Generic Long-Acting Injectables Development using QronoMetrics™

The Unmet Need: Generic Long Acting Injections

Long-acting injections (LAIs) that rely on complex microparticle formulations, such as Sandostatin® LAR (SLAR) and Risperdal® Consta® (RC), have been improving the lives of patients for nearly three decades, but to date there has not been a single generic LAI approved in the US. Availability of generic versions for these or other complex formulations would reduce billions of dollars in strain on our nation's healthcare systems and allow a broader range of patients to benefit from medications that improve adherence, improve patient outcomes, and improve overall quality of care. Yet patients lack generic formulations of these products, due in large part to the high burden of creating generics and demonstrating bioequivalence.

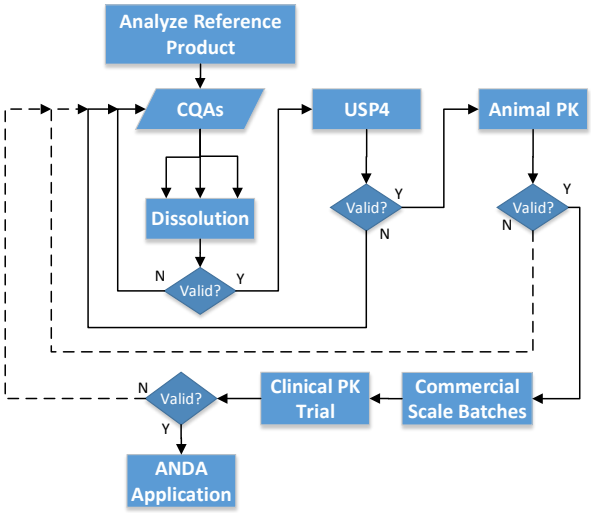

Figure 1 - Legacy long-acting formulation design process relies on reverse-engineering and iterative design.

Creating a bioequivalent (BE) generic LAI requires not only qualitatively (Q1) and quantitatively (Q2) matching the composition of the complex reference product, but also matching its dissolution and pharmacokinetic profiles. Further, the complexity of the microparticles found in SLAR, RC, and nearly a dozen other FDA-approved long acting medications means that their dissolution and pharmacokinetic (PK) profiles depend on multiple critical quality attributes (CQAs) not defined in a Q1/Q2 composition, such as microparticle size and drug distribution. If these and other CQAs were linked to the formulation's dissolution and PK, researchers could develop complex BE generics based on clear CQA target specifications, significantly de-risking in vivo translation and scale- up.

Legacy approach to reverse engineering of generic LAIs through analytical methods

The legacy approach to generating LAI target specifications is to analytically evaluate the reference product (Figure 1). One first acquires samples of the desired reference product, measures possible CQAs of the reference product by analytical methods, and then produces three or more formulations, varying the CQAs around the measured specifications. The dissolution of these initial formulations is then evaluated by comparing the data from reverse engineered formulation and reference product to FDA specifications for bioequivalence.

If one of these reverse engineered formulations happens to provide bioequivalent in vitro release, one could move on to a standardized USP4 dissolution assay and a preclinical pharmacokinetic model (e.g., rat PK). However, it is unlikely that this initial formulation design would encompass the entire set of reference product CQAs required for accurate, scalable generic LAI production. In order to map the full range of CQAs one will likely need to repeat the previous steps several or more times.

The complete range of CQAs is typically mapped using this iterative process as generic LAI production is moved to pilot/scalable batches analyzed with GLP USP4 assays and additional preclinical PK testing. If in vitro USP4 dissolution and the in vivo animal PK results are eventually bioequivalent to the reference product, one can then produce commercial-scale batches, initiate stability testing and start the bioequivalence clinical trial. The iterative process may continue through clinical trials if human PK results differ significantly from the preclinical PK results.

Once the clinical PK data for the generic product is bioequivalent to the reference product per FDA guidance, one can then move to file an ANDA application.

Computational Drug Delivery: A new approach to developing generic LAIs

QronoMetrics™-guided development of generic LAIs focuses immediately on achieving a bioequivalent clinical PK profile, eliminating much of the trial-and-error and risk of the legacy approach (Figure 2). Qrono starts with clinical PK data for the reference product published by the FDA to run an initial simulation using QronoMetrics™ predictive software and create a preliminary bioequivalent LAI design. This initial design is then produced and tested using USP4 to validate simulation results. Animal PK testing to further confirm the accuracy of the initial design simulation typically follows a successful USP4 study.

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+1.412.213.8788 • info@qrono.com • www.qrono.com

Preliminary in vitro and in vivo data are then added to the QronoMetrics™ predictive model, increasing the accuracy of the simulations. The design process is repeated using the refined models to finalize a bioequivalent formulation design. This bioequivalence simulation maps the complete design space and also identifies the tolerances of the bioequivalent product CQAs for scale-up to commercial production.

