Product Characterization and In Vitro Testing for Establishing Equivalence of Complex Products

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SESSION 1: Equivalence of Complex Products
FY 2017 GDUFA Regulatory Science Initiatives Public Workshop

Complex Products

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals, MDIs
- Complex drug-device combinations

Scope of this Session

- Complex active ingredients
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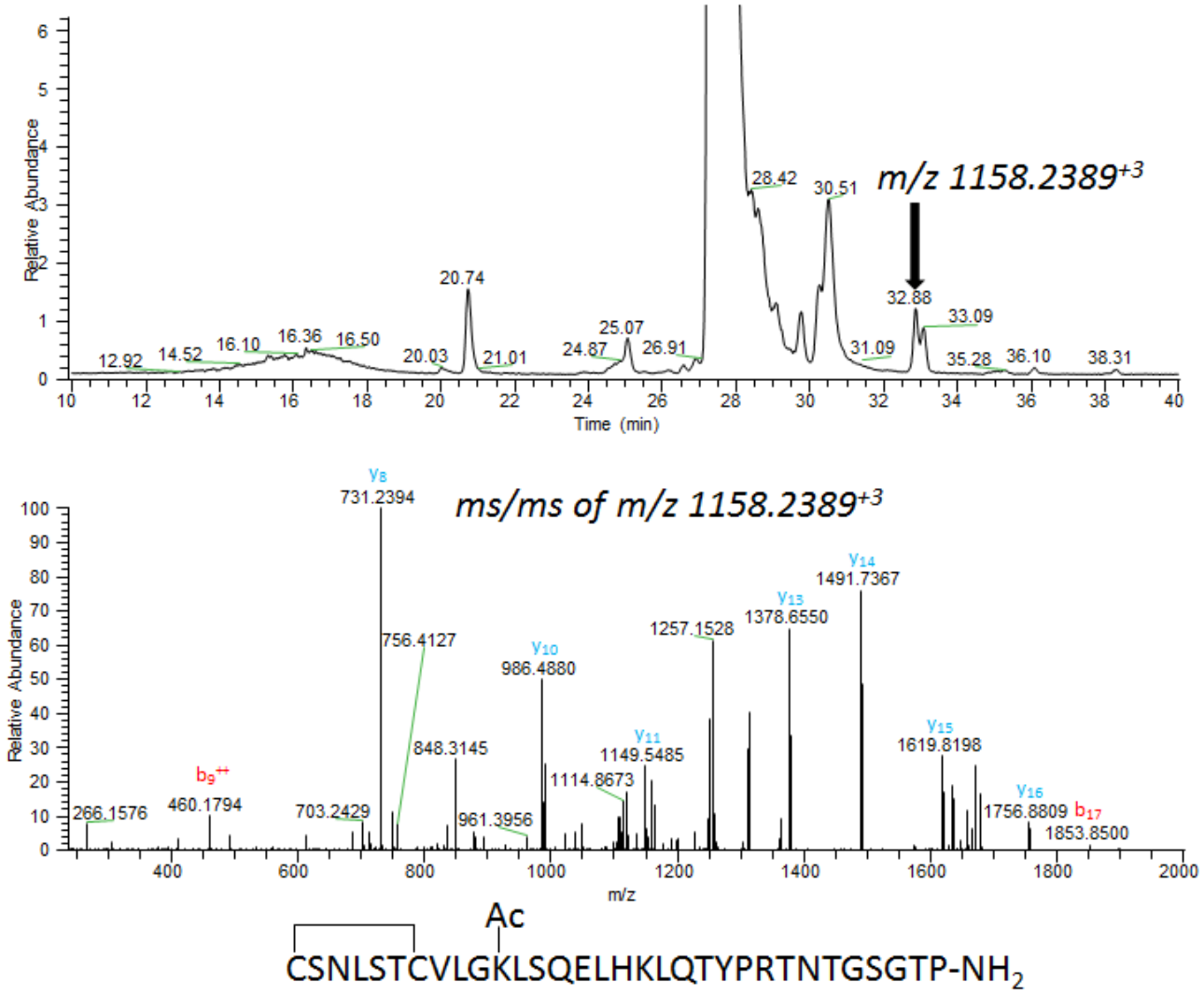
Complex Active Ingredients

- Research activities
  - External: grants/contracts on pentosan polysulfate sodium and crofelemer
  - Internal: peptide related impurity analysis and immunogenicity evaluations, sucralfate, high dimensional/multivariate data comparison
- Regulatory outcomes
  - Product Specific Guidance: colesevelam, omega-3 carboxylic acids, glatiramer acetate, ethiodized oil
  - Guidance agenda 2017: Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin

