Poster Number
03M0130

Searchable Database of FDA Product-specific Recommendations Used to Establish Therapeutic Equivalence of Generic Drug Products

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2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER
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PURPOSE

- The US Food and Drug and Administration (FDA) has been publishing product-specific recommendations (guidances) quarterly to share its current thinking on equivalence standards for generic drug development and to encourage the exchange of scientific knowledge and foster innovation[1].
- Currently, the guidances are posted individually in Portable Document Format (PDF), and sorted alphabetically by the active pharmaceutical ingredient(s) (API)[1]. Although it is convenient to obtain information for individual drug products in their current format, it is challenging to obtain summary information, search for similar guidances, or perform statistical analysis on the published guidances.
- We developed a keyword-orientated searchable database of guidances published through January 2016 to facilitate the availability and usability of guidances by various stakeholders.

METHODS

- Data elements were extracted from published guidances utilizing text mining approaches and were arranged in a searchable and user-friendly format with Microsoft Access.
- The structure of the database was designed to reflect the structure of guidances. Key terms consistently utilized in guidances were incorporated in the database as overarching categories to maintain the same or similar terminology and avoid confusion for the users. These categories included: the application number of the Reference Listed Drug (RLD) (unique to every drug product); the API; the route of administration; the dosage form; the type and design of the recommended studies as well as the population to be recruited, the strength to be tested and the strengths for which testing can be waived; the endpoint of the recommended studies and the recommended statistical method to be used; and, finally, the analyte proposed for quantification.
- When multiple RLD numbers are linked to the same guidance, all these RLD numbers are listed in the database and populated with the same guidance content.
- Further exploratory analysis on trends, patterns and descriptive statistics, where RLD numbers captured in the database are referred to as guidances in the results section, was performed.

RESULTS

Oral and Topical Are the Most Common Routes of Administration Tablets and Capsules Are the Most Common Dosage Forms In Published Guidances

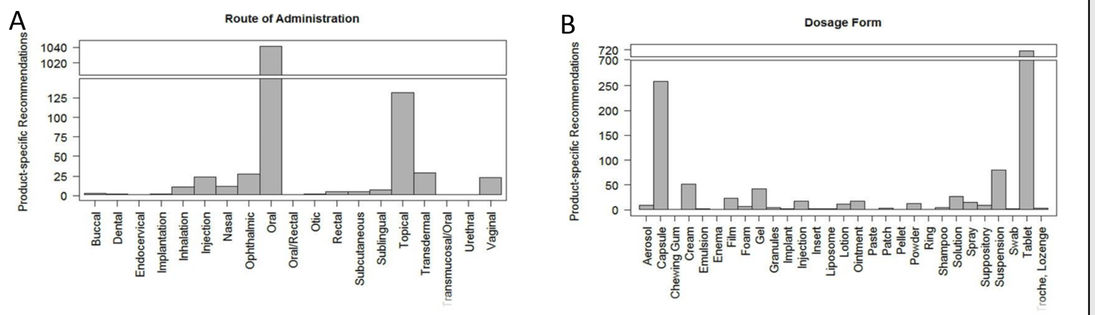

Fig 1. Guidances published by the Office of Generic Drugs based on their route of administration (A) and dosage form (B).

Pharmacokinetic Endpoint Studies for Oral Products and Clinical Endpoint Studies for Topical Products are the Most Popular Studies in Published Guidances

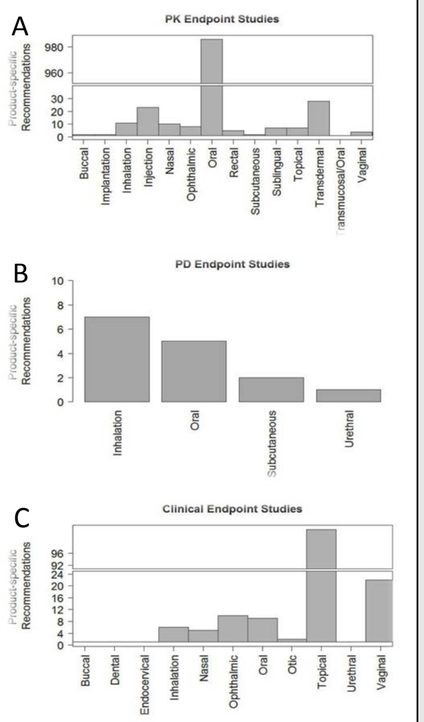

Fig 2. Guidances published by the Office of Generic Drugs for assessment of therapeutic equivalence of drug products for different routes of administration in in vivo studies with pharmacokinetic (A), pharmacodynamics (B) and clinical (C) endpoints.