Once the clinical PK data documents bioequivalence between the generic product and the reference product per FDA guidance, one can then move to file an ANDA application.

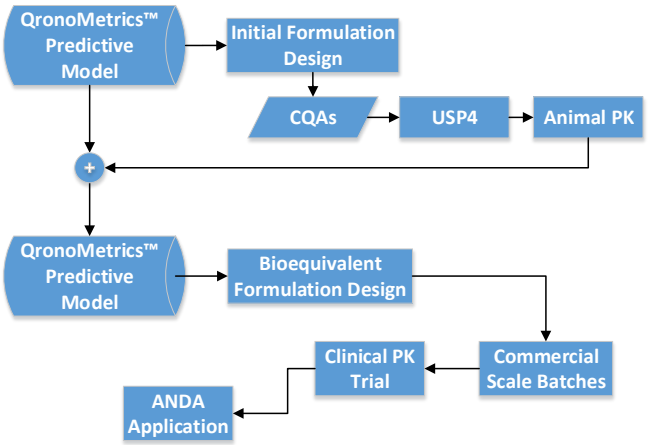

Figure 2 - Computational drug delivery using QronoMetrics™ streamlines the design process while reducing late-stage risk.

Benefits of QronoMetrics™-Guided Design

The criteria for the original approval of a reference LAI product, such as Risperdal®Consta® or Sandostatin®LAR, differ significantly from the criteria for approval of its bioequivalent generic. Therefore identifying and directly copying the reference product CQAs (i.e., reverse engineering) is unlikely to capture the entirety of the generic design space and, in the case of high variance products, might even encompass non-bioequivalent product specifications. Both of these scenarios create late-stage risk in a generic development project that can be minimized with simulation-driven design.

The QronoMetrics™ design space map built directly from clinical pharmacokinetic data:

- Reduces risk of late-stage bioequivalence failures during clinical translation of formulation designs optimized through dissolution testing.
- Fully characterizes more than ten CQAs with sensitivity analysis to eliminate scale-up risks from CQAs missed during initial analytical measurements or from analytical specifications not directly linked to bioequivalent drug delivery.
- Reduces experimental burden by three-fold or greater during in vitro and preclinical in vivo product development. Experiments are only needed to confirm accuracy of simulations.
- *Coming soon* Population bioequivalence simulations will predict clinical trial outcomes by cohort size, de-risking bioequivalence clinical trial design via simulation of cohort size and trial failure modes.

QronoMetrics™ Validation

QronoMetrics™ predictions have been validated against both in vitro and in vivo data. The graph in Figure 3 compares predicted release against measured release (either measured by Qrono or from publicly available data). The straight line represents perfect correlation. In more than 15 case studies, correlation is within the guidelines (80-125%, green shaded region) that the FDA would allow for bioequivalence.

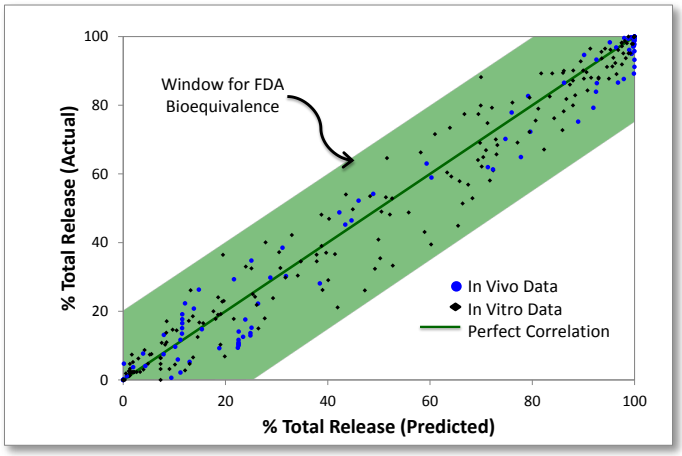

Figure 3 - QronoMetrics™ correctly predicts release profiles in more than 15 case studies.

LAI Development for 505(b)(2) Applications

The benefits of QronoMetrics™-guided LAI formulation design also extend to reformulating of FDA approved medications and new chemical entities (NCEs) to create new, LAI medications that will be submitted through the FDA 505(b)(2) regulatory pathway (i.e., supergenerics).

About Qrono

Qrono is a specialty pharmaceutical company focused on long-acting medications. Our pipeline focuses on therapeutic areas where LAIs offer high therapeutic and economic value, such as addressing high non-adherence or solving specific drug delivery challenges. Our pipeline also includes generic versions of several reference LAI products.

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