LC-MS and MS/MS of Salmon Calcitonin



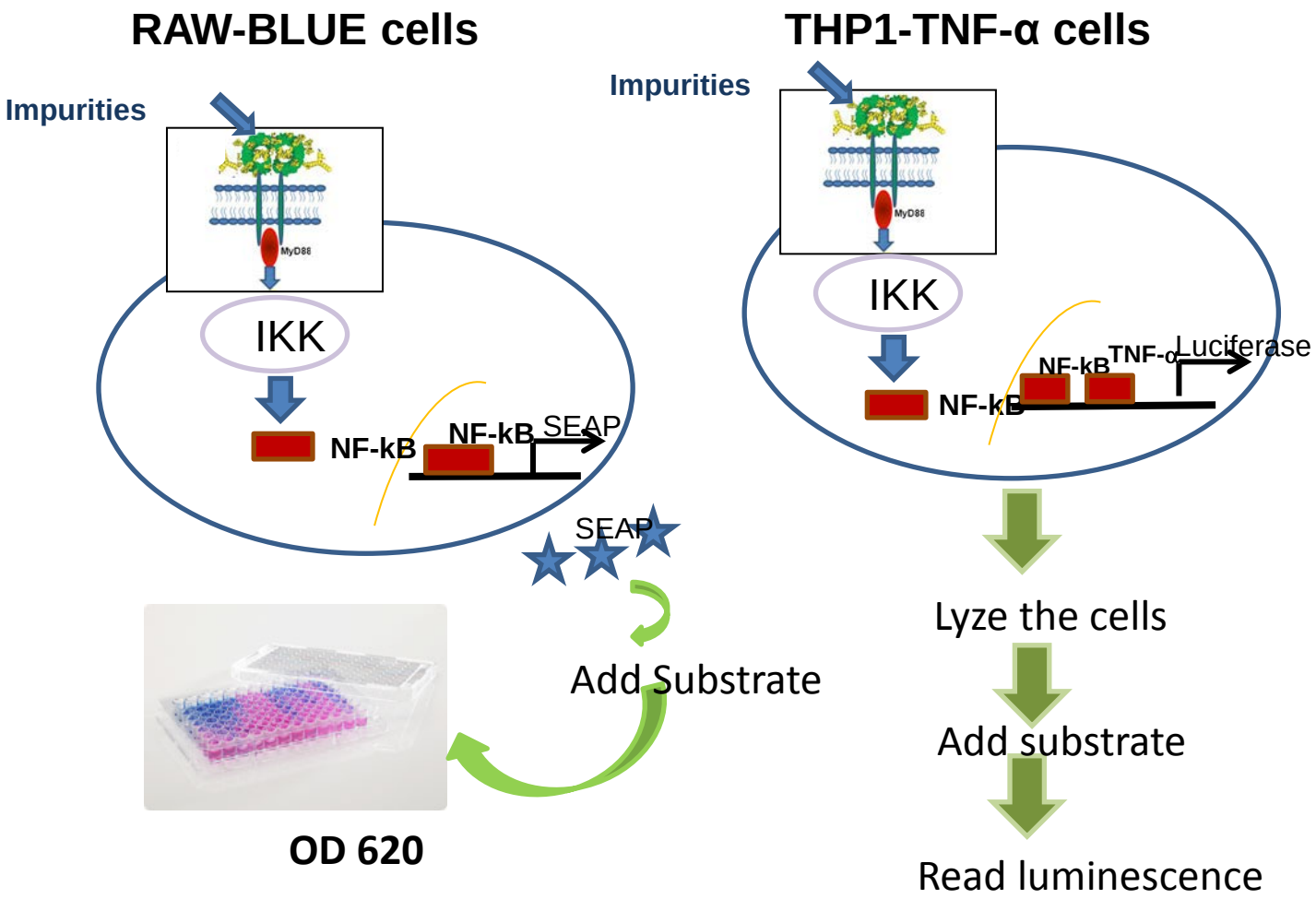
FDA internal study

LC-HRMS vs USP LC-UV

- For the calcitonin RLD LC-HRMS identified 12 impurities for a total of 2.6% (Area%)
- The same sample analyzed by the USP HPLC-UV method observe 6 impurities with a 2.0% total
- Detection limits for the 2 identified peptide impurities were below 0.1% (Area %) by LC-HRMS

FDA internal study

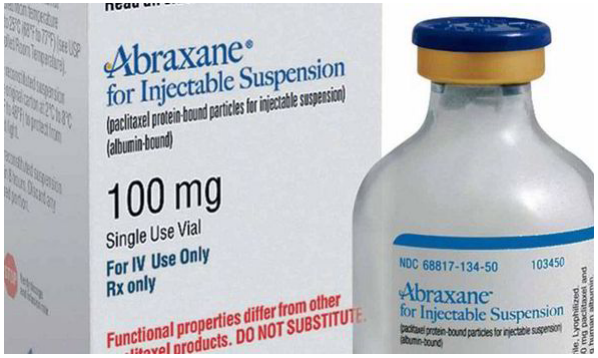
Cell Based Assays to Detect IIRMIs in Drug Products



