Regulatory and Other Requirements in Drug Development

Overview

This article describes how, in conjunction with good and comprehensive science, a knowledge of TGA/Regulatory requirements and guidelines at the earliest stages of drug discovery and development should enhance the quality of the development. In essence, the same principles apply for a drug, from initial development through to commercialisation, Irrespective of the drug type and technologies involved. Knowledge and abidance of these requirements and guidelines ensures good and efficient science, reducing the risk to need to repeat expensive and time consuming experiments and investigations, both *in-vitro* and *in-vivo*.

The pathway from drug discovery to the registration of a commercial therapeutic product is long, expensive and challenging. It requires a multiplicity of scientific expertises and experimentation. The organisational structures in the pathway vary, at discovery most likely as an exclusive research unit but upon development more likely a stand-alone or a multi-national company. No drug can be commercial unless it has been approved for supply by a Regulatory Agency (or Authority) such as the Australian Therapeutic Goods Administration (TGA). It is in the interest of scientific and management personnel in drug discovery/development organisations to have knowledge of and understanding of both the science and regulatory requirements for eventual product registration.

The end point of drug development is to have an Agency approved and registered formulation(s) or drug product, demonstrating established efficacy and safety. Active pharmaceutical ingredient (API) ie drug and its formulation(s) must be able to be manufactured consistently to a determined process and have realistic storage conditions and shelf life. Ultimately the cost of delays in ultimate drug product registration are the loss of sales income for delay periods.

The chemistry requirements of a drug and its formulation(s) can be found in the Quality module of the Common Technical document (CTD), as issued by the *European Agency for the Evaluation of Medicinal Products* (EMEA).

It is also in the interest of the TGA scientists/evaluators to understand the science (frequently now cutting edge) of a new drug and/or dose delivery system, enabling regulators to review and pass judgement on submitted documentation with appropriate and requisite expertise.

A challenge for early drug development institutions and their researchers is to recognise and understand these requirements and the benefits arising from such an understanding. These benefits include focused R&D with definitive milestones and end-points, defined by requirements to supply for a Clinical Trial (CT) and a subsequent "Application to Market" to an appropriate Agency. Requirement details vary from (international) region to region. The employment and guidance of regulatory and GMP consultants is recommended to all researchers, where most of whom (of researchers) are likely not familiar with detailed requirements.

R&D projects are likely to be sold or partnered with drug companies. It can be a problem for academica in identifying and making a deal with commercial partner(s). Difficulties can be reduced when unflawed and sound, cohesive documentation describing a Project's various parameters makes a project more collaborative or saleable. Researchers having performed required experiments with appropriate methodologies and sound documentation have enhanced project sale value. Collaborating or purchasing companies are loath to repeat experimentation in drug discovery and early development phases, both costly in monetary terms and time, to rectify shortcomings for Clinical Trial applications and subsequent product registration.

Having been provided with fulsome and reliable data and describing and concluding documentation, a purchaser has more confidence in the integrity and depth of data provided and of the scientists involved.

R&D – drug and formulation - New technologies and challenges

Drug discovery may include activities on small molecules, (new) biologicals or bio-similars and nano technologies. With the ever increasing ability to research i*n-silico* at the initial stages of design, drug designers can target a receptor more specifically.

Current R&D includes the discovery of new drug types and their presentations. Protein-based drugs present opportunities and challenges in particular. They can be more indicator and site specific; the challenge is to manufacture batches to give a consistent formulation and successfully minimise impurities. Revised manufacturing techniques may be needed, especially for upscaling and maximising process efficiencies. Where a sterilised product is required, can the API molecule (and other ingredients) be sterilised without decomposition, likely with heat or be filter sterilised without loss? Determination of parameters such as these and many others, together with their complete documentation, are requisite for drug development completion and eventual registration of end-product..

A major challenge of drug development is that the manufacture of the drug gives consistent physical properties of large molecules and control of impurities. Ingredient physical properties directly affect the performance of product presented in solid dose form. Consistency in these (and chemical properties) must be demonstrated so that a commercial product, post-registration, will have the same properties (and efficacy) as shown during development and described in registration documentation, ie the properties of post-registration batches must be the same as pre-registration batches.

These challenges are magnified with the development of bio-generics where they must match the properties of the innovator drug. (Government world-wide encourage generics as they are cheaper to subsidise.)

