Optimising bench science to withstand regulatory scrutiny

1. Introduction

The EU commission has on numerous occasions acknowledged that SMEs and research spinoffs are an intellectual driving force within the EU. The EU commission has also provided numerous funding initiatives to foster academic pursuit per se as well as state of the art research having a commercial/commercialisation prospect. However, translation of bench science to the clinic is a huge endeavour [1,2], where academics are seldom prepared for the challenges they face when taking laboratory findings to commercialisation (this would include also patent application and status) [1,3]. Furthermore, a proportion of drug discovery efforts fall through at the Regulatory approval process stage, and, although “unquantifiable”, it is assumed that during negotiations between academic spinoffs and start-ups with angel investors and the pharmaceutical industry, a devaluation of the academic work might occur. One of the reasons might be that academic efforts and scientific data generated do not withstand regulatory scrutiny. This aspect is not surprising since there is an un-heightened awareness of pharmaceutical regulatory concepts within academia.

Every investment made by research funding bodies should in principle be contributing towards sustainable innovation and therefore, the fact that data generated in academia is many times considered exploratory, intrigued us and as a consequence here we will share our regulatory experiences (since we have academic backgrounds but have taken on roles within regulatory bodies) to help raise awareness within academia of certain concepts that would help academic efforts withstand regulatory scrutiny. This will hopefully be of added value to bench science carried out by academia, in order to avoid that pharmaceutical industries re-do drug development process. Over the years we have learned several lessons related to specific processes and these are presented concisely for convenience. These might be of considerable interest to academia and academic spinoffs to take on board when moving forward with their research and product developments. We have also compiled a reading list of select texts and useful webpages (see Supplemental material) to give further context to lessons presented.

2. Recommendations

2.1. Regulatory strategy

2.1.1. Know the regulatory guidelines and EU laws regulating the area

A complex regulatory system for regulating medicines exists in the EU, however, industry and academia can benefit from guidelines outlining the pre- and post-marketing requirements. These are available on the European Medicines Agency’s (EMA) website www.ema.europa.eu and the European commission’s website “Notice to applicants”. A good understanding is key to deciding the best regulatory strategy to successfully develop a medicinal product and bring it to human trials.

2.2. Quality systems

2.2.1. Establish a quality system

It is important to establish, implement and maintain a Quality System designed to help monitor systems in place, facilitate continuous improvement and manage change. The quality system should be designed in a manner that will monitor the development of pre-authorised medicinal products to help detect any change to their potential risks or efficacy.

Standard operating procedures (SOP) should define clearly the available triggers for the start of the process as well as adherence to timelines as mandated by the European Commission (if applicable) as key performance indicators (KPI). These SOPs should also cross-link to other processes or other documents such as policies or guidelines. SOPs should incorporate risk-based thinking and be pragmatic but at the same time need contain the necessary details required to produce outputs of good quality.

2.2.2. Apply principles of good laboratory practice (GLP)

The principles of GLP promote the quality and validity of data generated in the testing of chemicals and prevent fraudulent practices, therefore if the laboratory is GLP accredited, this guarantees a certain quality and reassurance of the outputs carried out by the laboratory.

2.2.3. Record keeping

Procedures should be in place to maintain proper documentation and records. Such procedures should specify what documents should be retained for record keeping and for how long. Documents may be paper-based or electronic and the involved personnel should use Good Documentation Practices regardless of the medium used. When using chemicals and reagents in wet laboratories, Certificates of Analysis should be retained.

2.3. Chemistry manufacturing control

2.3.1. Characterise your active substance

When testing chemicals in biological systems it is important to start screening your compound and impurities early. Impurity profiles will have to be well characterised and detected unknown impurities will need to be qualified. Certificates of Analysis for batches tested and chemicals used in experiments need to be stored as they could provide insight when findings cannot be replicated in the same laboratory. Issues on potential genotoxic impurities will have also to be identified early. “Alerting structures” associated with mutagenesis present in the
starting materials and intermediates of drug substances should be avoided if possible.

The methods used to analyse impurities throughout the development of the drug substance need to be adequately validated. Analytical validation information including experimental data for the analytical procedures used for testing the drug substance (accuracy, precision, specificity, quantitation limits, and linearity) should be documented.

Physico-chemical and other relevant properties of the drug substance such as light-sensitivity, solubility, crystallization, polymorphism and batch size should be characterised. Investigators should document significant changes made to the manufacturing process of the active substance used in producing non-clinical, clinical, scale-up, pilot, and production batches.

2.4. Non-clinical development

2.4.1. Choice of animal models and evaluation of disease-relevant endpoints

The use of relevant and justified animal models should be documented. Animal models of human diseases are nowadays discussed with respect to three well-established criteria; face, predictive and construct validity. The methods used should be state-of-the-art. Investigators could engage in a scientific advice procedure (refer to section “Clinical Trials” for further explanation) with Regulators to obtain a view on the translational relevance of the animal model. Academia should explore if scientific advice procedures could be funded through research grants or feasibility studies.