IIRMIs: innate immune response modulating impurities

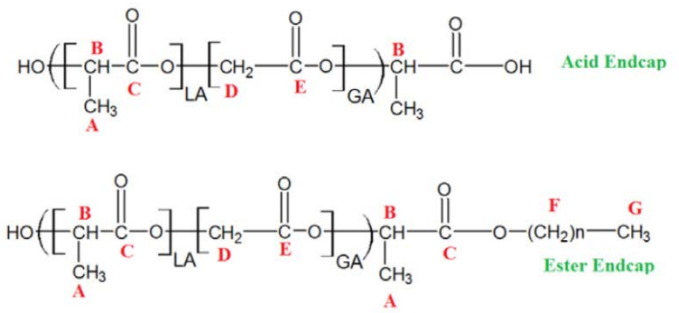
Haile LA, Puig M, Kelley-Baker L, Verthelyi D (2015) PLoS ONE 10(4)

Complex Formulations

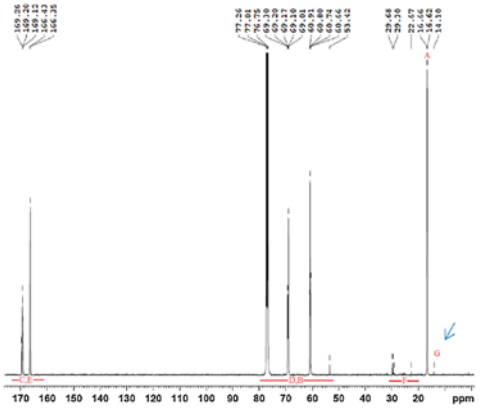


Characterizations of Complex Formulations

- Development of advanced analytical techniques
  - Characterize critical attributes for product equivalence, functional excipients, and bioanalytical methods for different forms of drugs *in vivo*



Garner J, et al. Int J Pharm. 2015 Aug 28;495:87-92



From product-specific guidance of risperidone injection

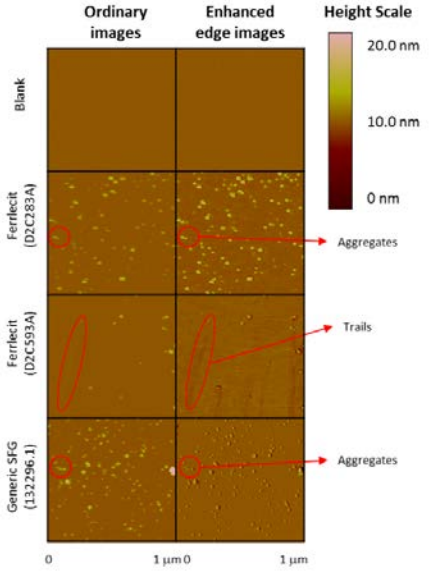
The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product for all strengths (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial). Please provide characterization data on poly(lactide-co-glycolide) (PLGA) for both the test and reference product including polymer composition (ratio between glycolic acid and lactic acid), molecular weight and weight distribution, and PLGA architecture (e.g., linear or star-branched PLGA). Additional data on PLGA characterization may be requested during the review of the ANDA.

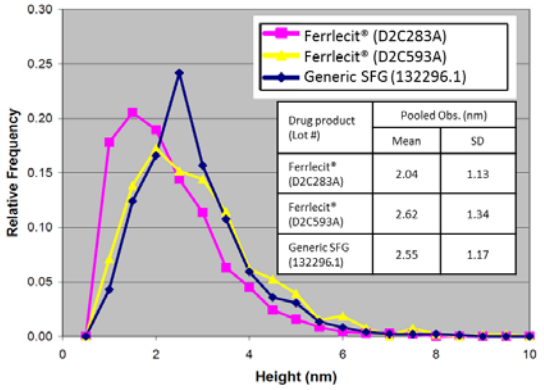
Physiochemical Equivalence Assessment of Reference and Generic Sodium Ferric Gluconate Complex

Dynamic Light Scattering (DLS):

Drug product (Lot #)	Z-average diameter (nm)	Intensity-weighted diameter (nm)	Volume-weighted diameter (nm)	PDI Value
Ferrlecit® (D2C283A)	11.5	13.9	9.0	0.163
Ferrlecit® (D2C593A)	12.1	14.5	8.8	0.158
Generic SFG (132296.1)	10.5	12.1	8.1	0.123