Analytical considerations

Drug development relies entirely on the authenticity and accuracy of measured (numerical) parameters and subsequent interpretations and decision making, based upon determined data.

Regulatory agencies rely on data, not opinion, in making adjudications. Consequently, the accurate measurement of a multiplicity of parameters is a fundamental requirement of drug development, from its earliest stages to completion of human clinical trials and stability trials of the packaged drug formulation (and drug itself). This includes parameters for such activities as analyses of physical and chemical parameters of an API, its formulation(s) and final packaged product as well as analyses associated with animal experiments and human clinical trials.

Whether using newer or older technologies, all test methods used in the chain of development need to be validated at the earliest opportunity during drug development so that the resultant test data is accurate and trustworthy. In particular, and where appropriate, stability indicating methods need to be developed and validated.

Significant and expensive decisions are based upon the integrity (or otherwise) of test result data.

The introduction of HPLC in the 1980s was epoch making as it enabled analysts to separate and quantitate soluble components rapidly. With the introduction of equipment computers and of MS detectors, rapid identification of components has improved and limits of detection and quantitation become smaller. This equally applies to the analysis of a drug, drug formulation and clinical samples.

Two important factors regarding analytical techniques should be considered. The adage that an analysis is only as good as the soundness of the sample still applies – perhaps more difficult now with smaller quantities of sample actually tested. Also, as many techniques are comparative, the accurate qualification and maintenance of Reference Standard is also of prime importance. Where available, Reference Standards should be certified by and obtained from an appropriate external Authority (eg British or US Pharmacopoeias).

It is vital that Reference Standards for new molecules must be developed, qualified and maintained at the earliest opportunity for their use in subsequent (comparative) analyses.

Impurities

Inevitably, drugs and formulations have impurities whose identities, levels and impact must be assessed. Impurities may be sourced from the extraction and/or synthesis processes, other chemicals (eg solvents) or storage breakdown products. As drug impurities must be assessed for their toxicology as early as pre-human clinical trials, the basic extraction/synthesis process of a drug is locked in at the very beginning of the drug development. Impurity guidelines are detailed in ICH Guidelines Q3A to Q3D.

Packaging and stability

Optimum packaging materials and pack design, together with appropriate storage conditions need to be established as early as possible for both API and formulation(s). Such choices may be the difference of the drug and formulation, by having a viable shelf lives under determined storage (and use) conditions being commercial or not, ie both a drug and its formulation, using optimal packaging must be stable for commercially and consumer reasonable temperature conditions and shelf life.

APIs and drug formulations, as packaged, must be designed to prevent or minimise variation and/or degradation over time. The stability of the API and formulation should be investigated at the earlier opportunity. APIs must be sufficiently and realistically stable for investigative and end-use. Clinical materials must be stable over the duration of a clinical trial.

No drug or product is registered by an Agency without data supporting proposed storage conditions and shelf life. No determined or realistic shelf life - no API nor product !

The ICH stability guidelines are found under ICH Quality guidelines
https://www.ich.org/page/quality-guidelines

Further stability requirements are described in Codes of GMP, described in the next paragraph.

Good Manufacturing Practice (GMP)

The principles and application of GMP relating to both drug and formulations should be understood at the research stage and certainly by early development stage. There is much valuable guidance for researchers involved in manufacturing processes, good laboratory practice, QA systems and requisite documentation.

There are separate Codes and Annexes for both Active Ingredient and Product manufacture and testing. These are found on TGA website *Manufacturing principles for medicinal products* https://www.tga.gov.au/publication/manufacturing-principles-medicinal-products under the paragraph *The PIC/S guide to GMP for Medicinal Products* .

Both Codes have Chapters specifically addressing materials produced for use in Clinical Trials.

GMP requires the qualification/validation of, in summary, environment control, manufacturing processes, packaging processes, cleaning procedures and test methodologies . Under a Validation Master Plan, validations must be initially performed and then re-performed at suitable and designated intervals on manufacturing environment, equipment, manufacturing processes and analytical methods. Validated processes and test methods ensure consistency of manufactured products and accurate and reliable test data.

Clinical Trials

For the best chance to assess whether the drug is a candidate for further development, its clinical trial formulation(s) must be optimised to present the best chance in presenting and assessing a drug with a patient. Inevitably, though perhaps wrongly, a failed (efficacy) clinical trial does not blame a poor dose formulation, which gives sub-optimal dose delivery.

