Recipharm

De-risking complex generic OSD development

A hybrid development case study combining QbD-driven formulation, discriminatory dissolution and reference-scaled average bioequivalence

When developing a complex generic oral solid dose (OSD) product, formulation performance, analytical strategy, bioequivalence risk and regulatory pathway all need to work together. Recipharm developed a film-coated immediate release tablet for a complex, poorly soluble active substance, using Quality by Design (QbD) principles to build product and process understanding from the outset. Inactive ingredients were matched to the scientifically and clinically relevant originator product, and the tablet was manufactured using a wet granulation process.

The programme also required a carefully defined regulatory strategy. The nationally designated reference product cited for regulatory purposes differed in strength and indication from the originator product used as the practical basis for formulation development and bioequivalence. Recipharm supported scientific advice with the regulatory authority before development began, helping align the hybrid application route and proposed bioequivalence strategy early and reduce downstream regulatory risk.

The active substance presented an additional challenge: a pronounced food effect and rapid pre-systemic metabolism resulted in high intra-subject pharmacokinetic variability. To address this, the pivotal bioequivalence study used a full replicate crossover design and a reference-scaled average bioequivalence (RSABE) approach.

This case study shows how Recipharm connected regulatory strategy, formulation science, analytical development and bioequivalence planning to progress a complex generic product towards filing and commercialisation. Product names and study-specific figures are excluded for confidentiality; project-specific data points that require completion remain shown as bracketed placeholders for the project team before external publication.

REGULATORY STRATEGY: SELECTING THE RIGHT HYBRID PATHWAY

The active substance is authorised in the EU under two distinct product profiles: an originator product reflecting the target strength, formulation and indication of interest, and a separate, long-standing national reference product authorised at a different strength. The originator product was used as the practical basis for formulation development and bioequivalence, while the national reference product was cited administratively as the designated reference medicinal product (RLD) in the dossier.

Because the two products differ materially in strength and indication, the application could not proceed as a standard generic under Article 10(2)(b) of Directive 2001/83/EC, and was instead progressed as a hybrid application.

THE EU HYBRID PATHWAY

Article 10(3) of Directive 2001/83/EC permits an application to rely in part on the reference product's non-clinical/clinical data and in part on new, applicant-generated data, where differences exist in strength, indication, pharmaceutical form or route of administration relative to the designated RLD. This was applicable here because the designated RLD could not itself support a standard bioequivalence-based generic claim at the target strength and indication.