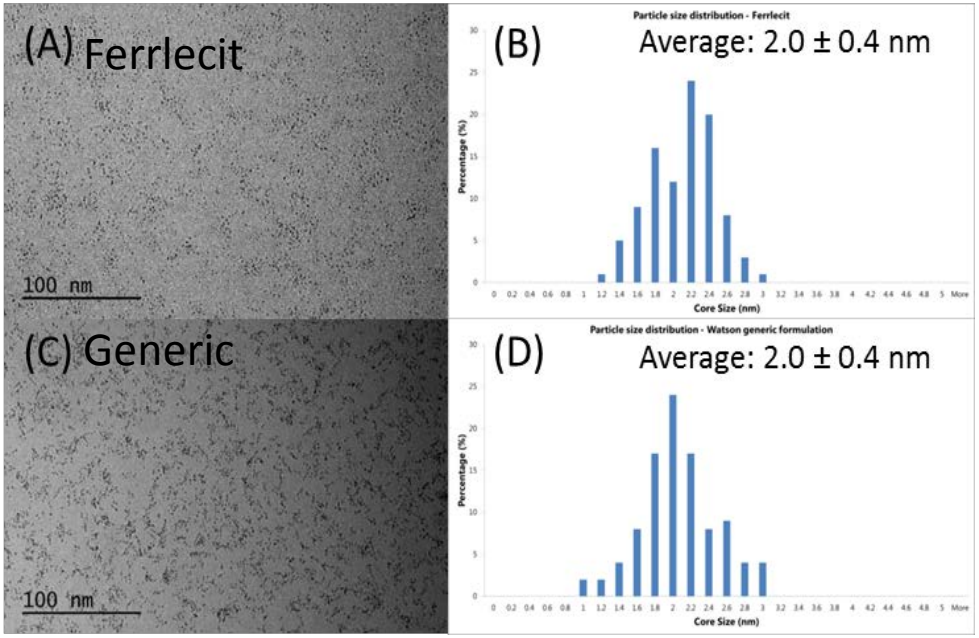
Atomic Force Microscopy (AFM):





Drug product (Lot #)	Pooled Obs. (nm)	
	Mean	SD
Ferrlecit® (D2C283A)	2.04	1.13
Ferrlecit® (D2C593A)	2.62	1.34
Generic SFG (132296.1)	2.55	1.17

Cryogenic Transmission Electron Microscopy (Cryo-TEM):



FDA internal study

Physiochemical Equivalence Assessment of Reference and Generic Sodium Ferric Gluconate Complex

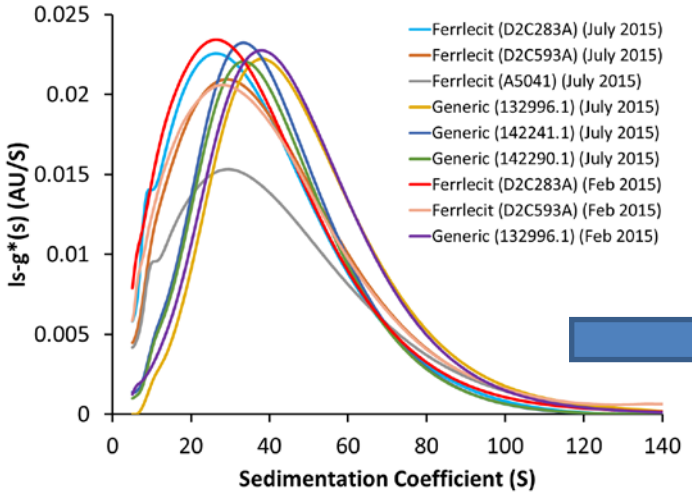
Gel Permeation Chromatography (GPC):

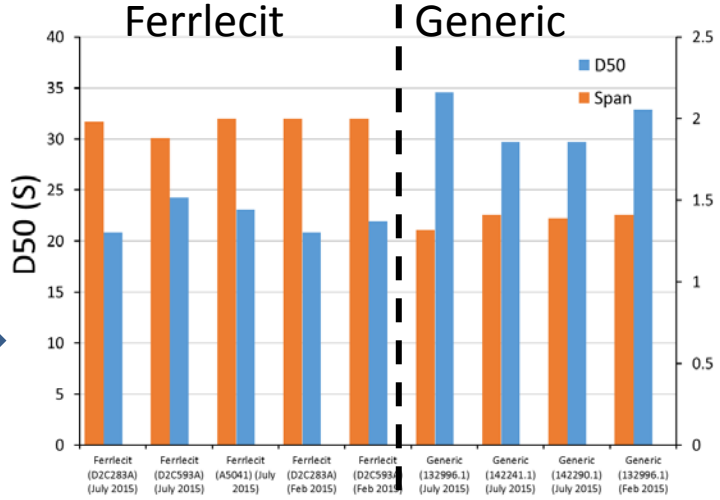
Drug product (Lot #)	M_w (kDa)
Ferrlecit (D2C283A)	384.7 ± 5.1
Ferrlecit (D2C593A)	393.4 ± 1.9
Ferrlecit (A5075)	467.7 ± 3.0
Generic SFG (132996.1)	387.4 ± 2.1
Generic SFG (142241.1)	365.9 ± 5.4
Generic SFG (142290.1)	363.7 ± 1.9

Asymmetric filed flow fractionation – multi-angle laser scattering (AFFF-MALS):

