A TOOL FOR PRIORITIZATION OF INVESTIGATION OF GENERIC DRUG INEFFECTIVENESS COMPLAINTS

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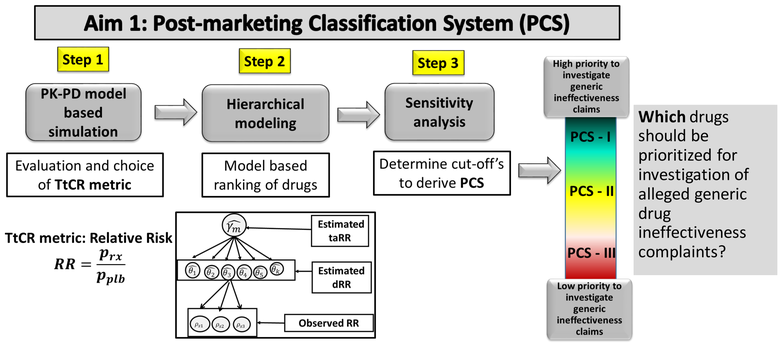
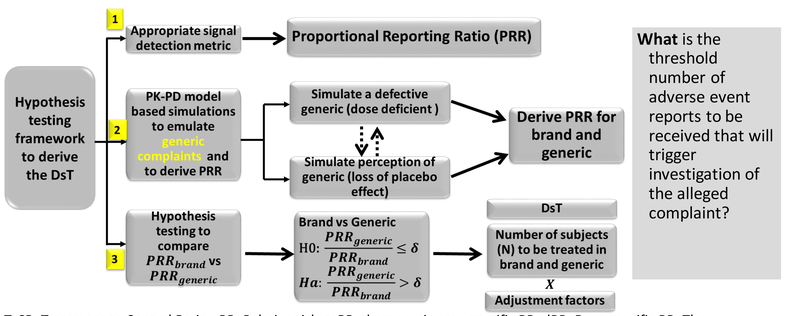
Background: Need to prioritize investigation of complaints

- Despite demonstrating bioequivalence of the generic to the reference listed drug (RLD), post-marketing complaints of generic drug ineffectiveness upon switching from the RLD persists.
- The perception that taking a generic is not effective may account for the ineffectiveness complaints.
- It is time and resource demanding for the Food & Drug Administration (FDA) to investigate such complaints. The process can be made efficient if there is a way to prioritize the investigation of the alleged complaints.
- The **main aim of the research** was to
  - To devise a methodology to perform an **objective and systematic assessment** of generic ineffectiveness complaints and develop a **web-based application** to simplify the go-no-go decision to prioritize the investigation.

Methods: Devising post-marketing classification system (PCS) & framework to determine drug-specific threshold (DsT)