In practice, the pre-clinical development program should also aim at establishing the medical plausibility that supports and/or complements the clinical data used as pivotal evidence to support the therapeutic indication claimed by prospective applicants. The goal of a medical plausibility approach is to direct the experimental design towards the measure of disease-relevant endpoints, and on the translatability of these measures to a potential clinical setting. This is of particular importance when considering drug development for rare diseases [4].

2.4.2. Drug product development

Appropriate efforts should be made in the development of the most appropriate dosage form, balancing between the need to keep it as simple and straightforward as possible and the need to cope with the unfavourable physico-chemical or biopharmaceutical properties of the drug substance.

The ICH Q8 guideline on Pharmaceutical Development should be followed in defining the Critical Quality Attributes of the Drug Product, capable of assuring the Quality Target Product Profile (QTPP). The underlying principles of Quality by Design (QbD) should be applied especially when a complex formulation is envisaged and/or when non-standard technologies are involved. The outcome of properly designed experiments will ease the further scale-up to commercial scale, allowing the critical process steps to be identified and properly considered in the validation plans.

A suitable bridging strategy between the dosage form(s) used in the early and pivotal clinical trials and the one proposed for commercialization needs to be implemented. With respect to comparability, a sound scientific background as well as a suitable statistical methodology should be used for the comparative assessment of pivotal quality attributes.

3. Clinical trials

Clinical trials carried out by non-commercial sponsors and academia, like all other clinical trials conducted in the EEA, must comply with EU laws on clinical trials. The Investigational Medicinal Product (IMP), in any clinical trial, has to be released according to Good Manufacturing Practice (GMP) from an authorised company, and a validated Qualified Person for Pharmacovigilance (QPPV) has to be settled at the beginning of the study. The European Commission has also issued a new Regulation for Clinical Trials that should come into force starting from 2020 [5].

Clinical Trial designs need to be agreed with Regulators through “Scientific advice”. Scientific advice is a procedure where applicants (academic/sponsors/NGOs) engage with Regulators to obtain advice on their clinical development programs. Areas of expertise at the EMA-CHMP’s Scientific Advice Working Party (SAWP) is available on all areas but specifically in non-clinical safety, pharmacokinetics, methodology and statistics and certain therapeutic fields such as cardiology, oncology, neurodegenerative disorders and infectious diseases including HIV/AIDS.

To withstand regulatory scrutiny, a fundamental concept is that research must be prospectively designed with pivotal endpoints established in order to eliminate potential biases in the interpretation of the results. To this effect the CHMP has published a series of guidelines on clinical evaluation of medicinal products used in different medical conditions that pertain to major therapeutic areas. These guidelines discuss which primary endpoints are suitable for the analysis of clinical efficacy and safety.

Protocol assistance is a dedicated tool by EMA that may help researchers from the academia to correctly design trials for investigating orphan medicines for rare diseases. To foster the development of medicines with major public health interest, the EMA launched the PRIME program in March 2016. This program is dedicated to all stakeholders who seek marketing authorisation for drugs that represent therapeutic innovation in unmet medical needs. It allows interactions with the regulatory system during the early development phase of medicinal products and provides enhanced regulatory guidance and accelerated assessment. Small medium enterprises and researchers from the academia may enter the program by providing only proof of principle evidence, i.e. sound pharmacological rationale, demonstration of relevant non-clinical effects of sufficiently large magnitude and duration, and tolerability evaluation in first in man trials [1].

4. Orphan medicinal product development

The EU Orphan regulation provides incentives for the development of medicinal products intended to treat, diagnose, or prevent rare diseases. The incentives provided to sponsors currently include access to protocol assistance at the EMA, access to the centralized procedure, access to 10-year market exclusivity, access to National incentives, and access to Community research programs. In order to obtain such incentives an Orphan designation status is required and should firstly be obtained. To successfully engage with the EMA’s COMP to obtain a positive opinion, applications should clearly establish the “significant benefit” of the proposed medicinal product in line with the proposed “medical plausibility” (see ‘Non-Clinical’ section above), in which a certain level of evidence is expected. Significant benefit is unique to the European Orphan medicinal products regulation and is defined as a clinically relevant advantage (e.g., improved efficacy or safety) or a major contribution to patient care (e.g., an improvement affecting quality of life).

5. Research funding

The EU has funding programmes for research and innovation. For example, academic researchers in the field of medicine development may be eligible for funding under the “Health, demographic change and wellbeing” thematic area of the Horizon 2020 work programme running until 2020. Applications should also present a position by the researchers that they are aware of the regulatory considerations (both legislative and scientific requirements) for the product they are developing, where applications should contain a description of the plan of obtaining regulatory approval (e.g., the clinical development plan for phase I to III trials) at a development stage. Funding applicants can also
make use of scientific advice procedures that the EMA or national regulators offer to further strengthen their research proposals.

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Appendix A. Supplementary data

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References


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