few chemical entities are readily druggable; POCs are most of the time done with liquid solution/suspension…Formulation development has then become more and more important since it will help the molecules showing weak biopharmaceutical properties to become bioavailable.
d) Toxicology studies performed according to current good laboratory practices (cGLPs) that will support clinical protocols for phase I. With startup companies, formulations of the test articles have not been fine-tuned therefore the toxicological profiles can be biased and underestimated when the drug candidate will be formulated for clinical trials on humans.
e) This step is the first drug development milestone which represents the discovery, synthesis and demonstration of the safety and efficacy of NME (and its back-ups) in the animal [3a].
f) The time allowed for 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 physiopathology is often a key element that helps in designing not only a good preclinical program but also in predicting some Pharmacodynamic effects that will be seen during clinical phases [3a].
h) To accelerate as much as possible the bioavailability prediction of an NME, a lot of IV/IVc equipment/tests are available but the best animal model for the human remains the human [3a].

2.2 Drug - Discovery – Chemistry

a) Thousands of molecules are discovered every year with the help of combinatory chemistry and high throughput screening. Far more drug candidates than ever have thus been generated for development [3a].

b) 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).
c) The API does not only represent the beginning of development but remains the most important ingredient of a formulation [3a].
d) 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 [3a]. As mentioned earlier, weaker biopharmaceutical properties of the small molecules increased formulation development importance. Thus, to correctly characterize molecules, wet chemistry showed its limitations and solid-state chemistry became more and more important to bridge the gap between biopharmaceutical properties and formulation development.

2.3 Drug - Discovery – Chemistry: Physical and Chemical Characterization of an Active Pharmaceutical Ingredient (API) [3a]

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 non-soluble APIs!
f) Salts versus parent molecule: Rationale 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].

2.4 Conclusion

a) A free moiety should not be killed because it is insoluble. It can be easily viewed on different agency websites that 30-50% of small molecules filed to any regulatory agencies to date, were BCS 4 class molecules, thus showing low solubility and permeability characteristics.
b) Bad druggability is then expected. Preformulation/formulation steps have become a crucial step in early drug development.

3. DRUG – DISCOVERY – CHEMISTRY: LEAD COMPOUNDS AND BACKUP OPTIMIZATION [7]

3.1 Objective

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

a) The success of the feasibility or proof-of-concept studies does not mean that the API is stable!
b) Be sure that the same polymorphic form/particle size distribution will be used for the preclinical and clinical phases. Each of these forms will have its own behaviour that could jeopardize the reliability of the overall drug product performance (differences between the preclinical and the clinic).
c) 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.
d) Once the crystal shape is selected, a robust crystallization process should be developed and be reliable and scalable.
e) 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.

3.2 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!

4. 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 were performed according to the current good manufacturing practices (cGMPs).
c) These processes occur in a simultaneous fashion as the preclinical activities.

4.1 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!

4.2 Other Considerations to Keep in Mind

a) Excipients are not necessarily inactive and should be selected carefully. As an example, lactose tends to be avoided for diabetic patients.
b) The dosage form and route of administration intended to be used in the 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. There is a gap between a proof of concept on animals and a reliable dosage form. Scientists are not aware enough of that. Another reason why seasoned development people should surround early drug development.
c) To be ahead of surprises that may be caused by formulation and route of administrations, a correlation between the formulation used in toxicology and clinical studies should exist (often neglected…).
d) Packaging is extremely important (neglected!). Dosage forms should be stable not only over the time of the clinical study but over a longer period of time, If the packaging is changed, a new stability study of the dosage form, in this new packaging will have to be carried out.

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

4.3 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. Quite often for cancer studies, multi-centric studies will be carried out to enhance the number of patients to be recruited and treated. However, the fact that FDA has accepted an IND does not mean that the same document will be accepted in Europe (MHRA), and Canada (CTA). This will impact the timelines and the go-no-go decisions for any development and financing related to the project.

Furthermore, it is highly recommended to ask for a pre-submission meeting to government agencies to clarify some questions that could not be answered by consulting guidelines. Pharmaceutical technologies are evolving and so are the guidelines [10].

4.4 The Clinical Studies

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

5. CONCLUSIONS AND FINAL THOUGHTS

a) Phase I drug development should be tailored around the CMC. It is quite difficult to make that assumption understood by stakeholders. A lot of

people think that, even in phase, money should be kept for what they think will be expensive: the clinic. However, CMC, proof-of-concepts and toxicology are more than often more expensive than a phase clinical study.

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).

Each scientific discipline (i.e. pre-clinical, pharmaceutical R&D, clinical, etc.) should work very closely, not sequentially, to minimize the risk of failure or costly delays.

5.1 It should be aware that

a) Few chemical entities are readily druggable (POC are usually 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 to fine-tune formulation.
d) Formulation affects toxicology support
e) A correlation between the formulation used in toxicology and clinic should exist (often neglected).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Biography of author(s)

Francois-Xavier Lacasse
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He is a seasoned executive, specializing in drug development with in-depth experience and scientific expertise gained as head of research and development activities as well as regular exchanges and discussions with regulatory agencies (Health Canada, EMA and FDA) through his 25 years of experience in the pharmaceutical industry.

He is an Associate professor at the Faculty of Pharmacy at the University of Montreal. He is recognized as being able to link the theory of pharmaceutical sciences and professional practice in drug development (transition from animals to humans, transposition of non-clinical toxicological results to humans). He is the winner of the prize for excellence in teaching as a career teacher in 2019 and 2023. He is responsible for several radio and television interventions on state TV and radio channels. His peer as a leader who demonstrates strong analytical skills, and rigour, while fostering a meaningful work environment and strong cohesion within a team, recognize him.

He is associated with the management, supervision and writing of the scientific and regulatory documents of more than 100 projects, including non-clinical (toxicology) and preclinical parts, clinical section, and chemistry and manufacturing and controls (CMC), for small molecules, biologics and complex molecule (including 505 b2, BLA……), under the different route of administrations (transdermal, oral, buccal, parenteral) and delivery systems (solid oral, parenteral and semi solids dosage forms, including dermal and nanoparticular and liposomal delivery systems).

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