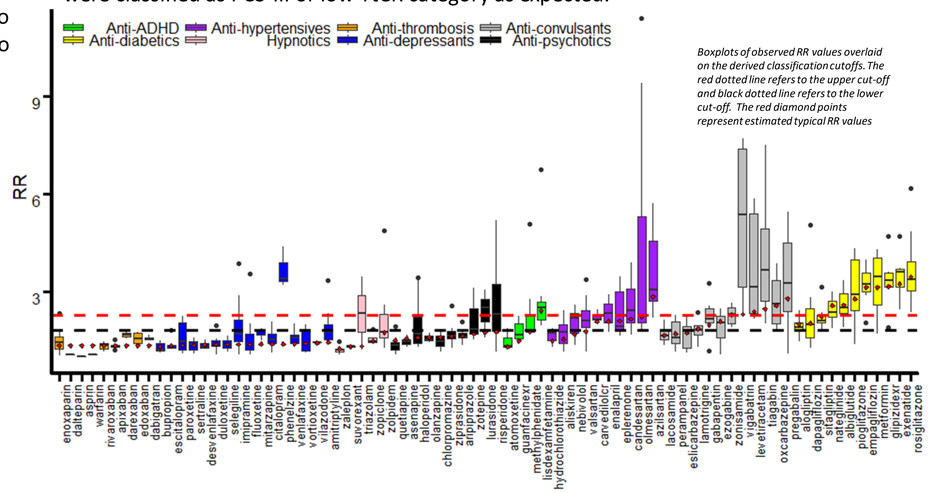


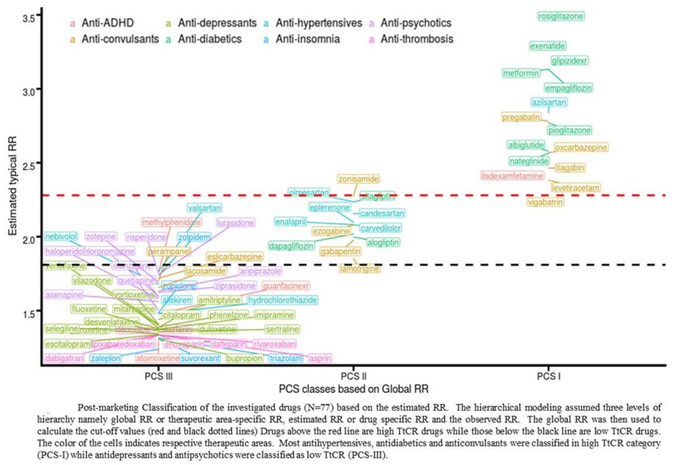
TtCR: Treatment to Control Ratio; RR: Relative risk; taRR: therapeutic area specific RR; dRR: Drug specific RR; The PCS was obtained for 77 drugs (Table below) using response rate data available at the time of approval from New Drug Application (NDA) reviews available at Drugs@FDA and/or peer reviewed publications; The cut-off's for PCS were obtained by dividing the range of RR's into three equal bins to obtain PCS-I, II & III categories.

Indication	Drugs	Studies	Sample size Drug	Sample size Placebo
ADHD	4	26	3182	2446
Diabetes	11	98	14458	12855
Hypertension	10	75	8995	7293
Insomnia	5	29	5093	4592
Major depression	16	114	17715	16115
Partial seizure	12	71	9502	9007
Schizophrenia	10	88	6236	5739
Deep Vein Thrombosis (Prophylaxis – knee surgery)	9	31	14258	14257

Results: PCS derived for 77 drugs from 8 therapeutic areas

- Effect size, relative risk (RR) and mahalanobis distance were identified as sensitive TtCR metrics. RR was further considered for deriving PCS.
- Using RR, the estimated global RR values were: Major depression (1.38), Insomnia (1.42), Schizophrenia (1.63), DVT following knee surgery (1.34), Partial seizure (2.15), ADHD (1.74), Diabetes (2.75), and Hypertension (1.99).
- Based on the PCS, most antihypertensives, antidiabetics and anticonvulsants were placed in the high TtCR category (PCS- class I) while antidepressants and antipsychotics were classified as PCS-III or low TtCR category as expected.





Post-marketing Classification of the investigated drugs (N=77) based on the estimated RR. The hierarchical modeling assumed three levels of hierarchy namely global RR or therapeutic area-specific RR, estimated RR or drug specific RR and the observed RR. The global RR was then used to calculate the cut-off values (red and black dotted lines) Drugs above the red line are high TtCR drugs while those below the black line are low TtCR drugs. The color of the cells indicates respective therapeutic areas. Most antihypertensives, antidiabetics and anticonvulsants were classified in high TtCR category (PCS-I) while antidepressants and antipsychotics were classified as low TtCR (PCS-III).

