A Model- and Systems-Based Approach to Efficacy and Safety Questions Related to Generic Substitution

Lesko, Lawrence J.[1] ; Biliouris, Konstantinos[1]; Samant, Tanay S.[1]; Combes, Francois P.[1]; Fang, Lanyan[2]; Schmidt, Stephan[1]; Trame, Mirjam N.[1]

1. Department of Pharmaceutics, University of Florida , Orlando, FL, United States, 2. Office of Generic Drugs, Food and Drug Administration, Silver Springs, MD, United States

Introduction

- The Office of Generic Drugs (OGD) at FDA occasionally receives reports of potential product failure after switching from brand to generic product resulting in failure of efficacy or an adverse event. It is difficult to interpret these reports and confirm them
- Bioequivalence in PK between drug products is typically evaluated using bioequivalence (BE) criteria [90% Confidence Interval (CI) for Area Under the Curve (AUC) and maximal concentration (C_{max})] as a surrogate for therapeutic equivalence[1]
- The objective of our research is to develop a scientific platform that allows investigators at FDA (or, industry and academia) to conduct a 3-step mechanistic investigation to determine whether or not the aforementioned generic drug report is possible or not. This poster demonstrates the process of using the scientific platform for the anti-epileptic drug (AED), levetiracetam (LVT). LVT is available as both branded and generic products. This is a hypothetical example as there are no known bioequivalence or therapeutic equivalence issues with LVT

Methods

The 3-step approach consisted of : I) FAERS data mining and systems pharmacology, II) physiological based pharmacokinetics (PBPK) modeling and III) population PK/PD modeling

I. Data mining and systems pharmacology to identify the frequency, nature and patient outcome of LVT Adverse Events (AE) using data from the FDA Adverse Event Reporting System (FEARS)[2].

1. To elucidate the top 20 molecular targets and pathways (CYP enzymes, transporters and pharmacological receptors) of LVT using the Molecular Analysis of Adverse Events (MASE) software platform[3]
2. To dissect the molecular link between AE and molecular targets/pathways for LVT

II. PBPK Modeling

1. To develop and qualify a PBPK model for Immediate and extended release (IR and XR) LVT based on *in vitro* release kinetics and system properties
2. To perform a sensitivity analysis on formulations and drug-dependent quality attributes to identify parameters which might possibly cause bioinequivalence
3. To simulate a range of PK profiles using the PBPK model to determine the range of effects of quality attributes on 90% CI criteria for generic products

III. PK/PD Modeling

1. To estimate basic PK parameters for brand and generic formulations based on available literature and from PBPK modeling and simulation
2. To simulate and to compare PK profiles or their BE metrics (AUC or C_{max}) based on the different simulated PK profiles

Characteristics of LVT Relevant to PBPK and PK/PD modeling:

- BCS class I drug: High solubility and high permeability
- Rapid and complete absorption (T_{max} around 1 h)
- Oral administration: Half-life of 7 h
- Dose: 500 - 5000 mg/day
- Steady state after 2 days
- Therapeutic concentrations: 12-40 µg/mL
- IR and XR formulations available
- Population PK model: One compartment with first-order absorption and first-order elimination[4]

REFERENCES

1. Food and Drug Administration. Guidance for Industry - Final guidance Statistical approaches to establishing bioequivalence
2. FAERS database: http://www.fda.gov/Drugs/
3. MASE software: https://mase.molecularhealth.com
4. Pigeolet E, *et al*, Clin Pharmacokinetics, 2007;46(6):503-512
5. Levetiracetam (Keppra XR), Clinical pharmacology/Biopharmaceutics review, FDA

ACKNOWLEDGMENTS

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Results

I.1. AE for Brand Name and Generic LVT

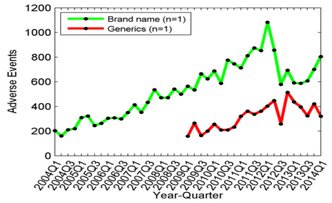

Figure I.1. **Frequency of AE per year quarter over a 10-year period for brand name and generic formulations of LVT.** Prescription data are required for an unbiased comparison of AE frequency

Table I.1. **Nature (percentage of total AE) of the 5 most common AE in brand name and generic LVT formulations.** The molecular basis of these AE can be mapped to LVT molecular targets, e.g. thrombocytopenia could be linked with prostaglandin g/h synthase 1 as the latter is listed in the top molecular targets of LVT (see Table I.2) and its excessive inhibition leads to thrombocytopenia

