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Ontogeny and Application of Pharmacogenomics to Pediatrics

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Pediatric Ontogeny: Ready for Incorporation into Modeling in Pediatric Drug Development?

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Disclaimer

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA
- All specific drug development questions should be discussed with the relevant review division
- I have no financial relationships to disclose relating to this presentation

Outline

- Product Labeling
  - Pediatric product labeling
  - Considerations for including PGx information in labeling
- Application of PGx information in labeling to pediatric patients
  - Implications of ontogeny
- Case examples
  - Cisplatin
  - Codeine

Why Focus on Product Labeling?

- Contains a summary of the scientific information needed for safe and effective use of the product
- Provides health care providers the information they need to prescribe drug products appropriately
- Must be informative and accurate
  - Prior to incorporation, the information has been critically reviewed and vetted by the FDA
  - Updated when new information becomes available
  - Consensus must be reached amongst the FDA review team; and agreement with the application holder

PGx Labeling Principles

- Labeling should include PGx information to:
  - Inform prescribers about the impact of genotype on phenotype
    - Should be clinically meaningful and inform prescribing decisions
  - Indicate whether a genomic test is available
    - If so, indicate whether testing should be considered, is recommended, or is necessary
- PGx information may include:
  - Information on allele frequencies
  - Description of functional effects of genomic variants
  - Descriptions of the effect of genotype on PK/PD
  - Recommendations regarding dosing and patient selection based on genotype
- If applicable, a "Pharmacogenomics" subsection (12.5) should be included in the CLINICAL PHARMACOLOGY Section

Guidance for Industry – Clinical Pharmacogenomics: Pre-Market Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling. January 2013.

Considerations for Establishing the Clinical Validity of a Gene-Drug Interaction

FDA

Data Sources

- Sponsor-conducted trials
- Published literature

Types of Evidence

- Cases reports/series (severe toxicity/ outliers)
- Retrospective case-control studies (severe toxicity/ outliers)
- Pro/retrospective cohort studies (efficacy, safety, PK)
- Enriched/stratified experimental studies (PK, efficacy, safety)

Causal Inferences

- Mechanistic information/ biological plausibility
- Consistency across studies, populations, designs
- Gene-dose response, concentration-response issues
- Magnitude of interaction and statistical significance

Adapted from presentation by Michael Pacanowski, Pharm.D.

Experience with Labeling Gene-Drug Interactions

Data emerge mostly in post-marketing setting, often external to sponsor's clinical trials

Clinical events are usually severe and gene-drug interaction is highly replicated with significant increase in relative risk

Many gene-drug interactions are extensions of known clinical pharmacology (e.g., drug interactions)

Prospective validation trials are less common; totality of evidence must be considered (PK-PD-outcome)

Adapted from presentation by Michael Pacanowski, Pharm.D.

Considerations for Deciding to Update Drug Labeling

- Reliability of the data
- Magnitude of the risk
- Seriousness of the event
- Plausibility of causality
- Extent of patient exposure
- Potential to prevent or mitigate the risk
- Effect on clinical practice
- Disproportionate impact on particular populations

Zineh I, Pacanowski M. Pharmacotherapy. 2011 Aug;31(8):729-35

Factors Guiding the Strength of Prescribing Recommendations

Points of uncertainty

- Effectiveness of genotyping to optimize benefit/risk (utility)
- Quality of studies to establish validity (design, assay, statistics)
- Gaps in empirical evidence (e.g., inference from PK-outcome relationship vs. direct subgroup analysis of outcomes)
- Generalizability to diverse racial/ethnic populations

Considerations

- Severity of the outcome
- Treatment context (benefit/risk of alternative treatments, clinical monitoring tools, dosage forms)
- Clinical performance attributes in the context of event rate
- Test accessibility and feasibility, likelihood of prescriber uptake

