Bridging Patient Needs with Regulatory Flexibility in Rare Disease Drug Development

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Disclaimer

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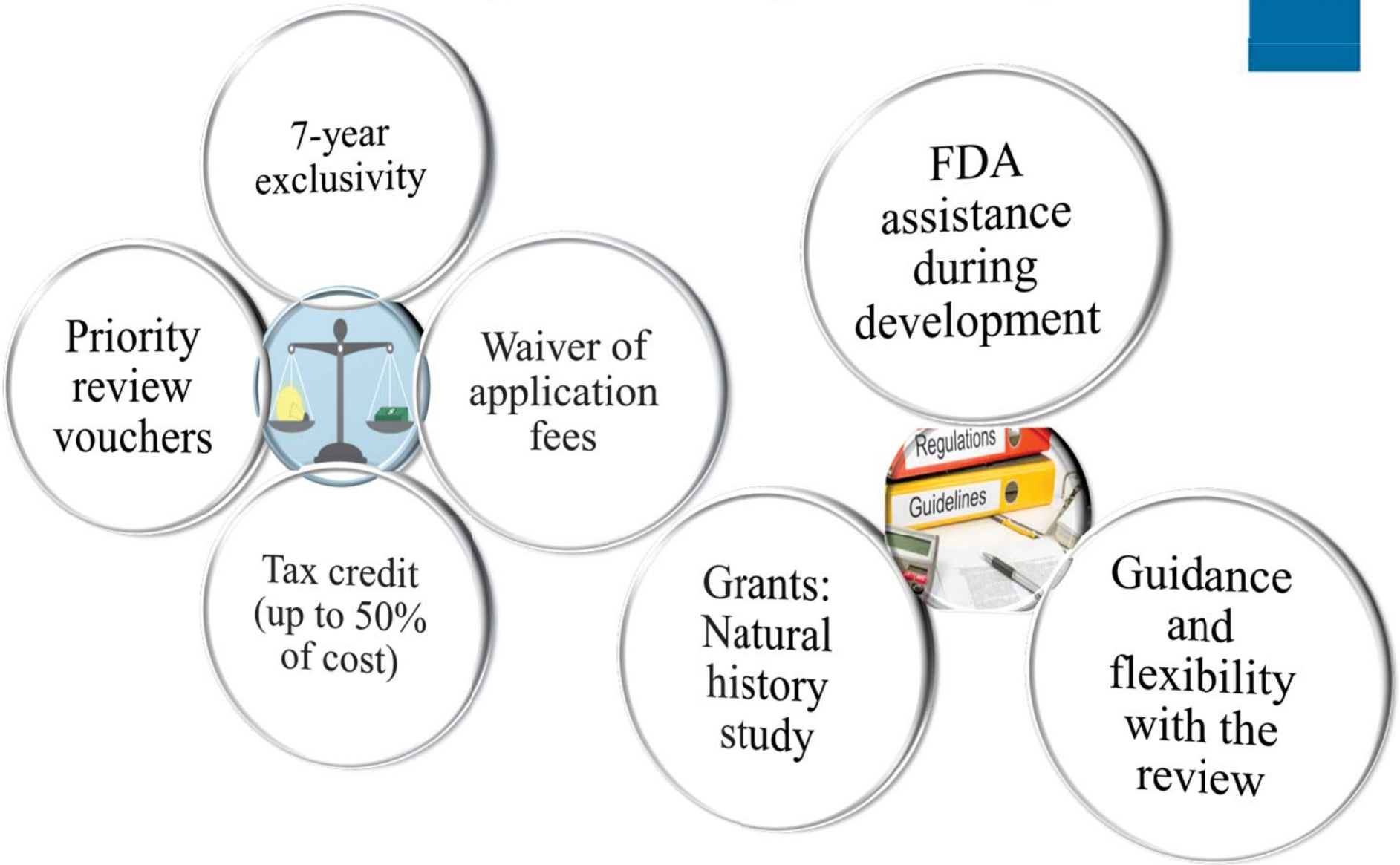
Challenges with Rare Diseases

