Impact of D-E-R Information on Regulatory Approval and Post Authorisation Commitments: FDA Perspective

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Disclosures and Acknowledgements

- **Disclosures**
  - **The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.**

- **Contributors to the ideas presented today**
  - **Division of Pharmacometrics**

Approval

- **Formoterol (asthma)**
  - **Only the low dose was approved even though both low and high doses were superior to placebo on efficacy**
- **Mirabegron (overactive bladder)**
  - **Only the low dose (studied in one trial) with optional up-titration was approved even though the high dose was repeated in three phase 3 trials and superior to placebo on efficacy**
- **Dabigatran (stroke)**
  - **Only the high dose (superior to low dose and warfarin on efficacy) was approved even though both doses showed non-inferiority relative to warfarin**
- **Indacaterol (COPD)**
  - **High doses were not approved in the 1st cycle**
  - **Low dose was approved in the 2nd cycle**
- **Cariprazine (schizophrenia and bipolar disorder)**
  - **FDA acknowledged that cariprazine clearly demonstrated efficacy**
  - **Complete response letter (not approval) to optimize dosing regimen**

PMC/PMR

Drug	Indication	PMC/PMR	Goal
Ponatinib	Chronic myeloid leukemia	PMR	Lower dose
Vandetanib	Medullary thyroid cancer	PMR	Lower dose
Cabozantinib	Medullary thyroid cancer	PMR	Lower dose
Adalimumab	Ulcerative colitis	PMR	Higher dose
Mozobil	Mobilize hematopoietic stem cells	PMC	Higher dose in low body weight patients
Herceptin	GI cancer	PMR	Higher dose
Ado-trastuzumab emtansine	Metastatic breast cancer	PMC	Higher dose
Ipilimumab	Melanoma	PMR	Higher dose
Omacetaxine mepesuccinate	Chronic myeloid leukemia	PMR	Higher dose
Radium Ra 223 dichloride	Prostate cancer	PMC	Higher dose

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PMC/PMR for Lower Dose

Year approved	Drug name (brand name)	Indications	Approved highest maintenance dose in adults[a]	Comments[b]
2011	Gabapentin enacarbil (Horizart)	Restless legs syndrome (RLS)	600 mg	PMR: additional dose–response studies that include lower doses (300, 450 mg/day) are needed to define the maximally effective, lowest dose to relieve moderate to severe symptoms of RLS
2011	Vilazodone (Viibryd)	Major depressive disorder (MDD)	40 mg	PMC: some important adverse reactions are dose related; request to further characterize the efficacy and safety to evaluate 20- and 40-mg fixed doses in MDD
2010	Dalfampridine (Ampyra)	Multiple sclerosis (MS)	10 mg twice daily	PMC: to evaluate the efficacy of 5-mg twice-daily dose in MS
2010	Cabazitaxel (Jevtana)	Hormone-refractory metastatic prostate cancer (mHRPC)	25 mg/m^2 every 3 weeks	PMR: to compare a lower dose (20 mg/ m^2) with 25 mg/m^2 in mHRPC
2010	Fingolimod (Gilenya)	Multiple sclerosis	0.5 mg daily	PMC: to evaluate a lower dose, 0.25 mg. The similarity in effectiveness of 0.5- and 1.25-mg doses suggests that a lower dose might be equally effective. The clinical findings of concern are clearly dose related
2010	Lurasidone (Latuda)	Schizophrenia	160 mg	PMC: to identify the lowest effective dose; to evaluate with a dose lower than 40 mg (e.g., 20 mg daily)
2009	Asenapine (Saphris)	Schizophrenia and bipolar mania	10 mg twice daily	PMC: to identify the lowest effective dose; to study a dose <10 mg twice daily (e.g., 5 mg twice daily) in bipolar mania and to study a dose <5 mg twice daily (e.g., 2.5 mg twice daily) in schizophrenia
2008	Rilonacept (Arcalyst)	Cryopyrin-associated periodic syndrome	160 mg weekly	PMC: to assess whether either lower maintenance doses or a longer interval between doses could be equally effective but potentially safer than the approved dose
2008	Desvenlafaxine (Pristiq)	MDD	50 mg	PMC: to evaluate efficacy at 10, 25, and 50 mg/day. The available data suggest a flat dose–response curve for efficacy between 50 and 400 mg/day. There is a clear dose response for adverse events as the dose increases from 50 to 400 mg/day
2006	Paliperidone (Invega)	Schizophrenia	12 mg	PMC: to conduct a study to explore for a minimal effective dose

Is This the Dose for You?: The Role of Modeling, S-M Huang, A Bhattaram, N Mehrotra and Y Wang, *Clinical Pharmacology & Therapeutics* (2013); 93 2, 159–162

Summary

- **Not sufficient to support the safety and efficacy of one dose relative to placebo/control**
- **Search for dosing regimen with optimal safety/efficacy profile or even individualized dose(s)**
- **Impact of dose-exposure-response information**
  - **Approval**
  - **PMC/PMR**