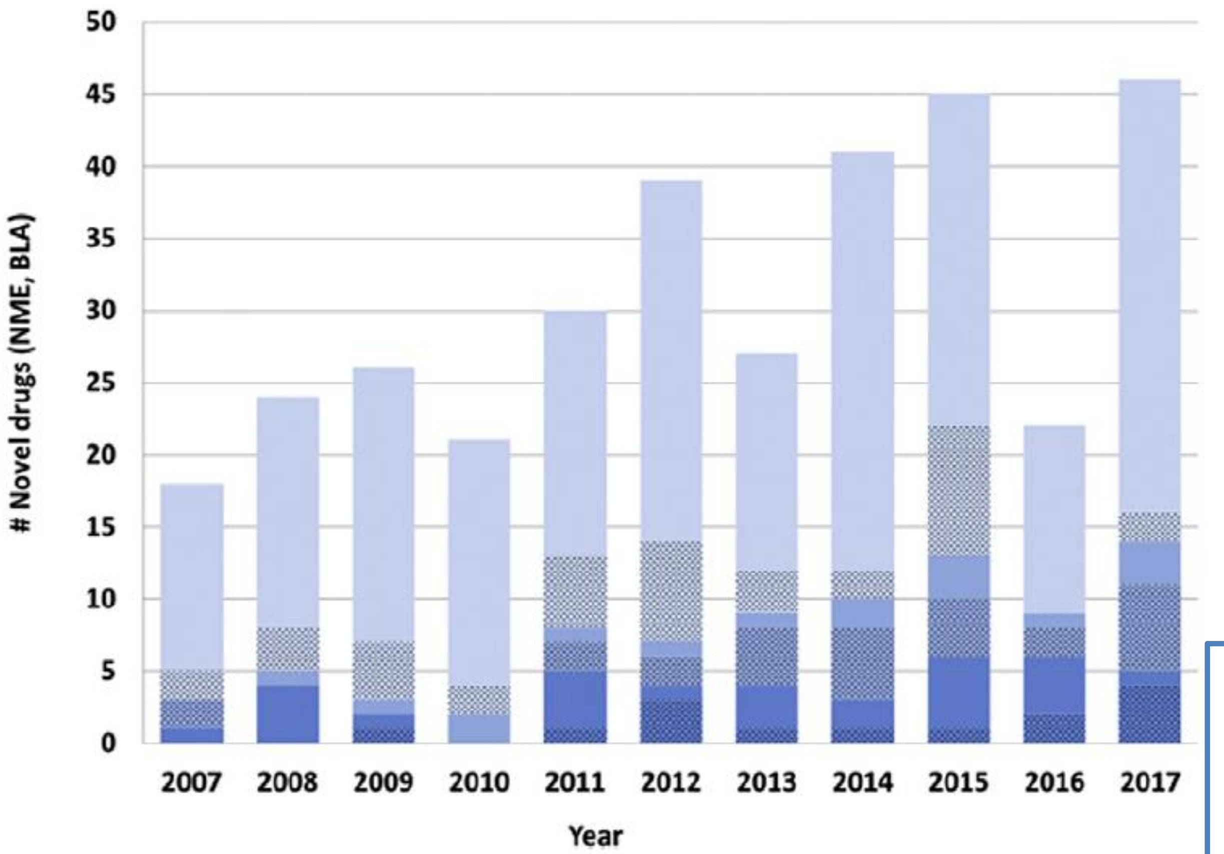
Adapted from presentation by Michael Pacanowski, Pharm.D.

Approaches to Incorporate Genetic Testing Recommendations

- Labeling is often silent on testing recommendations
  - Reference to ‘*known status*’ and ‘*consider*’ accommodates clinical judgment, uncertainty
  - Implicit that testing is essential when included in *Indications and Usage* or *Contraindications*
- When recommended, various approaches have been used
  - Test everyone (eliglustat, abacavir)
  - Test a targeted, at-risk subset (carbamazepine, valproic acid)
  - Test above a certain dose threshold (pimozide, tetrabenazine)
- Other considerations
  - Specific alleles are generally referenced
  - Population prevalence is not uniformly described

Slide courtesy of Michael Pacanowski, Pharm.D.