Drug product (Lot #)	Run	M_n [kDa]	M_w [kDa]	M_w/M_n
Ferrlecit® (D2C283A)	1	83.5 ± 2.3	316.7 ± 0.9	3.8
Ferrlecit® (D2C283A)	2	88.8 ± 2.6	317.8 ± 1.3	3.6
Ferrlecit® (D2C283A)	3	87.4 ± 2.1	319.1 ± 1.3	3.6
Ferrlecit® (D2C593A)	1	98.9 ± 1.5	329.1 ± 0.7	3.3
Ferrlecit® (D2C593A)	2	92.7 ± 2.4	329.9 ± 1.6	3.6
Ferrlecit® (D2C593A)	3	92.7 ± 2.5	330.7 ± 1.3	3.6
Generic SFG (132296.1)	1	218.4 ± 0.7	415.6 ± 1.2	1.9
Generic SFG (132296.1)	2	219.6 ± 0.7	418.3 ± 1.3	1.9
Generic SFG (132296.1)	3	222.2 ± 0.7	417.7 ± 1.3	1.9

Analytical Ultracentrifugation (AUC):



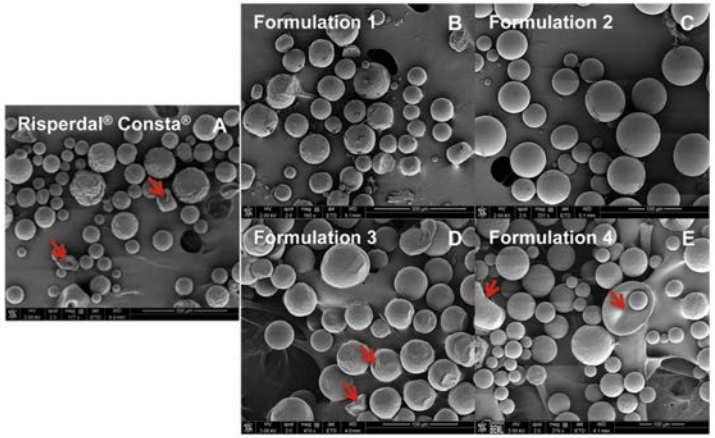


$S \propto R^2, M^{2/3}$
R = radius of spherical particles
M = molecular mass

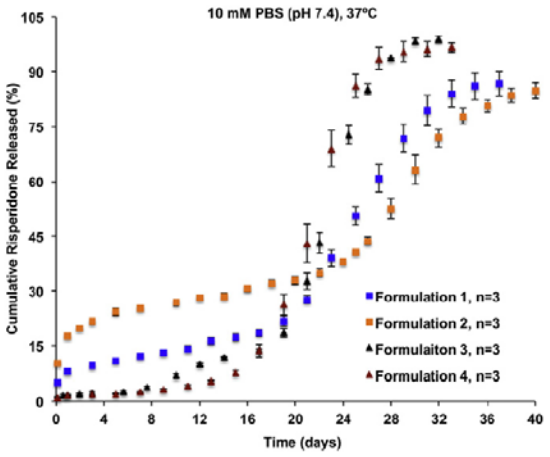
FDA internal study

Characterizations of Complex Formulations

- Study impact of manufacturing and formulation processes on the end product's critical quality attributes
  - Liposomes
  - Microspheres
  - Implants/inserts



Sample	Solvent	Preparation method	Porosity (%)
Risperdal Consta	--	--	43.97 ± 4.60
F1	DCM	Homogenization & dry sieving	43.19 ± 4.60
F2	DCM	Homogenization & wet sieving	46.04 ± 42.90
F3	EA	Vortex & wet sieving	54.98 ± 1.25
F4	EA	Homogenization & wet sieving	61.75 ± 1.08



Shen J, et al. J Control Release. 2015 Nov 28;218:2-12
Shen J, et al. Int J Pharm. 2016 Feb 10;498(1-2):274-82

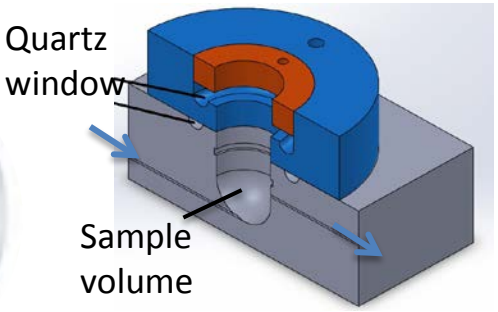
In Vitro Release Testing

- Development of new methods for *in vitro* release testing
  - ➢ Quality control
  - ➢ In vitro in vivo correlation