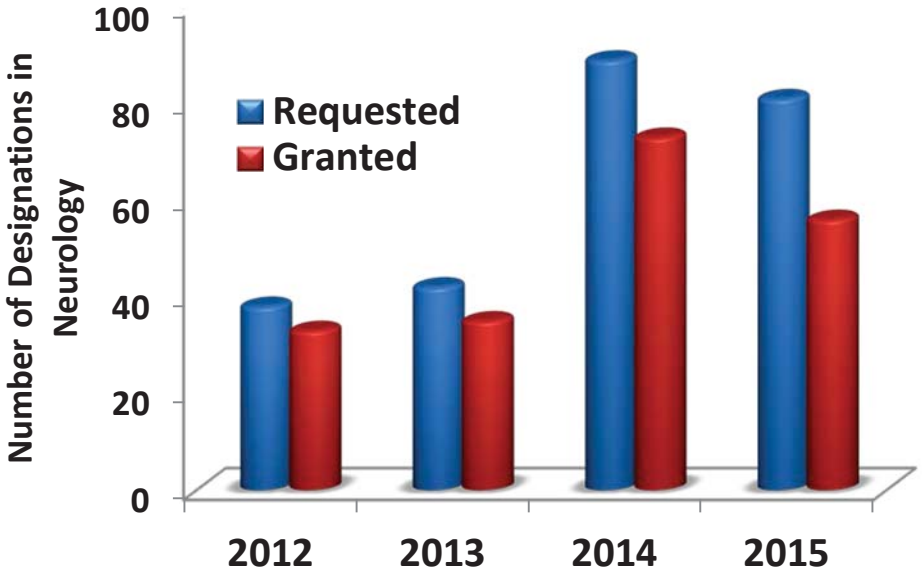
- Limited number of patients
  - Trial design challenges
  - Limitation of number of patients ➔ power
  - Recruitment
- Lack of understanding of disease, diagnosis and natural history ➔ Endpoint selection
- Discovery and development challenges
  - Lack of good animal models and translational PK/PD application :
    - Biomarkers
    - Dose selection

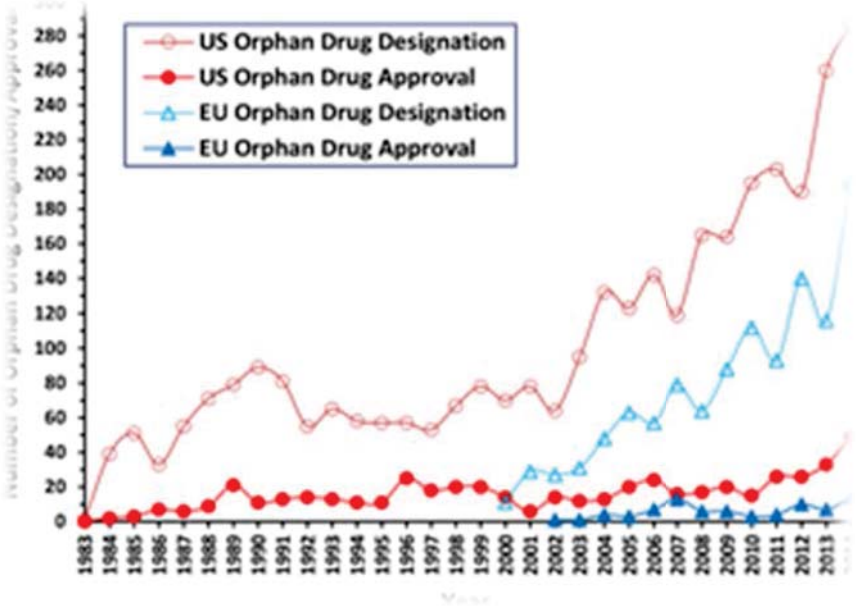
Incentives for Orphan Drug Development



Orphan Drugs Development in USA and EU

- Before the Orphan Drug Act → only 10 treatments had been developed for rare diseases
- More than 400 orphan products are approved currently.
- **Less than 20% of drugs receiving orphan drug designations get approved**



