# Working with Short Shelf-Life Products in Clinical Development – Driving Efficiencies and Overcoming Challenges

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## Abstract

The unnecessary generation of extended drug product stability data in early clinical research adds significant time and cost to the development process. Given these formulations do not typically progress beyond early phase studies, this shelf-life requirement is driven by supply chain inefficiencies in delivering investigational drug products (IMPs) from the point of manufacture to the point of clinical dosing. Operational strategies to reduce this burden of non-value added development cost and time are proposed which are designed to enable product dosing within days or even hours of manufacture. Such approaches are particularly important when the shelf-life of drug products will be inherently short, for example with the inclusion of radioisotopes due to radioactive decay or radiolysis induced chemical instability.

## Introduction

The primary purpose of early clinical research is to establish the safety and tolerability of new chemical entities (NCEs) in human subjects, as well as understand the systemic pharmacokinetic (PK) profile to assess potential drug development challenges. There is also an increasing use of biomarkers and pharmacodynamic (PD) assessments to confirm potential efficacy signals.

A primary goal is not however to perform extended stability studies on prototype formulations to be used in these studies, when the above success criteria have not been demonstrated. New approaches are therefore required to expedite cycle times for drug product manufacture and dosing, which will require both operational change as well as revised quality assurance and regulatory expectations.

This need is further driven by the fact that today's drug substance chemistry is presenting an increasing challenge to formulation scientists to design and develop fit-for-purpose, fit-for-phase oral drug products in early clinical development. It has recently been proposed that over 90% of NCEs are non-BCS Class 1 compounds [1] and hence their intrinsic dissolution, solubility or permeability properties will present biopharmaceutical challenges in obtaining adequate systemic absorption and bioavailability. Given the lack of fully predictive *in silico*, *in vitro* or preclinical models, compositional flexibility and/or the use of 'enabled' formulations is increasingly required, to ensure the clinical study endpoints described above can be met.

## Materials and Methods

Two current paradigms exist for the manufacture of drug products in early development, either *in situ* manufacture of simple "drug in bottle" products within clinical facilities (minimal stability data required, but limited formulation flexibility), or the production of formulations at GMP sites remote to clinical testing (greater formulation capability, but protracted supply chains and increased stability burden).

A hybrid model has been developed whereby "real time" drug product manufacture and dosing can be achieved, whilst maintaining full operational capability in regard to dosage form technologies to meet the biopharmaceutical drug delivery needs of the NCE. The requirements to achieve this capability are summarised in Table 1.

**Table 1. Factors required to work with IMPs with short shelf-lives**

| |
|---|
| • Biopharmaceutics driven formulation design |
| • Scientifically justified redacted QC specifications |
| • Product and process understanding to support quality assurance |
| • Risk-based Quality Management System (QMS) |
| • Regulatory positioning of abridged datasets within drug product IMPD |
| • Integrated GMP/GCP operational infrastructure |

This approach has enabled a dramatic reduction in quantum of stability data generated to assign a drug product shelf-life covering the period between manufacture and dosing in early clinical development.

A review was conducted of various drug product formulations, associated manufacturing, release and dosing cycle times, and corresponding assigned shelf-lives for Phase 1 studies recently conducted at Quotient Clinical (Table 2).

## Results and Discussion

Regulatory guidance recently published by the MHRA [2] has sought to enhance extrapolation of real-time data beyond that previously permitted in ICH guidance [3]. Based on 1 month accelerated 40ºC / 75% RH data it may be possible to request a 4 month shelf-life at room temperature. The use of shelf-life extension plans in regulatory submissions is also now encouraged whereby a stability testing plan is submitted along with an algorithm detailing how emerging data will be assessed and a revised shelf-life assigned by the Qualified Person (QP).

## Results and Discussion cont…

Neither of these initiatives however resolve the fundamental issue of generating unnecessary and costly stability data, typically up to 6 months, solely to cover protracted drug product supply chains. Furthermore, this restriction could prevent potentially successful, but as yet non-optimised, unstable early formulation concepts from being clinically evaluated.

**Table 2. Achieved manufacturing, QC and QP cycle times (days) for a range of IMPs**

| | M/f | QC | QP | Total | Shelf-life |
|---|---|---|---|---|---|
| Solution | 0.5 | - | 0.5 | 1 | 1 |
| IR tablet – dry granulation | 1.5 | 1 | 0.5 | 3 | 5 |
| MR tablet – wet granulation | 2 | 2 | 1 | 5 | 7 |
| EC tablet | 2 | 2 | 1 | 5 | 7 |
| Coated multiparticulate | 3 | 2 | 1 | 6 | 7 |
| Lipid solution in HGC | 2 | 1 | 1 | 4 | 5 |
| Nanomilled suspension | 3 | 2 | 1 | 6 | 7 |
| Spray-dried nasal powder | 2 | 3 | 1 | 6 | 7 |
| IV sterile solution | 1 | 0.5 | 0.5 | 2 | 2 |

Table 2 illustrates how an integrated approach can dramatically shorten the cycle time for manufacture and release of a wide range of IMPs. It is proposed that any oral drug product even with multiple processing stages can be made at small scale (<250 units), under full GMP conditions within a 3 day time period. Sterile parenteral solution formulations can be aseptically manufactured within a 24h period. Equally important is the subsequent ability for rapid QC release testing of the drug product. Typical release tests for these product types are illustrated in Table 3, all of which can be completed within a further 12 to 48h post manufacture. Finally the QA/QP release stage has been demonstrated to take no more that 24h prior to product transfer to clinic for dosing.

**Table 3. Typical risk-based QC release tests**

| Oral IMP | IV IMP |
|---|---|
| Appearance | Appearance |
| Identity | Assay/related substances |
| Assay/related substances | Absence of visible particulates |
| Uniformity of dosage unit | |
| Dissolution | |

## Results and Discussion cont…

These approaches therefore only require the generation of minimal stability data to assign shelf-lives of 7 days or less, saving both time and cost during the development stage (Table 1). Quality Assurance acceptance is enabled via both up-front demonstration batches confirming that defined processing conditions deliver product of the desired performance attributes, and also a risk-based quality management system (QMS) to ensure appropriate fit-for-phase controls are in place on materials, equipment, facilities, processes and methods. Clear science-based statements are then made in regulatory applications to justify redacted and streamlined approaches.

These approaches have proven necessary when working with radioactive drug substances and products. In the conduct of clinical studies with $^{14}C$ IMPs (e.g. ADME, microdose, microtracer programmes) chemical degradation from radiolysis or secondary decomposition can be problematic even at -20ºC or -80ºC storage conditions, requiring the time lag between manufacture and dosing to be minimised. Additionally, in the conduct of gamma scintigraphic imaging studies with $^{99m}Tc$ or $^{111}In$ isotopes due to radioactive decay (half-lives of 6 and 67 hours respectively) it is imperative that drug products can be manufactured, released and dosed within a short space of time.

## Conclusions

Operational excellence and infrastructure coupled with risk-based QC testing has expedited IMP availability for clinical dosing. Such approaches have reduced shelf-life requirements and hence minimise regulatory stability data packages. This model has delivered three principle benefits to the early development team – rapid entry for the clinical evaluation of NCEs, access to the full range of formulation technologies to address the biopharmaceutical drug delivery needs of molecule and real-time flexibility to adjust formulation compositions in response to arising clinical safety, PK or PD data.

## References

[1] Hauss (2007), Advanced Drug Delivery Reviews, 59, 667-676

[2] MHRA website: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/Additionalinformation/index.htm

[3] ICH Q1E Evaluation of Stability Data