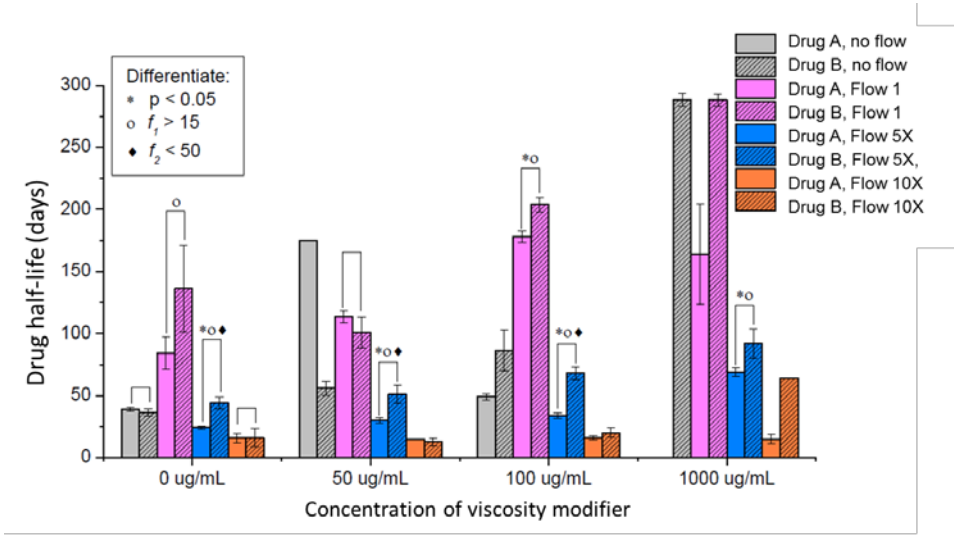
  – Various products: ophthalmic suspensions/ointments, periodontal inserts, parenteral suspensions, microspheres and implants, intrauterine systems…
  – Different methodologies: pulsatile microdialysis (PMD), modified USP II, USP IV, macro-fabricated flow cells

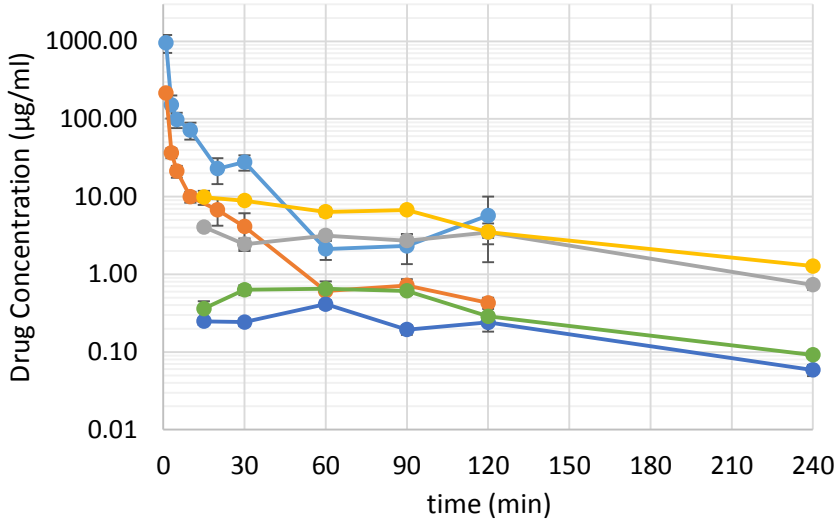
Critical Attributes and In Vitro Tests for Ophthalmic Drug Products

IVRT flow cells that mimic eye viscosity and flow rate



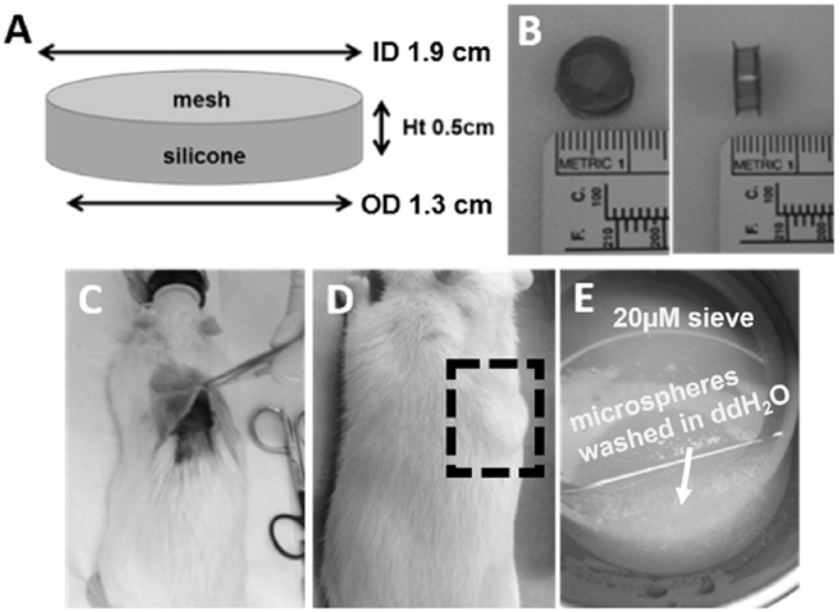
In vivo animal tests to measure how formulation properties affect local pharmacokinetics