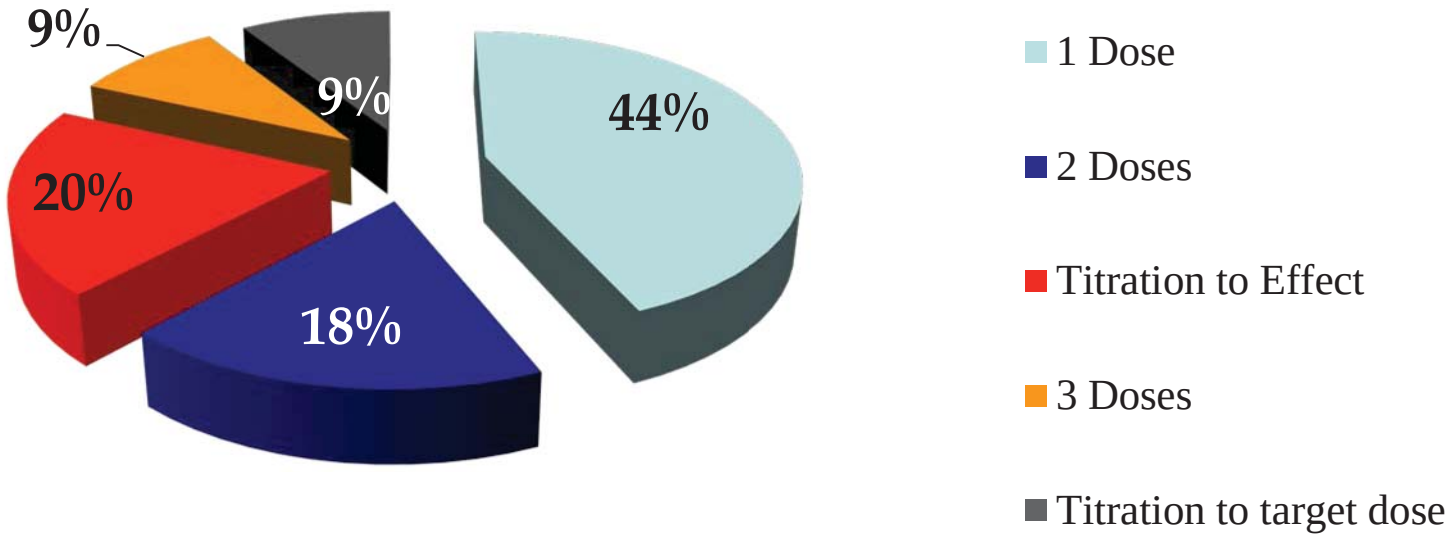


Oo_et_al-2016-The_Journal_of_Clinical_Pharmacology.pdf
NR NORD-Neurological-Rare-Disease-Special-Report 2015

Role of Clinical Pharmacology In Rare disease drug Development

- Dose Finding
- Dose Individualization (Effect of Intrinsic and extrinsic Factors)
- Biopharmaceutical Challenges
  - PK bridging to clinical trial formulation (CTF)
  - Case study (Deflazacort for DMD)