Results: DsT determination with a proposed decision tree

DsT determination to trigger investigation of complaints

Information needed:

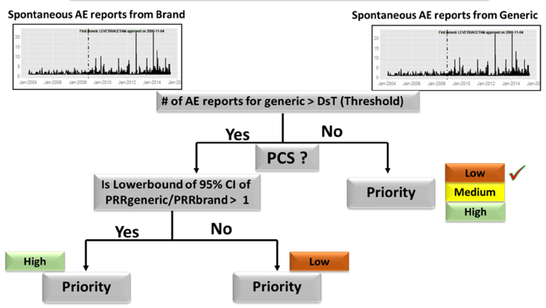
1. Total number of subjects (N) to be treated by a given drug necessary to assess true PRR differences (from PK-PD simulations involving hypothesis testing).
2. Adverse events (for drug ineffectiveness) reporting frequency during brand-name drug market exclusivity period.
3. Total patient population on the drug of interest during brand market exclusivity.

$$DsT\ (Threshold\ number\ of\ reports\ for\ generic\ drug\ X) = Pr_{AE_{brand}} \times N,$$

where, $Pr_{AE_{brand}} = \frac{Average\ AE\ reporting\ frequency\ for\ brand}{Number\ of\ subjects\ treated\ during\ the\ brand-name\ drug\ market\ exclusivity\ period}$

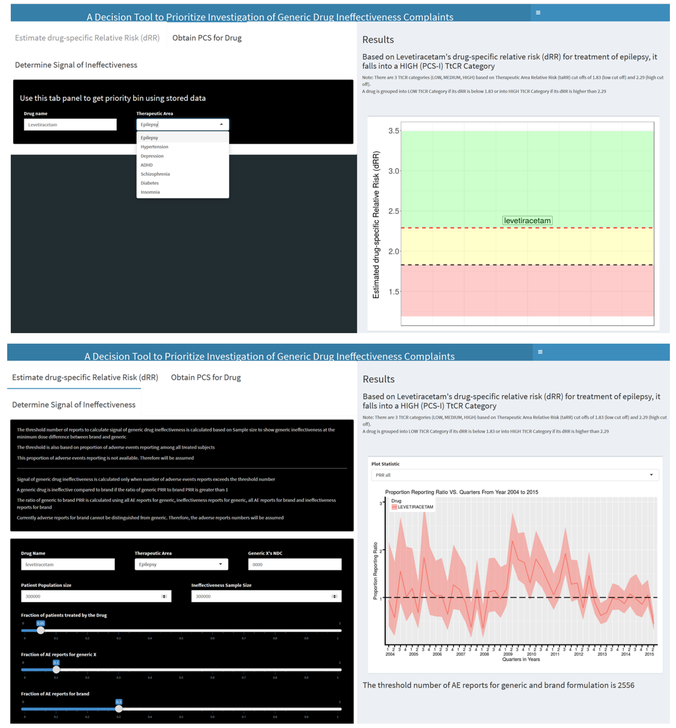
Obtain Pr_{AE_brand} from databases such as insurance claims or IQVIA database.

During a specific time period (Quarterly/Yearly)



- In order to trigger an investigation based on the reports received during a specified time period, the research proposes utilization of two pieces of information namely,
  - Post-marketing classification (PCS) category of a given drug and the drug specific threshold (DsT) for the number of AE reports of ineffectiveness
  - If the number of AE reports for a generic from the spontaneous reporting is greater than the determined DsT for the generic drug, then considering the PCS category of the drug would lead to providing a priority rank for the investigation as either low, medium or high

Results: Prototype R-Shiny application



Conclusions

1. A tool and framework to prioritize investigation of post-marketing complaints of generic product ineffectiveness has been developed. [Post marketing Classification System]
2. Strategy for determination of threshold number of adverse event reports for assessment of complaints is proposed. [DsT to trigger investigation of complaints]
3. An easy to use web-application is developed to assess the generic ineffectiveness claims.

POTENTIAL IMPACT: The tool and framework can potential be used to assist FDA with an objective and an efficient way to assess and prioritize investigation of post-marketing generic ineffectiveness claims.

Funded by FDA grant #1U01FD005192-01. This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.