FIGURE 1 Novel Drugs Approved (NME/BLA) Between 2007 and 2017 With Genomic and Other Selected Biomarker Information in Labeling



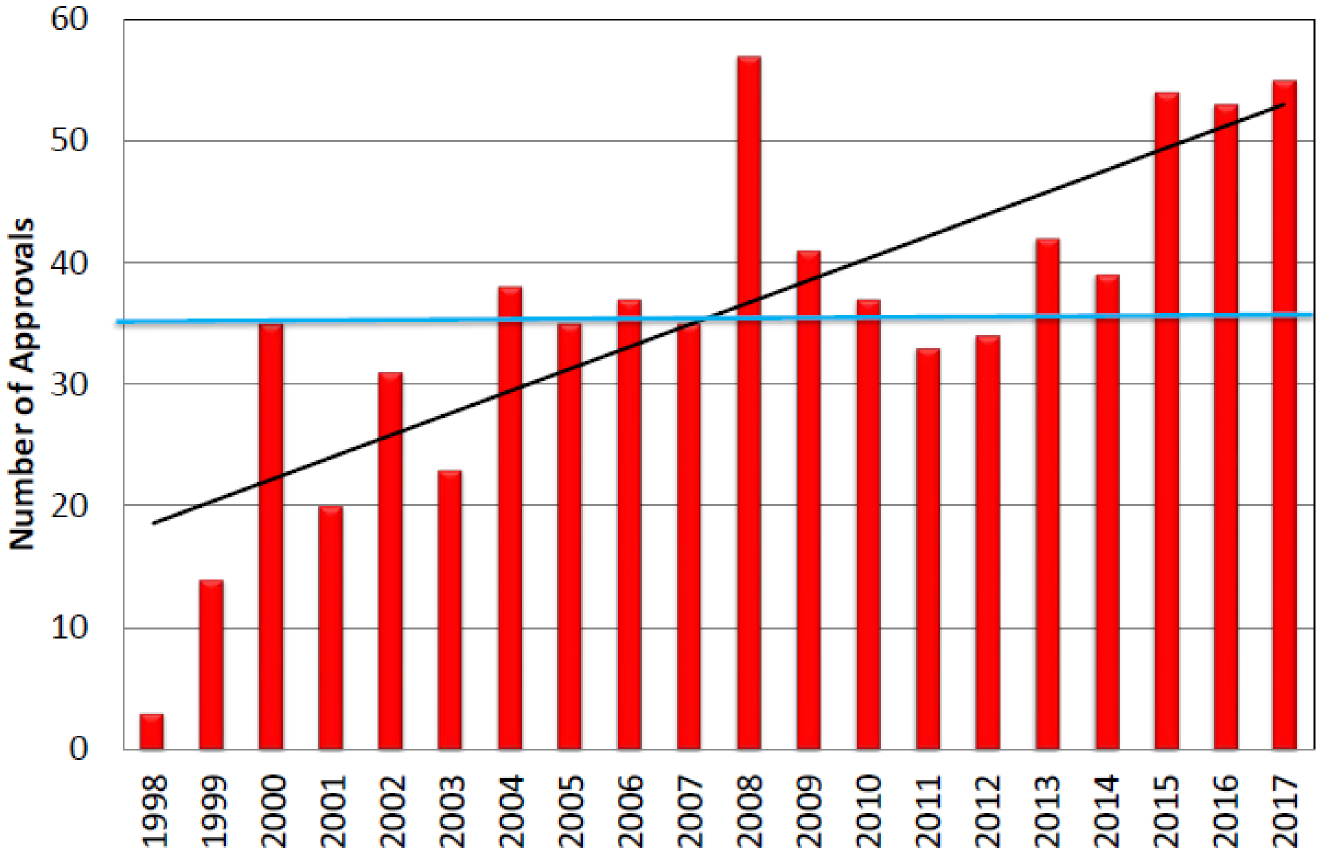
Actionable information = specific prescribing recommendation in:
Boxed Warning;
Indications and Usage;
Dosage and Administration;
Contraindications;
Warnings and Precautions

Drozda K, Pacanowski MA, Grimstein C, et al. JACC Basic Transl Sci. 2018 Aug 28;3(4):545-549

Why Focus on Pediatric Labeling?