Brand name (% of total)	Generics (% of total)
Convulsion (3.84)	Convulsion (7.24)
Drug exposure during pregnancy (3.30)	Product substitution issue (2.01)
Thrombocytopenia (1.53)	Drug ineffective (1.96)
Condition aggravated (1.10)	Pregnancy (1.75)
Grand mal convulsion (0.95)	Spontaneous abortion (1.74)

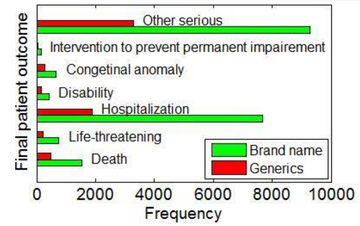

Figure I.2. **Outcome of AE in brand name and generic LVT formulations.** The majority of AE resulted in Serious outcomes or Hospitalization for both brand name and generics

I.2. Top 20 Molecular Targets of LVT

Table I.2. **Top 20 targets of LVT separated into CYP enzymes, transporters and other molecular targets and ranked according to proportional reporting ratio (PRR).** These targets are related either to the PK effect (CYP enzymes, Transporters) or to the pharmacodynamics effect (Molecular targets)

CYP450 Enzymes	AE	PRR (CI PRR)
2c18	3527	2.67 (2.60-2.74)
2b6	5828	1.90 (1.87-1.93)
2e1	3585	1.59 (1.55-1.63)
3a5	6452	1.56 (1.54-1.59)
2a6	3391	1.52 (1.48-1.57)
2c19	7466	1.51 (1.49-1.53)
3a7	5302	1.50 (1.47-1.53)
2c8	6539	1.29 (1.27-1.31)
1a2	5919	1.25 (1.23-1.28)
2c9	6766	1.19 (1.17-1.21)
3a4	8073	1.14 (1.13-1.15)
2d6	5084	0.96 (0.94-0.98)

Transporters	AE	PRR (CI PRR)
Canalicular multispecific organic anion transporter 1	11404	6.17 (6.15-6.19)
Multidrug resistance protein 1	11404	2.00 (1.99-2.00)
Serum albumin	3908	1.49 (1.46-1.53)
Solute carrier family 22 member 6	3615	1.32 (1.28-1.35)

Molecular Targets	AE	PRR (CI PRR)
Voltage-dependent n-type calcium channel subunit alpha 1b	11404	22.32 (22.19-22.46)
Gamma-aminobutyric-acid receptor subunit alpha-1	3347	3.47 (3.37-3.57)
Prostaglandin g/h synthase 1	3229	1.21 (1.17-1.24)
Synaptic vesicle glycoprotein 2a	11404	n/a

II. PBPK and Sensitivity Analysis

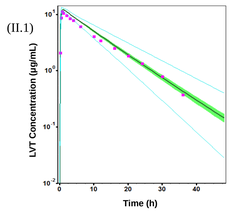

Figure II.1: PBPK model for IR[5] LVT; Solid dots: Observed plasma concentration; Black line: Simulated profile; Green band: 90 % C.I.; Blue line: 95 % Probability.

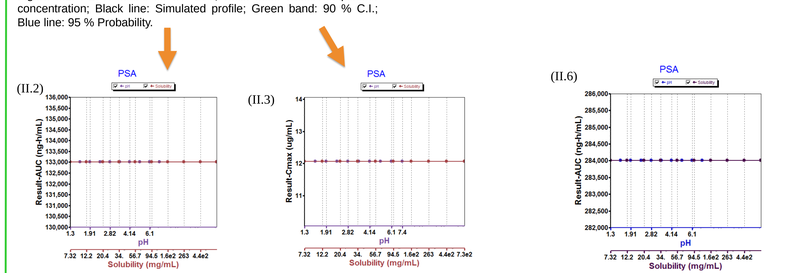

Figure II.2, II.3: Sensitivity analyses for effects of formulation and drug dependent parameters on C_{max} and AUC for the IR formulation of LVT.

