# A Summary of the Pharmaceutical Development Process, the Changes and Challenges and Future Opportunities

**In this white paper, Broughton summarises the 'historical' development plan for pharmaceuticals, the changes that have occurred with regards to differential development including the requirements for biologicals, the typical challenges the industry faces now and, in the future, the opportunities this brings.**

**This white paper forms a simplified reference point for developing pharmaceuticals both now and the future and some of the choices/challenges companies have.**

Many scientists working within the pharmaceutical sector over the past 30 years will recognise the typical pre-clinical safety development plan (see figure 1).

The duration of discovery activities is defined by the speed of success and the amount of screening conducted, therefore they are included here for completeness only. Once promising targets are identified via efficacy studies, disease models and Pharmacokinetics (PK) studies, the initial safety screening occurs with in-silico structure activity modelling and *in vitro* mutagenicity assays to candidate selection with *in vivo* screens to identify target organ toxicity and cardiovascular endpoints.

Once candidate selected, and in many cases, this may involve multiple compounds of the same class, development begins in earnest with dose-range general toxicology studies re-assessing the previously identified target organ toxicity with an aim to defining early exposure safety margins in both rodent and non-rodent species. Concurrently, costly drug synthesis is green lit alongside key formulation development activities, analytical method development and validation exercises. To coincide with the arrival of the GMP drug substance with appropriate certificate of analysis, the safety assessment studies comprising a battery of general toxicology, safety pharmacology, genetic toxicology and formulation stability will commence to support entry into the clinic. The readout of these studies, subsequent regulatory submission and internal safety board swiftly leads into the first clinical trial, typically in healthy volunteers.

The development of a drug does not cease during these short First Time In Human (FTIH) trials, moving into early reproductive toxicology studies looking at Embryofoetal Development (EFD) and also starting longer term general toxicology which not only serves as a means to further investigate target organ toxicity and margins of safety but also to act as dose range finders for the lifetime carcinogenicity studies, the protocols for which require advanced Food and Drugs Administration (FDA) approval. Chronic toxicity studies in rodent and non-rodent species continue the comprehensive safety assessment battery of studies alongside and coinciding with fertility studies in both male and female rats and also phase 2 clinical trials, which are multi layered trials in patients. Lifetime carcinogenicity studies in rats and mice (the latter now benefiting from a shorter 6 month study in transgenics) commence alongside a multi generation peri and postnatal development study which now concludes the reproductive and developmental process from pre-mating to sexual maturity of offspring.

Once the phase 3 efficacy clinical trial commences, the road to Marketing Approval Application (MAA)/New Drug Application (NDA) submission and marketing is almost over, assuming proof of concept and no carcinogenicity is proven, not withstanding the timely and arduous regulatory submission process.

**The Challenges**

The timescale for this development process is rarely as little as the 5.5 years illustrated in Figure 1 since the key phases and