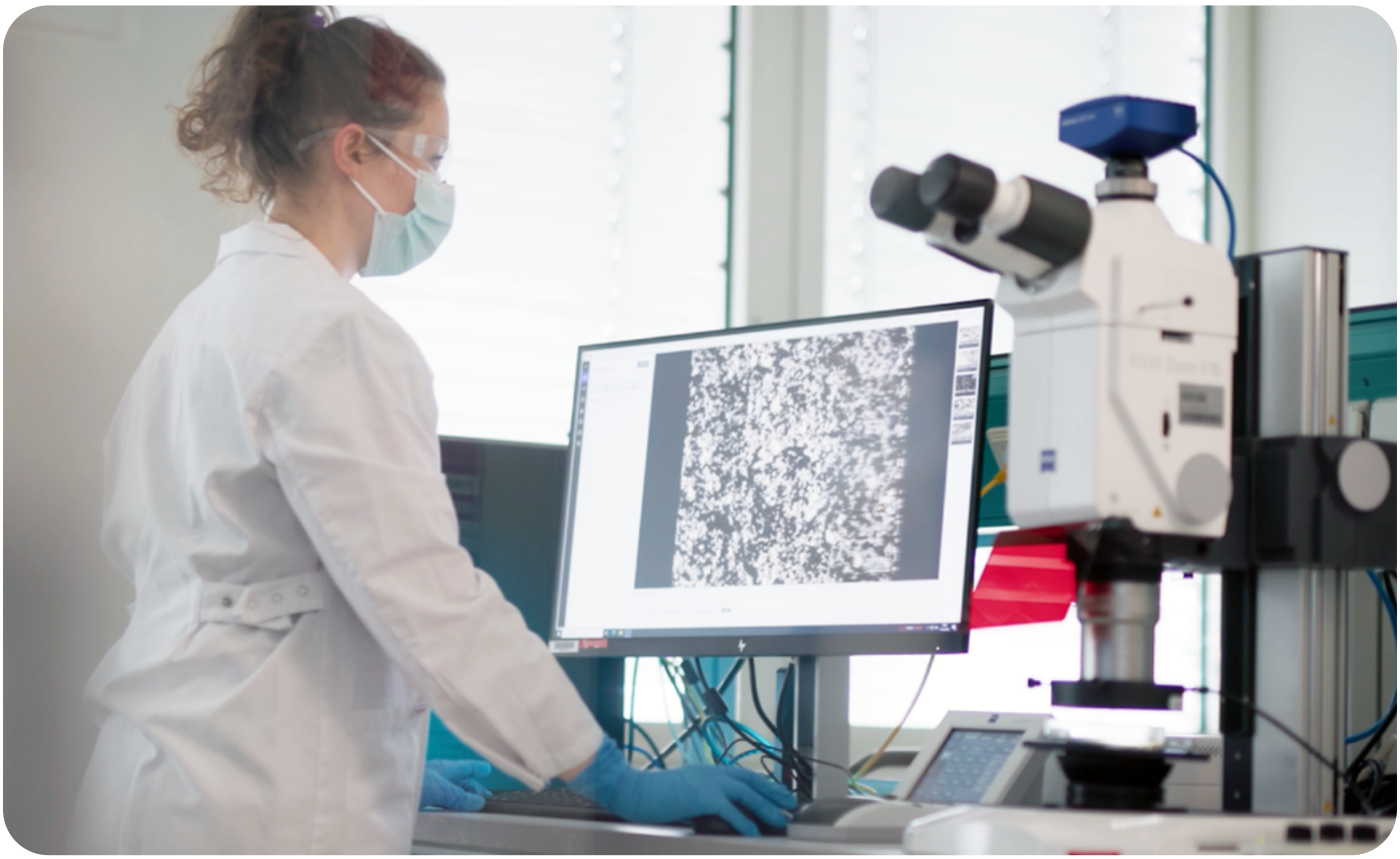
The applicant is required to demonstrate that any differences from the designated RLD do not raise clinically significant concerns for safety or efficacy. This was supported by the pivotal bioequivalence study conducted directly against the originator product, together with published data associated with its marketing authorisation, to justify the strength and indication sought.

EARLY SCIENTIFIC ADVICE TO REDUCE REGULATORY RISK

Before development work began, Recipharm supported a scientific advice meeting with the regulatory authority to align the overall regulatory and bioequivalence strategy. This created a clearer development path before formulation and pivotal study activities began.

- The rationale for the hybrid application route, given the difference between the designated RLD and the originator product used as comparator, was presented and discussed.
- The proposed classification of the active substance as highly variable, and the intended full replicate crossover bioequivalence design, were outlined for early feedback.
- The proposed reference-scaling methodology for Cmax, and the anticipated fed-state study conditions, were discussed against EMA's bioequivalence guideline for highly variable drug products.

By aligning the hybrid route and proposed bioequivalence approach early, the programme reduced the risk of late-stage strategic changes and provided a stronger basis for formulation and study planning.



FORMULATION DEVELOPMENT: A QBD-LED APPROACH

Formulation development was run as a Quality-by-Design (QbD) programme, aligned with ICH Q8(R2), Q9 and Q10. The objective was not simply to reproduce a tablet composition, but to build the product and process understanding needed to support robust manufacture, discriminatory testing and bioequivalence readiness.

QUALITY TARGET PRODUCT PROFILE AND CRITICAL QUALITY ATTRIBUTES

- A quality target product profile (QTPP) was defined to match the originator product's strength, dosage form, appearance and in vitro release performance.
- Critical quality attributes (CQAs) were identified, including assay/content uniformity, dissolution, related substances, and moisture content.

FORMULATION: MATCHING INACTIVE INGREDIENTS

Inactive ingredients were matched, qualitatively and, where relevant, quantitatively, to the originator product's composition as the starting point for prototype development, then optimised using standard pharmaceutical development practice and compatibility studies.

MANUFACTURING PROCESS: WET GRANULATION

Wet granulation was selected as the manufacturing process for the tablet core, based on the flow and compressibility characteristics of the active substance and blend.