- The Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) have substantially increased the number of pediatric studies conducted and the amount of pediatric information in drug labeling

Pediatric Labeling Changes 1998 - 2017



The Ultimate Goal

783 drug labels updated (as of April 30, 2019)

↓

708 with new pediatric studies; **70** with no new pediatric studies

↓

Information in product labeling that informs the safe and effective use of medications in the pediatric population

https://www.accessdata.fda.gov/scripts/sda/sdnavigation.cfm?sd=labelingdatabase

PGx Information in Drug Labeling

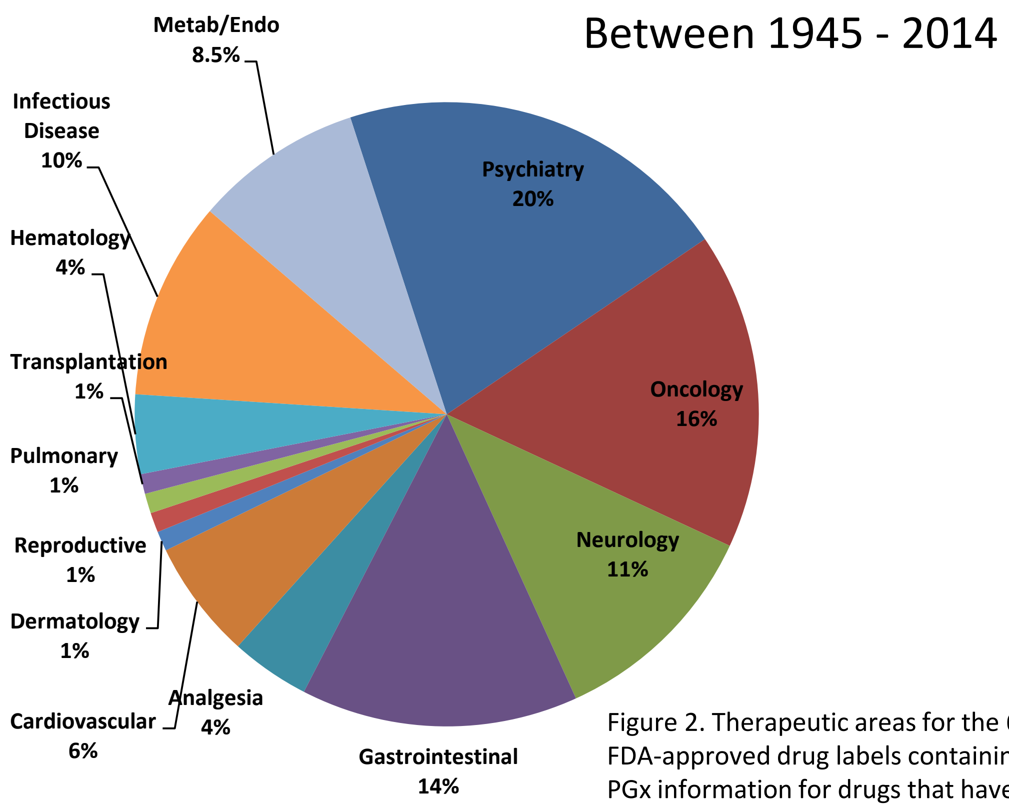


Figure 2. Therapeutic areas for the 65 FDA-approved drug labels containing PGx information for drugs that have been studied in pediatric PK, safety, and/or efficacy studies.

65 drugs, 31 biomarkers

- 56% metabolism/ transport
- 27% target/pathway
- 16% susceptibility
- 4% immunologic

- 68% safety
- 27% efficacy
- 6% both

28 “actionable”

- Otherwise, descriptive of study design feature or presence/absence of gene-drug interaction

Green D, Mummaneni P, Kim IW, et al. Clin Pharmacol Ther. 2016 Jun;99(6):622-32

PGx Information in Labeling: Application to Pediatric Patients?