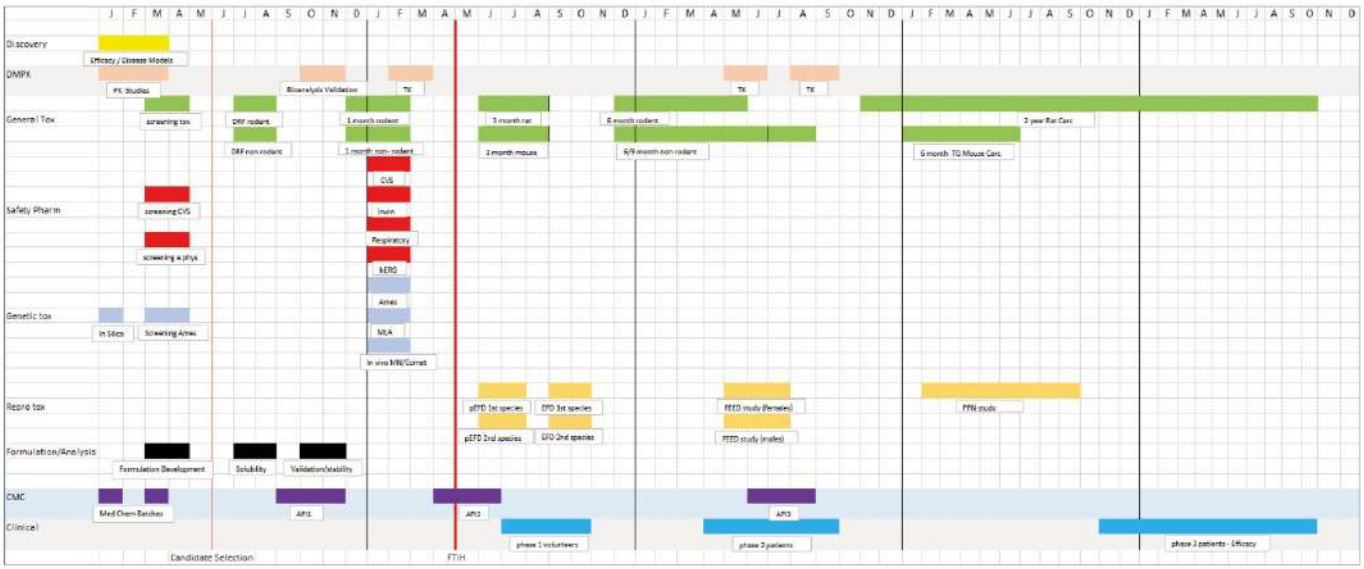


*Figure 1. Classic Development Plan for new medicine*

decisions made during discovery, candidate selection, FTIH and prior to each large spending milestone (carcinogenicity studies, phase 2, 3 clinical trials) often require high boardroom-level cost-benefit discussions which prioritise a portfolio leading to acceleration or deceleration of the process for a particular drug. This timescale also assumes timely method development and validation of analytical work, drug synthesis, stability, analysis and release and no additional studies, investigations or delays due to toxicity. A popular school of thought suggest if the development has no challenges, the drug's efficaciousness will!

This is where the first dichotomy begins, do you try to maximise return on investment by speeding up the development plan thereby beating competitors to market and maximising the patency for exclusivity or do you take the conservative approach, preventing costly delays to studies or cancellation charges thus minimising unnecessary spend on new drugs that may never make it to market?

Pharmaceutical companies have attempted to answer this question by the landscape over the last 20 years. The main change has been selection of the *in vivo* Contract Research house (CRO) more often, which at its best involves using experienced 'contractor' staff only when you need them thereby freeing up your own staff for the more complex or confidential science. This also leads to minimising the spend and maintenance on building new labs and animal houses, that you would rarely fill. At its worst, it involves an equally expensive monitoring oversight ensuring the CRO's run the studies exactly as the sponsor wishes, and ultimately as there is greater reliance on CRO's who largely now own the expertise, demand has driven the price upwards and consequently, the CRO availability, not to mention animal availability, has reduced. Ultimately, there are often now delays waiting for studies to start at a CRO which may have been prevented if they were conducted in house. This is the second dichotomy. Do you save 'apparent' costs and staff by outsourcing your most resource intensive work but in doing so lose control of the timing, or do you keep control of the timings yet potentially have empty buildings and under-utilised staff? A flexible model, that allows studies to be conducted in house when CRO slots do not exist seems a logical move but one that pharmaceutical companies have largely opted against.

To overcome this, is to plan well ahead of time and selecting carefully your CRO partners (preferred suppliers) that can give you those study slots at a cost you have planned for and at a time you need them. Herein lies the bigger problem. There is always a delay somewhere in the development process. Whether it's a funding decision, which is heightened when you are paying an external customer, an ongoing toxicology investigation, a problem with the drug manufacture, release or analysis or more recently, the availability of animals, delays are inevitable. *In vivo* CRO's and manufacturing/analytical CRO's also need to avoid empty space, so will typically charge delay/cancellation fees or at best, re-use your study slot for another client. So having back-up CRO's with a good understanding of the development pitfalls is a must.

Despite these challenges, the outsourcing strategy has gathered pace with a greater desire to externalise many more activities to reduce internal burden. However, these decisions are often taken within departments, at a level where inter-departmental needs are not balanced against intra-departmental gain. This has resulted in expertise being lost from the pharmaceutical companies and further delays as the lead time for some activities can no longer be conducted instantaneously.

**Gaps in the Pharmaceutical Armoury**

The space between Safety Assessment and Pharmaceutical Development is a clear example of gaps in the pharmaceutical armoury. Having expertise and industry-leading technologies to develop clinical formulations is pivotal to pharmaceutical companies, however, this is prioritised significantly higher than expertise required for developing pre-clinical formulations, which are typically very different.

