Overview of Chemistry, Manufacturing, and Controls Activities

Stuart R. Gallant, MD, PhD
sgallant@sandpiperpharma.com

	IND/IMPD	Phase 3
Analytic and Stability Methods	• Select, optimize, and qualify analytic methods • Forced degradation of drug substance • Qualify methods as stability indicating	• Validate analytic and stability methods
Reference Standard	• Manufacture and qualify 1st lot of reference standard • Establish a stability program for reference standard	• Assess adequacy of reference standard supply • Manufacture and qualify additional reference standard lot(s) • Bridge to new lot of reference standard as necessary • Continue the reference standard stability program
Raw Materials	• Do a raw materials risk assessment • Paper audits are typically acceptable at this stage	• Continue raw materials quality program • Consider which vendors will require site visits
Process Development and Formulation Development	• Develop Generation 1 process (for animal tox). • Continue to Generation 2 (for First in Human) • Develop lead formulations and screen down to 1 or 2 formulations based on accelerated stability • For parenterals, have media fills been completed at manufacturing facility?	• Consider both quantity and quality of drug substance and drug product; develop Generation 3 process which will be able to meet commercial quality and quantity demands • Conduct FMEA analysis and establish Master Validation Plan • Validate Generation 3 process
Manufacturing	• Compliance audits of manufacturing facilities to US/EU GMPs • Manufacture and release initial Phase 1/2 clinical lot(s) • Release of the first DP lot is typically rate limiting on regulatory filing	• Review of quality systems to confirm adequacy for Phase 3 • Manufacture and release Phase 3 clinical lots
Comparability	• Confirm comparability of Gen 1 and Gen 2 DS/DP	• Confirm comparability of Gen 1, Gen 2, and Gen 3 DS/DP
Stability Program and Retest Dating	• Place development lot(s) of DS and DP on stability (the sooner the better—there's nothing as good as real time stability data) • Place clinical lot(s) on stability • Establish initial DP retest date(s) for clinical lot(s); monitor real time stability data and update as retest as necessary	• Monitor DS and DP stability data and confirm based on real time data that stability is adequate • If DP stability is inadequate, may have to consider a formulation change (conduct risk assessment for change) • Place additional DS and DP lot(s) on stability • Monitor real time data; update DP retest date as necessary