- For 86% (56/65) of the drugs, the genetic biomarker data described in labeling was derived from adult studies
  - Of the 9 cases when PGx labeling was directly informed by pediatric studies, the majority involved diseases originating primarily in childhood

- The application of PGx information from adults to pediatrics was deemed
  - suitable for 71.4% (n=40) of drugs
  - unclear for 28.6% (n=16) of drugs

- Of those deemed unclear:
  - 11 cases involved children 2 years of age or younger and either a clear, conflicting, or unknown effect of ontogeny on the ADME-, susceptibility-, or immunologic-related genetic biomarker
  - 5 cases involved a target/pathway-related biomarker which was specific to the adult disease and which differed substantially from the pediatric disease studied

Green D, Mummaneni P, Kim IW, et al. Clin Pharmacol Ther. 2016 Jun;99(6):622-32

Application to Pediatrics: Key Takeaways

- The majority of PGx information in drug labeling is derived from studies in adults
- Developmental differences in gene expression, drug response, and drug disposition can result in an inability to universally assume similar genotype-phenotype relationships between adults and all pediatric age groups
- The application of adult-derived PGx information to pediatrics is particularly challenging when:
  - Attempting to apply findings to the youngest patients (e.g., neonates, infants)
  - There are differences between the adult and pediatric disease

Incorporation of Pediatric PGx Information in Labeling: Select Drug Safety Examples

- Cisplatin

- Codeine

Differences in the Incidence of Pediatric & Adult Drug-Induced Hearing Loss

- Cisplatin – is a platinum based chemotherapeutic agent
  - FDA-approved since 1978 for the treatment of multiple adult cancers
  - Not approved for use in pediatrics
  - Critical and effective component of treatment regimens for many pediatric solid and CNS tumors

- Risk: drug-induced ototoxicity
  - Occurs in up to 10-25% of adults vs. 26-90% of children
  - High frequency, bilateral, sensorineural hearing loss
  - Irreversible, progressive
  - Negative impact on cognitive and social development
  - MOA unknown
  - **Younger age increases risk** (Pediatric Ontogeny???)

- Source: published literature (retrospective case-control study)
  - Association identified between variants in the TPMT gene and cisplatin-induced ototoxicity in pediatric patients

Differences in the Incidence of Pediatric & Adult Drug-Induced Hearing Loss

- Dec. 2011 – Cisplatin label updated
  - Informational only (regarding TPMT association and study description), stressed importance of aggressive monitoring for hearing loss, no testing recommendation
- Subsequent independent study published; failed to replicate findings (study design and study cohort were slightly different)
- 2013 – Cisplatin label updated
  - Information only, mentions genetic factors may be associated with increased risk and lists TPMT as an example; study description removed