- A risk assessment (e.g. FMEA) was used to identify critical process parameters (CPPs) across granulation, drying, blending and compression.
- Design of Experiments (DoE) studies were used to explore the design space around key CPPs and to define the resulting control strategy.

DISCRIMINATORY DISSOLUTION METHOD DEVELOPMENT

Given the active substance's poor aqueous solubility, a dedicated discriminatory dissolution method development exercise was carried out:

- Multiple media, surfactant levels and apparatus/agitation conditions were screened for their ability to discriminate between formulation and process variants while maintaining adequate sink conditions.
- Water containing 1% Tween was finalised as the discriminating dissolution medium, and used both for comparative profiling against the originator product and as the basis for the proposed release specification.

DEVELOPMENT OUTCOME

Together, the QbD-led formulation and process strategy, wet granulation control strategy and discriminatory dissolution method created a mechanistically justified, high-confidence generic composition ahead of the pivotal bioequivalence study. This helped reduce avoidable formulation iteration and strengthened the evidence base for progression into the clinical programme.

IMPURITY RISK ASSESSMENT: ELEMENTAL IMPURITIES AND NITROSAMINES

Elemental impurities (ICH Q3D)

A paper-based elemental impurities risk assessment was performed during development, in line with ICH Q3D, evaluating potential contributions from the active substance, excipients, the manufacturing process/equipment and the container closure system, to determine whether routine testing for elemental impurities was warranted.

Nitrosamine impurities

A nitrosamine risk assessment was also performed, in line with EU/EMA and equivalent global requirements. Initially, this was a paper-based assessment carried out during development, covering both process- and excipient-related ('classical') nitrosamine risk and the potential for a nitrosamine drug substance-related impurity (NDSRI).

- The active substance's structure does not contain a secondary or tertiary amine, and therefore does not present a structural basis for an NDSRI; the paper-based assessment accordingly focused on classical, process- and excipient-derived nitrosamine risk (e.g. arising from raw materials, reagents, catalysts, recovered solvents or nitrite-containing excipients).
- As part of the regulatory query response following submission, a GC-MS method was developed and validated for the quantitation of N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) in both the active substance and the finished formulation, to support control of these nitrosamines against the applicable acceptable intake limits.

BIOEQUIVALENCE STRATEGY FOR A HIGHLY VARIABLE DRUG PRODUCT

The active substance's pharmacokinetic profile - including a pronounced, food-dependent increase in bioavailability and rapid first-pass metabolism - is consistent with classification as a highly variable drug product (within-subject CV typically >30% for Cmax). For products with this level of variability, conventional fixed 80.00-125.00% bioequivalence limits can drive impractically large study sizes despite genuine product comparability.

WHY REFERENCE SCALING WAS APPROPRIATE

- EMA's bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1) permits widening of the Cmax acceptance range for highly variable drugs, provided the reference product's variability is demonstrated in a replicate-design study and the widening is justified by a lack of safety/efficacy concern for Cmax.
- AUC, the primary extent-of-exposure parameter, remained subject to the conventional 80.00–125.00% acceptance range.
- A full replicate (TRTR/RTRT) crossover design was used, with the originator product administered twice within the sequence, to generate the within-subject reference variability (swR) needed to scale the Cmax limits.
- The Cmax acceptance range was widened proportionally to swR, using EMA's regulatory constant of 0.294, capped at a maximum widening of approximately 69.84%–143.19% (reached once swR ≥ ~0.50, i.e. CV ≥ ~50%).

PROGRAMME OUTCOME

The product was successfully filed in the UK and the EU. Regulatory query responses are currently being addressed, with approval anticipated shortly and commercial launch anticipated to begin in the first quarter of 2027. The programme demonstrates how early regulatory alignment, formulation and analytical depth, and a fit-for-purpose bioequivalence strategy can help progress a complex generic product towards launch with greater confidence.