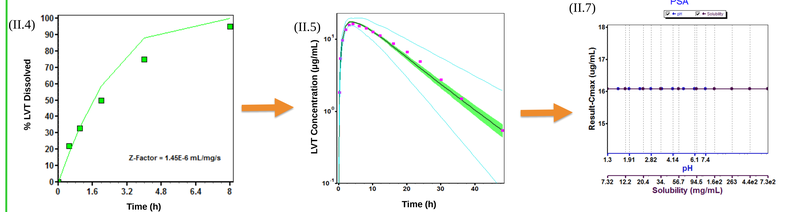

Figure II.4 *In vitro* dissolution model for XR[5] LVT. Solid dots: Observed dissolution profile; Green line: Fitted dissolution profile

Figure II.5: PBPK model for XR[5] LVT; Solid dots: Observed plasma concentration; Black line: Simulated profile; Green band: 90 % C.I.; Blue line: 95 % Probability.

Figure II.6, II.7 Sensitivity analyses for effects of formulation and drug dependent parameters on C_{max} and AUC for the XR formulation of LVT.

Virtual trial (1000 subjects) simulated data from PBPK analysis or from a literature research were analyzed using Non-Linear Mixed Effects (NONMEM®7.2)

III.2. Bioequivalence outcomes

Table III.2. **PK metrics (AUC and C_{max}) along with ratio of the logarithmic mean of PBPK *vs* published computed using simulated BE trial.** The four formulations from III.1 were used for simulation

Estimate	Published IR	PBPK IR	Published IR	PBPK IR
$AUC_{0\rightarrow\infty}/F$ (mg.h/L)	219.6	258.8	200.7	273.9
Ratio *vs published*	1	1.18	1	1.36
C_{max} (mg/L)	19.26	21.85	12.59	15.02
Ratio *vs published*	1	1.21	1	1.22

III.1 Population PK Model

Table III.1. **Final estimates for XR and IR formulations using published data or simulated data from a PBPK analysis**. RSE stands for Relative Standard Error

Formulation	CL/F (L/h)	V/F (L)	k_a (h^{-1})
Estimates (RSE) based on published concentrations			
XR	4.59 (14)	45.9 (4)	0.399 (7)
IR	4.96 (3)	42.7 (2)	5.86 (7)
Estimates (RSE) based on PBPK simulated concentrations			
XR	3.54 (1)	39.5 (0)	0.497 (0)
IR	3.81 (1)	37.1 (0)	3.48 (1)

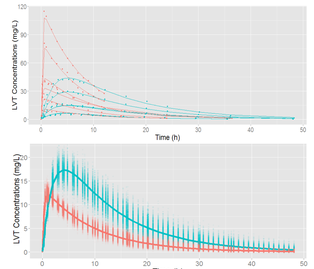

Figure III.1. **Predicted (lines) *vs* observed (points) concentrations for published data (upper panel) and and PBPK simulated data (lower panel), for both IR (red) and XR datas (blue).** Several doses were used for published data, when PBPK data were simulated for 500mg (IR) and 1000mg (XR)

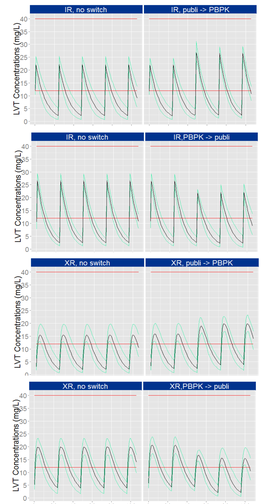

Figure III.2. **Simulated switchability between IR (2 upper graphs), or XR (two lower graphs) formulations, when the subjects start the treatment with the published (upper panel) or the PBPK (lower panel) formulation**. Lines represent the median (black) and 9-95% percentiles (green) of the predictions, and the upper and lower therapeutic concentrations (Red)

Conclusion

I. Data-mining & Systems Pharmacology:

- Data mining in FAERS allowed for comparing the AE frequency, AE nature and final patient outcome of brand *vs* generic formulations of LVT. However, prescription data (pending request) for each product is required for an unbiased comparison
- Systems pharmacology tools enabled mapping molecular targets of LVT to purported AE in FAERS

II. PBPK

- Based on the sensitivity analysis, none of the selected formulation or drug dependent parameters were likely to lead to bioinequivalence due to a significant change in the AUC or C_{max}
- The sensitivity analysis results can be used for hypothesis testing of BE and compared with probable therapeutic inequivalence between brand and generic LVT from FAERS data mining

III. PK/PD

- Estimation of PK parameters from PBPK simulated data gives results similar to those found in the literature or those estimated using published data
- This methodology allows the simulation of PK (plus PD) of brand vs generic drug products to test the relative risk of a generic product being potentially bioinequivalent