CYP2D6 Polymorphism Alter Morphine Exposure and Response

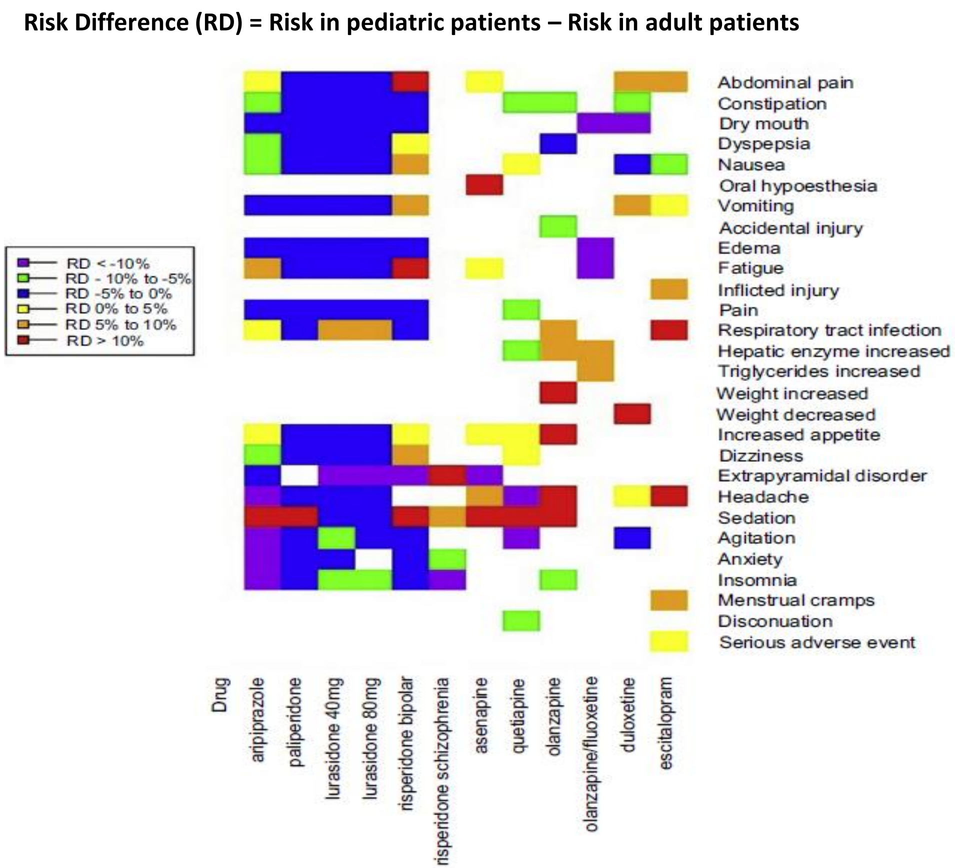
- Codeine
  - is a prodrug
  - must be metabolized into morphine for activity
  - CYP2D6 is the metabolizing enzyme in the liver
- PM phenotype
  - Reduced biotransformation to morphine
  - Poor analgesia
- UM phenotype
  - Rapid and complete conversion to morphine
  - Higher than expected serum morphine levels
  - Possible toxicity
- Risk: respiratory depression; death
  - **Pediatric population at greater risk**
- Source: published literature (case series; PK studies)
  - 5 cases of respiratory depression or death in children with obstructive sleep apnea treated with codeine following tonsillectomy/adenoidectomy
  - Similar events in infants of breast-feeding mothers

CYP2D6 Polymorphism Alter Morphine Exposure and Response

- Aug. 2012: FDA issued a safety alert regarding the use of codeine in children after tonsillectomy, adenoidectomy, or adenotonsillectomy
- Feb. 2013: FDA added a box warning to the label of codeine and codeine-containing preparations advising health care professionals to prescribe an alternative analgesic for postoperative pain control in children undergoing tonsillectomy and/or adenoidectomy and added a contraindication of use in this population
- Apr. 2017: FDA added a contraindication of use in children younger than 12 years to treat pain or cough; a new warning recommending against use in adolescents (12-18 years) who are obese or have sleep apnea or severe lung disease; and strengthened warnings recommending mothers not breastfeed if taking codeine
- Jan. 2018: FDA restricts use of prescription codeine pain and cough medicines in children less than 18 years of age

Pediatrics and PGx Future is in Drug Safety:

Are differences in the incidence of ADEs in pediatric patients a developmental/PGx related phenomenon?



Key Points

- 10 FDA-approved antipsychotic or antidepressant agents (2007 – 2017)
- 300 drug and ADE combinations
- 113 (36.7%) had significantly different incidence in pediatrics compared to adults
- 68 (60.2%) of these had a higher incidence in pediatrics than adults
- Sedation was higher in 6/10 drug and drug combinations (RD: 9.6% – 36.6%)

PEDIATRIC ONTOGENY???

Liu XI, Schuette P, Burckart GJ, Green DJ, et al. J Pediatr. 2019. doi: 10.1016. [Epub ahead of print]

Summary

- PGx information is increasingly being incorporated in FDA-approved product labels and can facilitate tailored drug therapy for the individual patient by providing important information to prescribers;
- To date, the majority of PGx information in labeling has been derived from studies in adults;
- Previous recommendations of exercising caution when attempting to apply adult PGx guidelines to children below 2 years of age still holds true;
- The quantitative data necessary for modeling certain PGx markers in pediatrics is still lacking and further research is needed; and
- Continued PGx/ontogeny research focused on drug safety and understanding the mechanisms contributing to differences in ADEs between pediatrics and adults is warranted

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