Developing a poor pre-clinical formulation can lead to de-selection of a perfect drug candidate and the subsequent loss of profit to the pharmaceutical company and potentially the loss of clinical benefit to the patient. It also leads to ethical concerns with adverse clinical effects on the animals and ultimately wasted and repeated studies. Developing a pre-clinical formulation uses a different set of skills to develop a clinical formulation, as you have to consider the needs of the studies to be supported e.g. dose versus dose volume versus concentration versus duration, the nuances associated with each pre-clinical species (pH, osmolality etc) and the capabilities of each CRO. You also need to understand specifics like scalability, compatibility with infusion equipment or perhaps just importance of short-term stability knowing when each formulation will be dosed. Most importantly, you must understand the toxicity of excipients in each species by each route and in combination with each other. Every excipient is both safe and lethal in equal measure, it's just the quantities that determine where on that spectrum you sit. By developing a good formulation, you get to maximise the power of each study, optimised enough to provide the required exposure margins, without having any excipient toxicity, but crucially, being simple enough that it is easily transferable and not unnecessarily arduous to prepare.

Some clinical formulations are the same as those used pre-clinically, e.g. biologicals, long acting injectables. However, it is imperative that conversations between the biologists and chemists occur to ensure clinical formulations are fit for purpose for the needs of the pre-clinical studies.

Similarly, when it comes to issues with the test substance and documentation, the acceptability of impurities and degradation products (including nitrosamines and extractables and leachables), the knowledge surrounding salt (counter ion) selection, not to mention endotoxins (for biologicals), it is unclear where the responsibility lies. An example of this is with the development of a nitrate salt. This may provide for a stable and cost-efficient drug but when it causes renal toxicity not associated with the active substance, those decisions seem poor. It should also be noted that many challenges exist that are associated with the regulations. The *in vivo* CRO's work to GLP and whilst the assumption from chemists that GMP is of a higher standard than GLP is often made, the differences are only realised when comments are made by the regulatory agencies (FDA/Medicines and Healthcare Regulations Agency (MHRA))


*Figure 2. A Formulation Optimisation process*

detailing deficiencies and why a study will need to be repeated. GLP and GMP are different standards both utilised for specific purposes.

In figure 2 below, you will see a step-wise approach to pre-clinical formulation design, demonstrating the need for a comprehensive safety assessment and GLP knowledge.

Another couple of examples also demonstrate the need for a biological mindset over a chemical one.

Inhalation characterisation, which is required prior to costly pre-clinical inhalation studies to ensure accurate dose delivery, whether it is a dry powder system where the selection of packing pressures, blend strength or canister size determining the aerosol concentration or a liquid formulation where the concentration and constituents determine the durability in solution in a pressurised nebuliser system; both require deep knowledge of the delivery systems and dosing practicalities to ensure success.

Another example is the development of a hERG *in vitro* formulation. Considering the aim to maximise exposure, the use of various acceptable solvent/buffer systems and the fine line between a solution that has microscopically insoluble particles, hardly visible opacity or a concentration so low that insolubility is invisible, all at a concentration where stability is difficult to prove, understanding the aims of the study is of utmost importance.

In all these examples, it is also important to have a thorough understanding of both chemistry and biology needs to calculate drug requirements. Sufficient to successfully run each study with a sensible overage but not too much to make manufacture unnecessarily expensive and wasteful.

Strangely, whether its planned or unplanned delays to development, pharmaceutical companies when looking at the cycle time of a drug to market, overlook the reasons for each delay in favour of the means. These metrics point towards a lack of compliance in meeting study targets, however, a slightly deeper dive will reveal poor choices the companies have made.

**Differential Development**

One improvement over the past 10–15 years is the concept of differential development and the remarkably large reductions in animal use as a result of questioning study design. In some cases, whole studies have been removed, certainly shortened in duration, and in some case a study bolted on to another one.