The Majority of Pharmacokinetic Endpoints Are Cmax and AUC While FEV1max and AUEC Are the Most Popular Pharmacodynamic Endpoints in Published Guidances

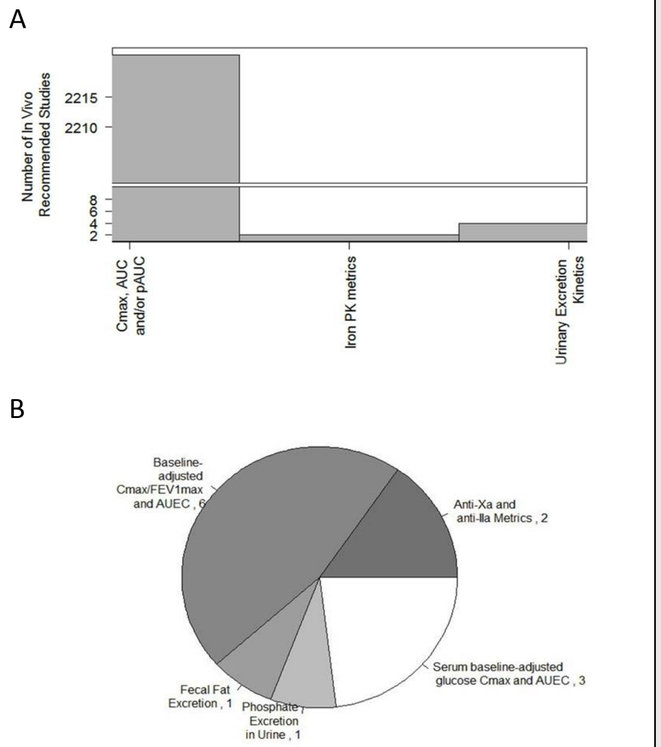

Fig 3. Pharmacokinetic (A) and pharmacodynamic (B) endpoints utilized to assess therapeutic equivalence between brand name and generic drug products in vivo studies recommended in guidances published by the Office of Generic Drugs.

In Vitro Studies on Physicochemical Properties and Product Performance Are Typically Recommended Alone or In Combination With Fasting/Fed In Vivo Studies In Published Guidances

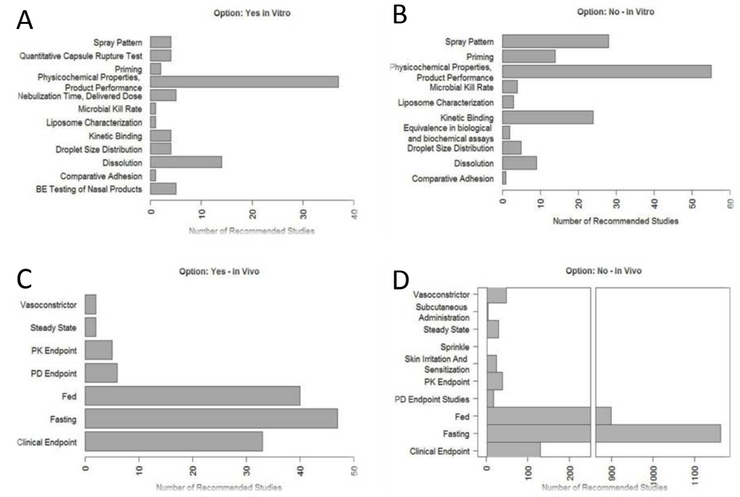

Fig 4. Type of in vitro (A and B) and in vivo (C and D) studies detailed in guidances issued by the Office of Generic Drugs for establishment of therapeutic equivalence. The agency has provided the option of conducting merely the vitro (A) or in vivo (C) studies listed under the "Option: Yes" or the in vitro (B) or in vivo (D) studies listed under the "Option: No". "Option: Yes": the sponsor is provided with more than Options/approaches available (eg. In vitro studies alone or in vitro and in vivo studies) to establish bioequivalence. "Option: No": the sponsor is provided with only one Option/approach to establish bioequivalence.

CONCLUSIONS

- Language standardization observed in guidances increases the capability of performing cross-guidance analyses.
- Searchable database on the content of guidances issued by the Office of Generic Drugs developed.
- Our results suggest that the developed database could serve as a useful tool in future guidance development and generic drug product development.

REFERENCE, ACKNOWLEDGEMENT, AND DISCLAIMER

Reference:
1. U.S. Food and Drug Administration. Drugs. Product-Specific Recommendations for Generic Drug Development., http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm.

- The authors would like acknowledge scientific discussions and support of Drs. Robert Lionberger and Yih Chain Huang.
- This work was supported in part by an appointment to the ORISE Research Participation Program at CDER.
- Disclaimer: This article reflects the views of the authors and should not be construed to represent the FDA's views or policies.

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