

# Regulatory Considerations

Mike Pacanowski  
FDA/CDER/OCP

*Research Directions in Genetically-Mediated Stevens-  
Johnson Syndrome/Toxic Epidermal Necrolysis*

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# Overview

- General considerations
- SJS/TEN case study
- Pathways to inform regulatory decisions

# Labeling and Communication Considerations

## Labeling (CFR 201.57)

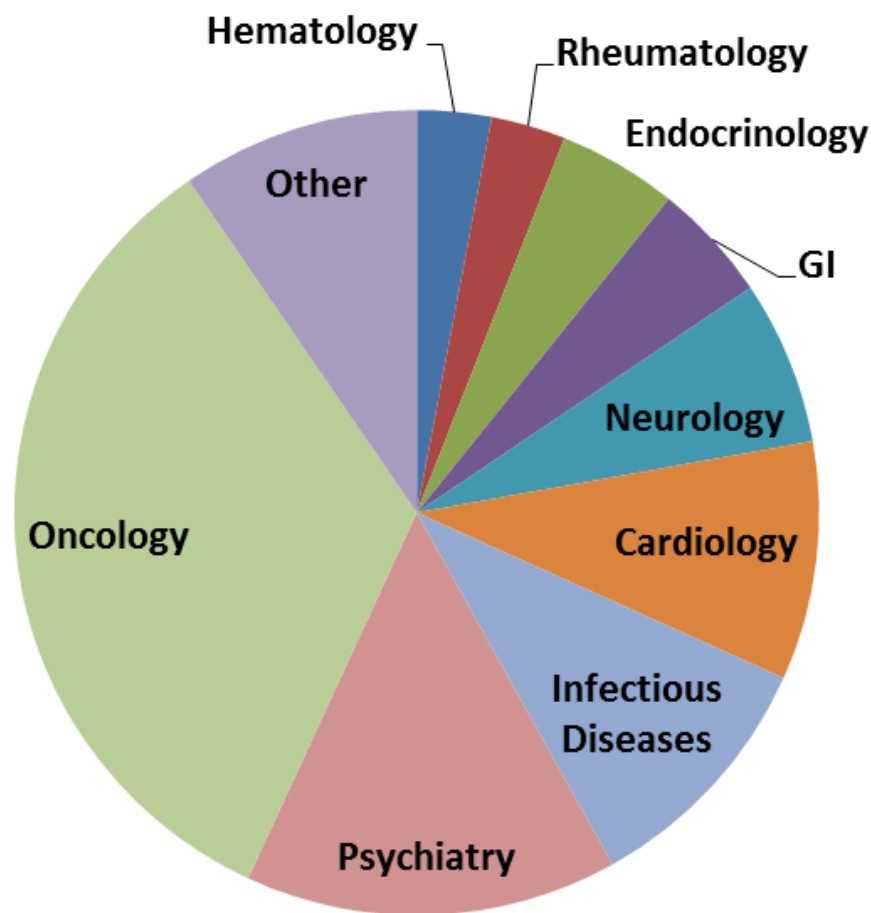
- “...labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association...”
- “...warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box”

## Drug Safety Communications

## Evaluating emerging risks:

- Reliability of the data
- Magnitude of the risk
- Seriousness of the event relative to the disease
- Plausibility of a causality
- Extent of patient exposure
- Potential to mitigate the risk
- Effect on clinical practice
- Disproportionate impact on particular populations
- Consultation with Drug Safety Oversight Board, AdComm

# Biomarkers and Genetic Factors in Labeling



**169 gene-drug pairs**

141 drugs, 45 biomarkers

*47% metabolism/transport*

*30% target/pathway*

*23% immunologic/other safety*

**76 actionable\***

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

## PGx in Labeling: What Have We Learned?

- Data emerge mostly in post-marketing setting, external to sponsor's development program
- Clinical events are usually severe with large, highly replicated biomarker interactions
- Many gene-drug interactions are extensions of known pharmacology (e.g., drug interactions)
- Prospective validation trials are exceptional; totality of evidence must be considered (PK-PD-outcome)
- Treatment context should be amenable to screening (alternative treatment, clinical vigilance, dose adjustment)