The table below lists a few of these changes:

| Study Type | Description | Study Type | Description |
|---|---|---|---|
| 28-day general tox study | Routinely now often 1–14 days depending on FTIH strategy and therapeutic use | Irwin study | Maybe combined with a CVS study with multiple endpoints |
| *In vivo* genotoxicity micronucleus/ COMET assays | Often now bolted on to definitive tox study | EFD/FEED (embryofoetal development/ fertility studies) | These maybe combined with the Peri and Postnatal study to create an ePPN reproductive tox and developmental study |
| 2-year mouse carcinogenicity study | Now universally replaced by a 6-month transgenic mice assay | Dual routes of administration for general tox | Typically, the clinical route of administration plus a top up route to increase exposure |
| Rat screening assay | Now doubled up to act as a rat range finding study | FEED (fertility study) | Often run as part of a general tox study |

*Table 1. Examples of Pre-Clinical Study enhancements*

In essence, this concept of differential development has already been in place for anticancer drugs where late stage or advanced disease treatment morally outweighs the comprehensive safety assessments needed. This has resulted in the removal of studies to test for genotoxicity, safety pharmacology, reproductive toxicology and carcinogenicity.

Another change has occurred with the introduction and proliferation of biologicals including monoclonal antibodies, recombinant proteins, oligonucleotides, etc, where previously accepted convention is replaced with a bespoke fit for purpose safety plan. Here, drug product is often dosed intermittently and the need for *in vitro* assays/genotoxicity/carcinogenicity are unwarranted and safety pharmacology is assessed within the general toxicology study. An example of a development plan for these large molecules is shown below:

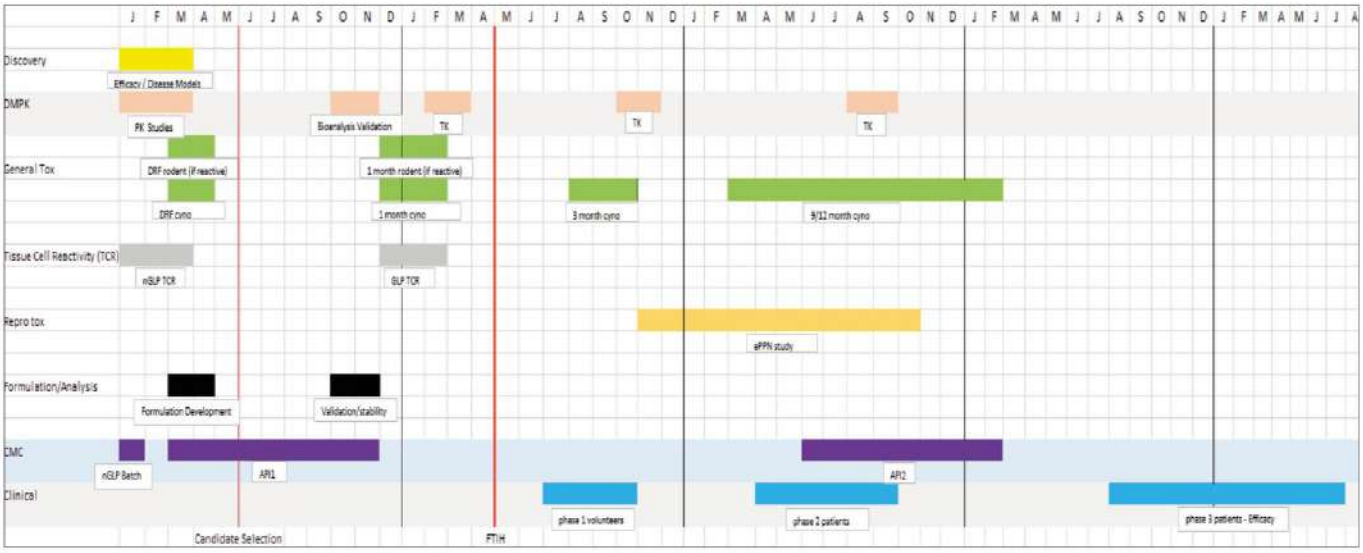


*Figure 3. Development Plan for a biopharmaceutical*

Here, the discovery phase is most definitely longer than small molecules and the animal studies are largely restricted to species where the desired epitope is expressed. Where no suitable species exists, a relevant transgenic subset is selected as a surrogate. Suitability of species involves an *in vitro* tissue cell reactivity assay to define the relevancy and then an abridged plan developed, typically involving one species (commonly non-human primates) being dosed weekly or monthly (with immunogenicity as a prime focus) and a single extended pre- and post-natal development (ePPND) study in the same species handling the reproductive liability. Whilst the development plan has far fewer components, each study is more complicated and costly and the timelines are lengthened by the much longer biotechnology manufacture and testing times which can easily take 8–9 months.