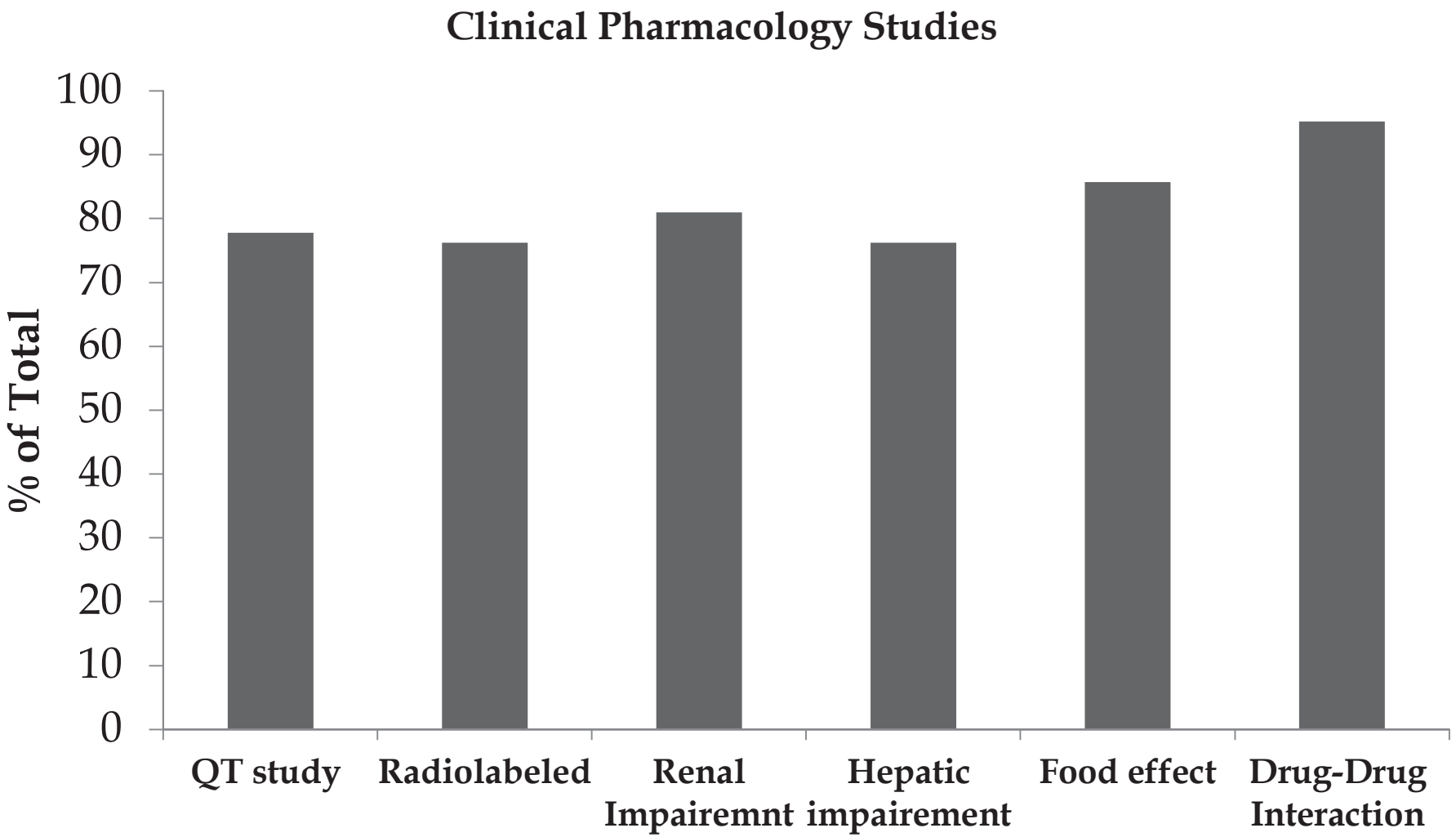
Dose finding



>60% are either a single dose or TTE

- Translational PK/PD and PBPK
- Biomarkers for efficacy
- Animal models
- Tissue distribution and target site concentration

Dose Individualization based on Clinical Pharmacology Studies



AbuAsal et al. American Academy of Neurology 2017

Clinical Pharmacology Studies Post-Approval

Studies of effects of renal or hepatic impairment potentially can be **deferred until after approval, or even waived**, if the patient population and metabolic pathways of the drug, considered together, suggest a low likelihood of clinically meaningful effects on pharmacokinetics or pharmacodynamics.

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm450229.pdf

Dose Individualization Early (Effect of Intrinsic & Extrinsic Factors)

- More inclusive Phase 3 studies
  - Extrinsic/Intrinsic factors characterized
  - Mitigate safety concerns
- Individualization of dose
- No feasibility issues (not disease population)
- FDA accepts only plausible and justified flexibilities
  - PBPK waiver with DDIs
  - Collect PK samples in P3 studies
  - PopPK and Exposure Response Analyses

Case Study: (Deflazacort for Duchenne muscular dystrophy (DMD)

- DMD is a rare disease (1 in 3,500 live male births) that occurs as a result of mutations in the dystrophin gene.
- These mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration.

- Approved Drugs:
  - Eteplirsen(Exondys 51®)
  - Deflazacort (Emflaza®)

  Deflazacort, a glucocorticoid, is an oxazoline derivative of prednisone, and has demonstrated anti-inflammatory and immunosuppressant effects.

Deflazacort (EMFLAZA®)Development Program

- **Efficacy Registration Studies:**

Study	Doses (mg/kg)	Duration	Control	1o Endpoint
MP-104-NM-001	0.9, 1.2 QD	12-week	Placebo or 0.75 prednisone	Muscle strength
MP-104-NM-002	2 QOD	2 years	Placebo	Muscle strength

- **Clinical pharmacology studies:**
- Renal impairment (ESRD Patients)
- Hepatic impairment
- DDI (CYP3A4 inhibitors and inducers)
- Food effect ; Bridge the suspension to tablets
- Bridge Calcort ® ➔ To-be marketed formulation
- PK in pediatrics and adolescence (DMD Patients)

PK Bridging to the Clinical Formulation

Issue:

- Study was conducted 20 years ago ➔ Clinical trial formulation is not available (No PK bridge to TBMF)
  - No PK data in efficacy studies.
  - No dissolution data, not a class 1.