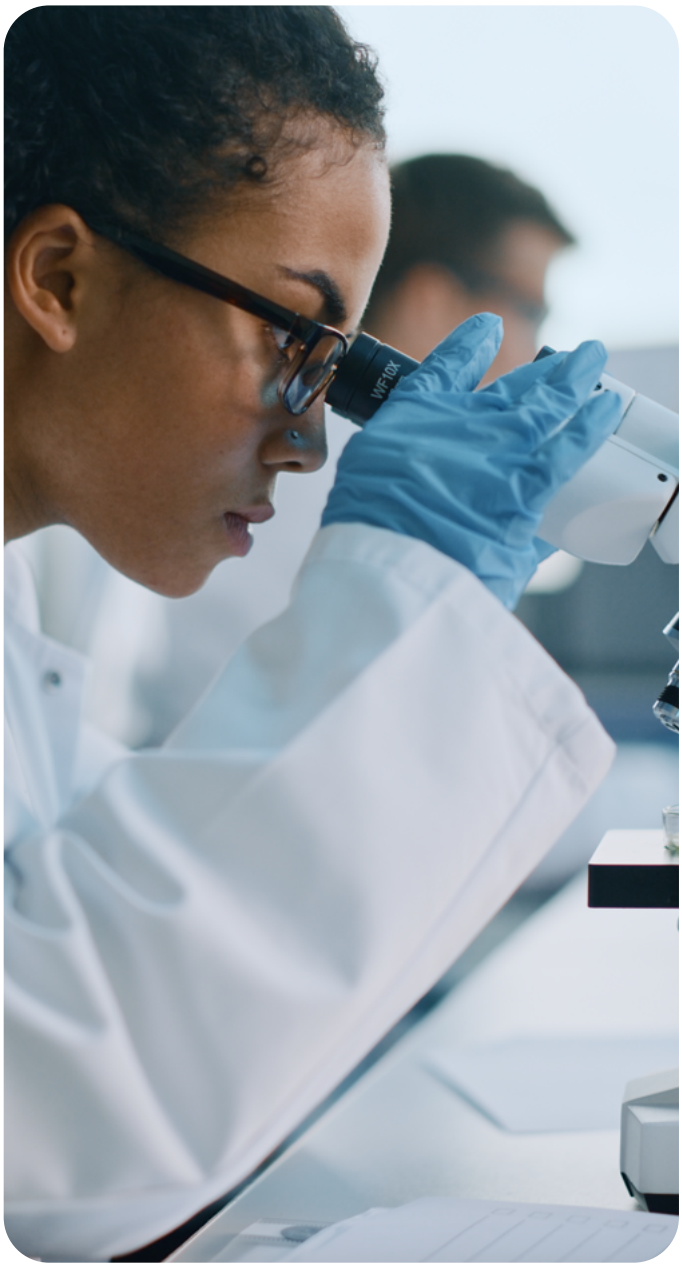
CONCLUSION: CONNECTING DEVELOPMENT DECISIONS TO FILING AND COMMERCIAL READINESS

Complex generic programmes can demand more than a conventional single-reference bioequivalence strategy, particularly when the legally designated reference product does not match the strength or indication being sought. In this programme, a hybrid application under Article 10(3) of Directive 2001/83/EC provided the appropriate regulatory route: the designated reference product was cited administratively, while the substantive pharmaceutical and bioequivalence package was generated against the originator product.

Scientific advice before development helped align that strategy with the regulatory authority. From there, Recipharm connected QbD-led formulation development, inactive-ingredient matching, wet granulation process understanding and a purpose-developed discriminatory dissolution method to establish a robust composition ahead of bioequivalence testing.

A full replicate, reference-scaled average bioequivalence strategy then addressed the active substance's high intra-subject variability while remaining aligned with EMA guidance for highly variable drug products.

Taken together, the programme illustrates our science-led approach to complex generic OSD development: bringing formulation, analytical, regulatory and bioequivalence thinking together to reduce development risk, strengthen filing readiness and support progression towards commercial supply.



About us

Recipharm is a leading Contract Development and Manufacturing Organisation (CDMO) employing over 4,500 employees. Recipharm provides expertise in development and manufacturing across oral dosage sterile, fill & finish, and biologics; clinical trial material development and manufacturing services; and, pharmaceutical product development. Its Biologics segment works with customers to develop and commercialise advanced therapy medicinal products (ATMPs): pre-clinical to clinical and commercial development and manufacture for new biological modalities. The company operates development and manufacturing facilities in France, Germany, India, Italy, Portugal, Spain, Sweden and the US.

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