Application to perform a clinical trial should include impurities determination and evaluation, determination of shelf life (both drug and its formulation). The formulation for a clinical trial must have demonstrated stability over the course of the trial. Without a stable formulation, clinical results can be skewed and misleading owing to loss of potency of the drug during this and/or toxic decomposition products being presented to a trial candidate.

Note that for a parenteral dose, even in Phase I, for ethical and possible insurance claim reasons, it is very much recommended that a suitably licensed sterile manufacturer produces the dose form. Also note that (in Australia) manufacture for Phase II trials is required to be by a licensed or overseas accredited manufacturer. This includes Release to Supply of the product to the Clinical Trial site. Expert advice on the GMP status of an existing or potential batch of product and its use in a clinical trial of any Phase should sought, well prior to the commencement of preparing an application for a clinical trial. Such requirements vary from region to region.

In particular, it is recommended that all researchers are familiar with the manufacturing and quality requirements for Release for Supply to a Trial, whether in Australia or overseas.

Details of Clinical Trial products manufacturing requirements are complex and are described on the TGA site https://www.tga.gov.au/book-page/manufacturing#manexe

Documentation

There is an adage “If it’s not written down, it hasn’t been done”. Detailed and accurate on-going documentation during all phases of R&D is essential for current and future use, ie decision making and applications for IP protection and sale, project sale, application for clinical trials and eventual product application to market. Such documentation, especially experimental is not an *aide memoire* but is most likely to be needed, edited and used by other personnel, perhaps months or years later and likely by personnel of another organisation.

All documentation must be permanent, accurate and be appropriately and responsibly "signed off" and dated.

Specifications

Specifications define those test parameters and their limits, leading to and maintaining safety and efficacy of drug and other formulation raw materials. Draft specifications should be introduced at the earliest opportunity of drug development to produce, measure and control drugs and their formulations, ensuring consistency or improvement through their development.

As well as chemical identity and purity/impurity levels, specifications also define physical, and microbiological/viral parameters of raw materials and products. The consistency of physical parameters (eg polymorphs, particle size and shape etc) is vital to ensure consistent performance of drug products, both during manufacture and dose delivery.

Specifications are also required for packaging materials, cleaning materials, processing environmental conditions, product in-process storage and transport conditions etc.

Australia uses the British, European and United States US Pharmacopoeias as default standards. These Pharmacopoeias variously have specific raw material, finished product monographs, together with the "Introduction" and "General Notices". The General Notices include and describe requirements of ingredients, product type (eg tablets, capsules, injections etc), packaging materials and general analytical and microbiological test techniques.

While there may not be a specific API or product monograph, registered products must comply with the relevant General Notices. The Pharmacopoeias are an invaluable source of information regarding all aspects of drug products and their constituents, associated "good science" and as a guidance in the development of new product specifications. A description of usage of the BP can be found on the BP website https://www.pharmacopoeia.com/how-to-use-the-bp.

TGA – Resource and Opportunities

TGA scientists and reviewers are required to keep abreast of the latest developments of drug design and formulation/dose delivery systems. Eventually, TGA reviewers will assess their suitability for commercial sale and so must be cognisant of the science presented in a drug or Product *Application to Market*. This assessment also applies to new and existing manufacturing methods, analytical and microbiological test techniques when data describing a test method development and results using a subsequently validated method are presented.

TGA scientists are initially educated at an academic institution. Employment opportunities involving regulation of medicines continue to increase at TGA, as does the opportunity to liaise with the R&D sector though scientific societies and directly.

RACI and other Societies

The RACI has a number of entities focussing on therapeutic goods R&D and commercial supply. These include:

- Medicinal Chemistry and Chemical Biology Division
- Bioactive and Discovery Group (NSW)
- Pharmaceutical Science Group (NSW)
- Pharmaceutical Sciences Group (SA)

To a greater or lesser extent these entities interface with the TGA and periodically invite TGA presenters to address seminars or conferences.

It was noteworthy that a significant proportion of presentations at the 2017 Congress involved medicinal chemistry presentations.

Has RACI got a coordinating role with the TGA in promoting learning and activities of mutual interest within the scientific community? Only if volunteers on all sides work to establish and coordinate relevant contacts and activities.

Other organisations involved are the RACI kindred Society, ARCS (representing those working in regulatory affairs, clinical research, health economics, medical information regulatory affairs personnel in drug supply and also Ausbiotech (representing Australia's biotechnology industry).

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