Issue resolving approach:

TBMF Exposure > 0.9 mg/kg Or Exposure <0.9 mg/kg

- Clinical Experience (Exposure Response)
  - 0.9 and 1.2 have similar efficacy
  - Bridge against Calcort ® (Deflazacort Not approved for DMD in Europe) ➔ Safety is not an issue if EMFLAZA has higher exposure
- Different formulations have similar BA
  - Suspension, Crushed tablets, different tablet formulation.
  - No Food effect with different formulation
- PBPK absorption prediction

Mechanistic Prediction of Fraction Absorbed (Fa)

Fa: is the fraction disappearing from the lumen

Formulation changes for oral small molecules are expected to affect only Fa.

Tablets =Suspensions

- Although suspension has solubilizing agents but still Tablets are as good
- Tablet hardness is not an issue

Dissolution Factors

- PSD, pH Solubility and Physiological PH. Precipitation time

PBPK Simulations

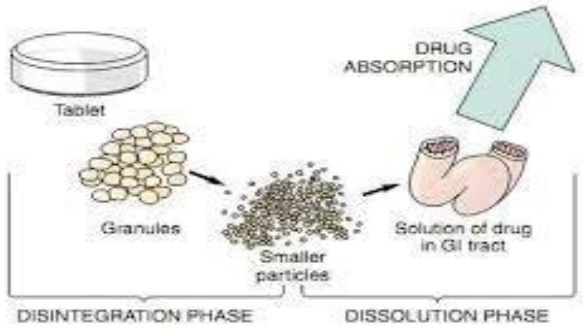
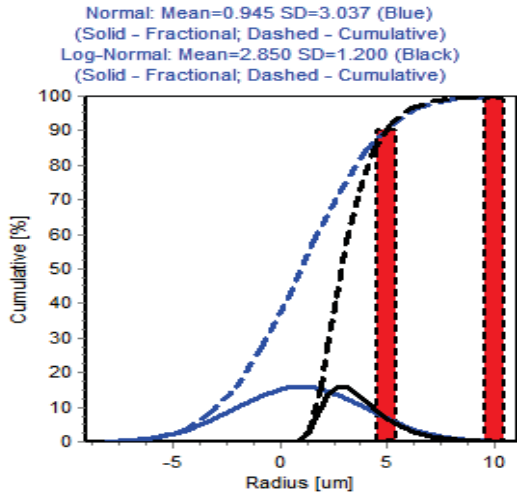


Figure 29-1 Phases of Solid Drug Absorption

Biopharmaceutical and Physicochemical properties in relation to absorption

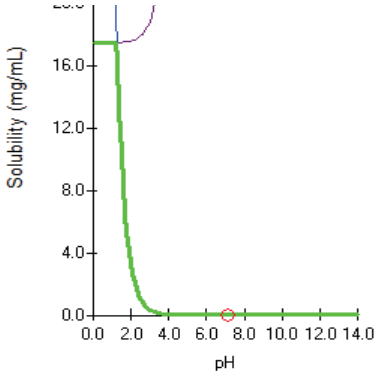
Biopharmaceutics & formulation related parameters

Dose and dosage form
Dose volume
Precipitation time
Diffusion coefficient
Particle size distribution
PH solubility profile
Permeability



PSA:
Prec time: No effect
Permeability: No effect

$$\frac{dM_D}{dt} = \frac{D_{eff}}{\rho h r_t}\frac{(1+2s)}{s}(C_s - C_l)M_{u,t}$$



Fraction absorbed: 99%
Dissolution number: 2.4 >1
Absorption number: 6.4 >1
Supportive evidence

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000ClinPharmR.pdf

Interactions with the FDA

- Interaction and dialogue with the FDA is important
- Applications for which a pre-NDA meeting with the FDA was not held have a more than eight-fold (OR = 8.33; 95%CI = 1.6–44.6) increase in the probability of rejection

- Talk to us; we can help

. Drug discovery Today 2011 Jan;16(1-2):73-80. doi: 10.1016/j.drudis.2010.11.006. Epub 2010 Nov 20.

Interactions with the FDA

Pre-IND EOP I EOP II Pre-NDA Labeling

- CPIM is a means by which CDER and investigators from industry, academia, patient advocacy groups, and government can communicate to improve efficiency drug development.
- **Scope:** Biomarkers, Clinical outcome and endpoints, Emerging technologies, natural history studies, novel trial designs

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm00

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THANK YOU

They are like orphans in that they require special care–Henry Waxman