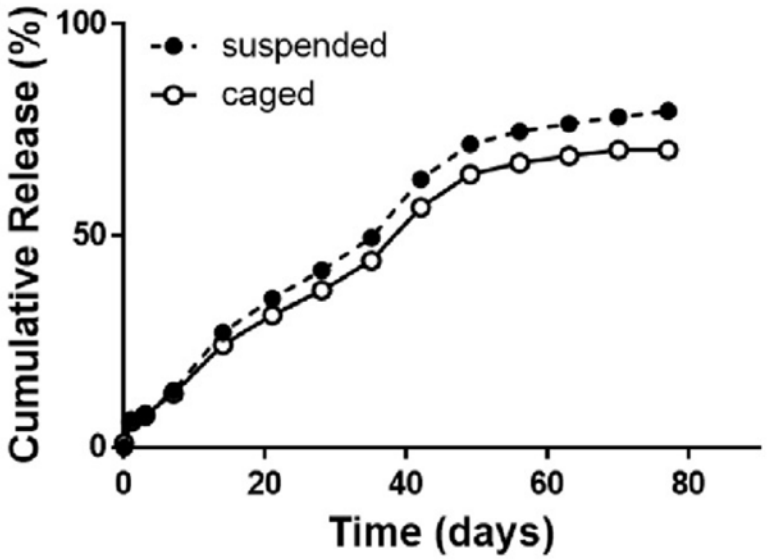


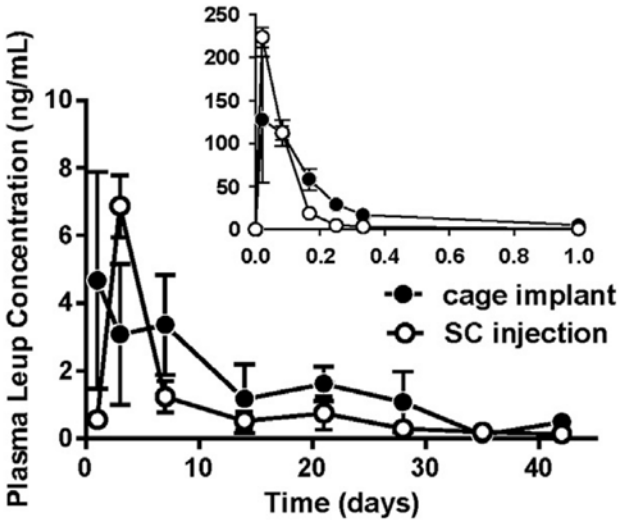


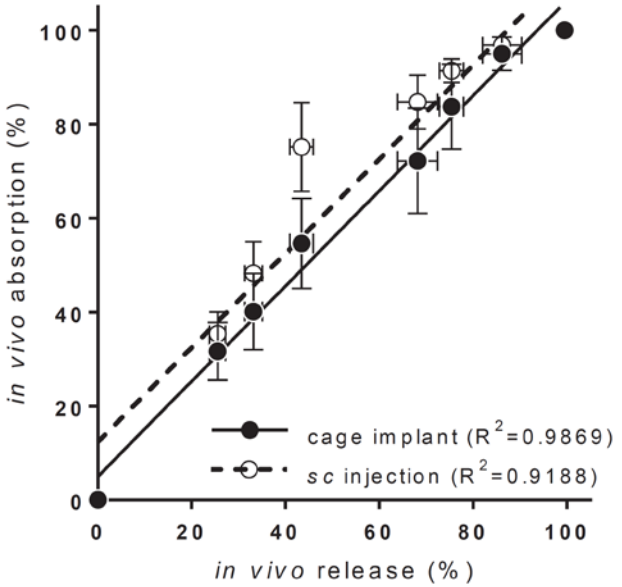
Urtti A, et al. AAPS 2016; Grant 1U01FD005180-01
Sailor MJ, et al. CRS 2016; Grant 1U01FD005173-01