Cell and gene therapy is another clear example where bespoke development plans are designed. Here, adenoviruses act as vectors to deliver the product or analogous substances into 'appropriate' animal species often genetically diseased to better understand the relationship of dose to activity and toxicity. Early communication with the regulators is of paramount importance here to ensure aligned thinking for studies to assess pre-clinical safety (USFDA, 2013).

In essence, there now seems to be a greater acceptance from regulatory authorities to accept differential development including hybrid or novel bespoke studies both in the name of reducing animal usage but also expedition of the process and the responsibility is now on the pharmaceutical company to navigate an appropriate path. A recent example of this is with long acting injectables where a monthly injection requires a case by case approach but one which bears no resemblance to any ICH guidance.

With this onset of fit for purpose drug development, it is important that the most appropriate regulatory submission pathway is also chosen. Whilst the hybrid (reg 52) or generic (reg 51) submissions are the clear alternatives to the full application (reg 50) in the UK, and the Abbreviated New Drug Application (ANDA) approach an alternative to the NDA in the US, less is known about facilitated regulatory pathways (Fast Track (FT)/ Breakthrough Therapy (BTD)/Priority Review (PT) /Accelerated Approval (AA)) to expediate drugs with high benefit or 'orphan drug' status for those with high benefit yet low potential profitability, Innovative Licensing and Access Pathways (ILAP's) to accelerate drugs to market for innovative medicines, those claiming 'Well Established Use' or those more commonly used for combination products or for 'informed consent' amongst others. An engineered development and submission pathway is a must to maximise a drugs clinical and earnings potential.

**The Future**

Very recently, in the US, the FDA modernization Act 2.0 has been passed which refutes the mandate for animal testing (PubMed, 2023).

Whilst there is no expectation this will lead to immediate wholesale changes to development plans, it does give companies the legal framework to challenge the regulators and replace animal testing with novel *in vitro* methodologies and artificial intelligence. Many of these *in vitro* models have been around a while, currently utilised alongside *in vivo* testing for screening and mechanistic investigations.

However, the change in the law may allow models to be accepted in isolation, where justified. An example of this is within the field of inhalation toxicology, where *in vitro* human models have been demonstrated to be better indicators of human toxicity than *in vivo* animal studies. The Epi airways and Immulung 3D models are clear examples of this. Alongside this are the advances in organoids, where embryonic or pluripotent stem cells create miniature but functional and complex organ systems. The diagram below shows a schematic of the process for an organoid system.

The advent of 3D organoids, spheroids, mini organ cultures and organ-on-chip MPS Micro Physiological Systems (MPS) only demonstrate the huge amount of research that is already happening in this field, and companies ready to understand the possibilities will also be those ready to reap the benefits. A human organoid re-creates the architecture and physiology of human organs in remarkable detail and therefore should