Cage model to assess in vivo release of microspheres





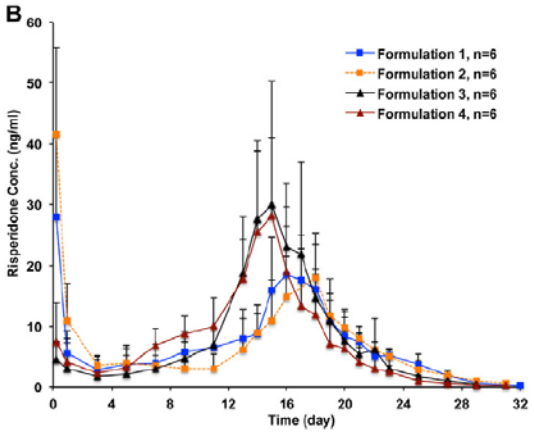




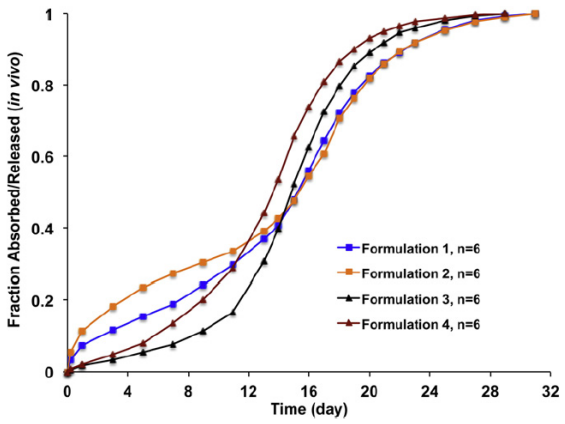
Doty AC, et al. Biomaterials. 2016 Dec;109:88-96

IVIVC of Risperidone Microspheres

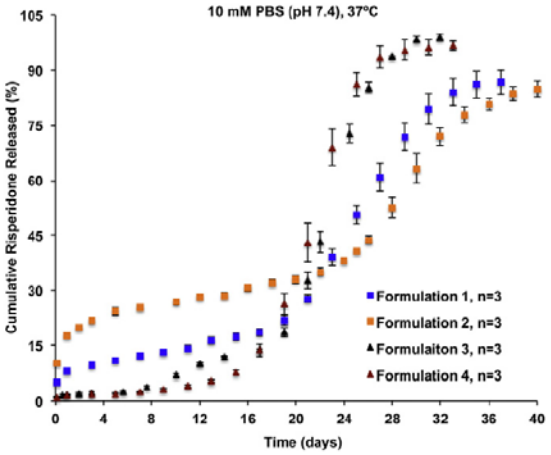
In vivo PK profiles



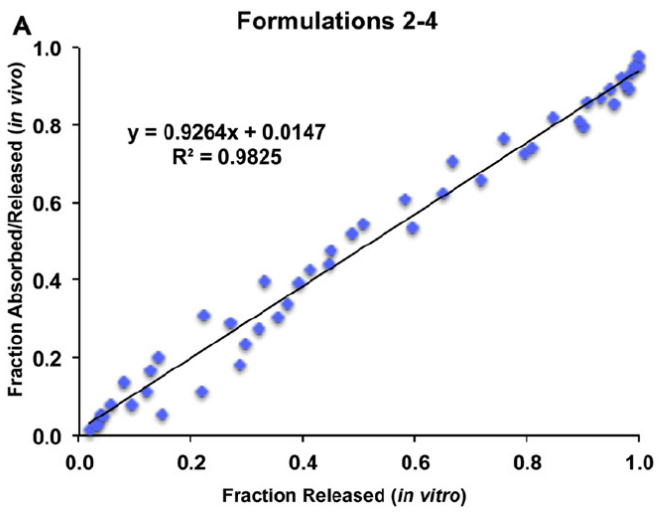
Deconvoluted profiles:

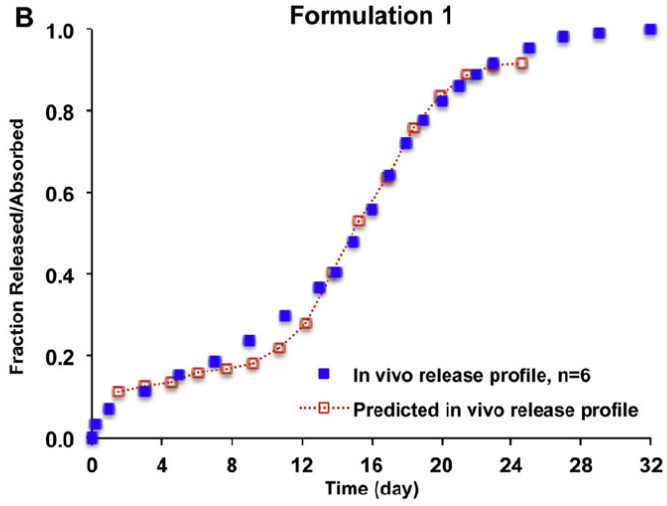


In vitro release profiles



Level A IVIVC





Shen J, et al. J Control Release. 2015 Nov 28;218:2-12

Summary

- Access to complex generics is accelerated by analytical advances that:
  - Ensure equivalence of critical attributes
  - Enable alternatives to in vivo BE studies
- Two categories of advances
  - Characterization
    - New technology and new characteristics
    - New analysis methods for complex data
  - In vitro performance testing
    - Biological tests to ensure equivalence of proposed generic products
    - Release tests under similar physiological conditions

Priorities for the Panel

- New advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients
- Predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products
- Particle size, shape and surface characterization based bioequivalence for suspended and colloidal drug products
- Predictive in vitro BE methods for long-acting injectables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