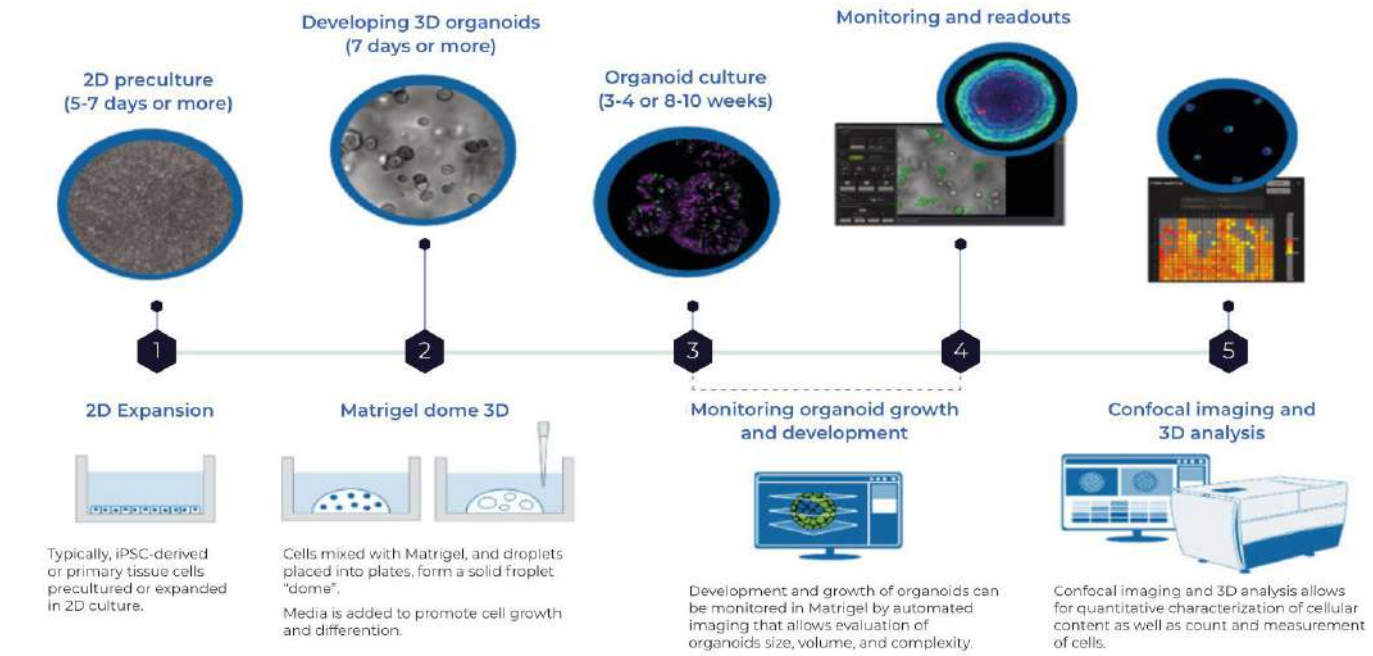


*Figure 4. 3D Organoid Development*

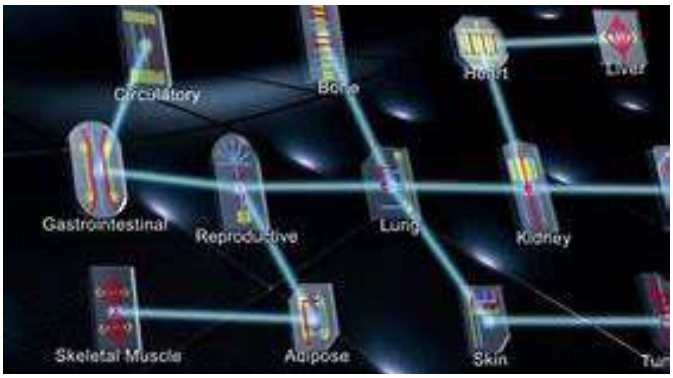


*Figure 5. Organ-on-chip Schematic*

address the concerns that reliance on animal models on human diseases and treatment have (Kim *et al.*,2020). The schematic below shows the potential and direction of an array of organ-on-chip systems.

**Summary**

The drug development process has developed considerably over the years to meet the demands of the pharmaceutical company, regulators and the patient. The strive to outsource has gathered huge pace as an attempt to cut costs and free up resource, however, this has left some big gaps in expertise at pharmaceutical companies, most specifically where chemistry meets biology. The future of life after animal testing also begins here, it won't be instantaneous, but it will ultimately be beneficial for the 'forward-thinking' companies and of course ethically. In addition, navigating the regulatory pathways and understanding how or when the regulators will accept the novel approaches will be key to obtaining regulatory approval quicker.

Here at Broughton, we have built a reputation for delivery of projects with high customer focus and satisfaction. We have a great team of consultants from toxicologists to chemists and regulatory experts, all willing to go the extra mile for our clients and modern GMP/GLP facilities for comprehensive testing. Knowing all the development options, pitfalls and future opportunities and having expertise which fills the gaps between the pharmaceutical companies and the *in vivo* CRO's, places Broughton at the forefront of these exciting times.

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Dean joined Broughton having enjoined a successful career in the pharmaceutical industry with over 30 years of experience with GlaxoSmithKline. Senior Toxicology Consultant; Formulation, Analysis and Test Article Expert Significant GLP, Safety and Controlled drug experience; Drug development expertise across all study types (*in vitro*/*in vivo*); He started his career as an *in vivo* Toxicologist, becoming a Study Director, Study Monitor, and Project Toxicologist, before finally managing an industry-leading Formulation and Analysis department. He has extensive expertise *in vitro* and *in vivo* drug delivery including inhalation and drug development of both new chemical entities and biologicals. Has worked as a Project Specialist providing key opinions relating to test articles and off-target toxicity (quality, documentation, excipients, impurities, counter ions, etc.), to meet GLP regulatory guidelines and expectations. He is a problem solver with great attention to detail. A great communicator with a can-do attitude who is focused on meeting customer needs.