## PGx in Labeling

- Labeling is often silent on testing recommendations
  - Reference to '*known status*' and '*consider*' accommodates clinical judgment, uncertainty
- When recommended, various approaches may be used
  - Test everyone (eliglustat; abacavir)
  - Test a targeted subset (CBZ, VPA)
  - Test above dose threshold (pimozide, tetrabenazine)
- Other considerations
  - Specific alleles of relevance generally referenced except for CYP2D6 and NAT
  - Population prevalence and relationship to other risk factors not uniformly described

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# Carbamazepine Warnings

## WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B\*1502 ALLELE SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B\*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B\*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B\*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS, LABORATORY TESTS)



# Carbamazepine Warnings

- **SJS/TEN and HLA-B\*1502 Allele**
- Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B\*1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity.
- Across Asian populations, notable variation exists in the prevalence of HLA-B\*1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B\*1502, averaging 2% to 4%, but higher in some groups. HLA-B\*1502 is present in less than 1% of the population in Japan and Korea. HLA-B\*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans).
- Prior to initiating Tegretol therapy, testing for HLA-B\*1502 should be performed in patients with ancestry in populations in which HLA-B\*1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B\*1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Tegretol should not be used in patients positive for HLA-B\*1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN (see BOXED WARNING and PRECAUTIONS, Laboratory Tests).
- Over 90% of Tegretol treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on Tegretol.
- The HLA-B\*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from Tegretol such as maculopapular eruption (MPE) or to predict Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- Limited evidence suggests that HLA-B\*1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B\*1502 positive patients, when alternative therapies are otherwise equally acceptable.
- ...
- Application of HLA genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B\*1502-positive and HLA-A\*3101-positive patients treated with Tegretol will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in HLA-B\*1502-negative and HLA-A\*3101-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN and other hypersensitivity reactions, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring, have not been studied.

← Who

← Allele distributions

← What to do

← Screening considerations

← Lesser SCAR

↔ Uncertainty

# Carbamazepine Warnings

## *Hypersensitivity Reactions and HLA-A\*3101 Allele*

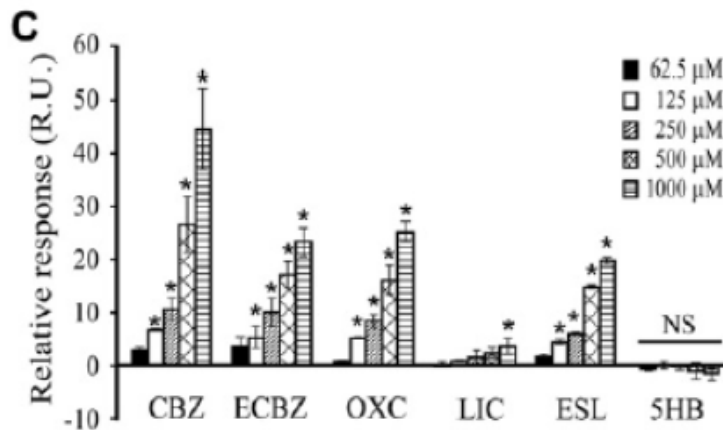
Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLA-A\*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. These hypersensitivity reactions include SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms (see DRESS/Multiorgan hypersensitivity below).

...

The risks and benefits of Tegretol therapy should be weighed before considering Tegretol in patients known to be positive for HLA-A\*3101.

# Carbamazepine Warnings

- Alternative antiepileptics may carry similar risks with respect to HLA-B\*1502
  - OXC and phenytoin: published data suggesting HLA-B\*1502 involvement
  - ESL: no well-validated reports of SJS with HLA-B\*1502 involvement (at the time of approval)



Experimental models identified common structural elements that interact with HLA-B\*1502

Figure 2. Binding responses of HLA-B\*1502 recombinant protein toward CBZ-related compounds

## Eslicarbazepine Post-marketing Requirement

A study based on routine postmarketing safety surveillance, pharmacovigilance and clinical trial reports will characterize clinical and genomic risk factors associated with the development of serious dermatologic reactions in eslicarbazepine acetate-treated patients, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophilia and systemic symptoms (DRESS). The study must include a control group of eslicarbazepine-tolerant patients and use high-throughput genotyping approaches to determine whether specific genotypes are associated with the development of these serious skin reactions.

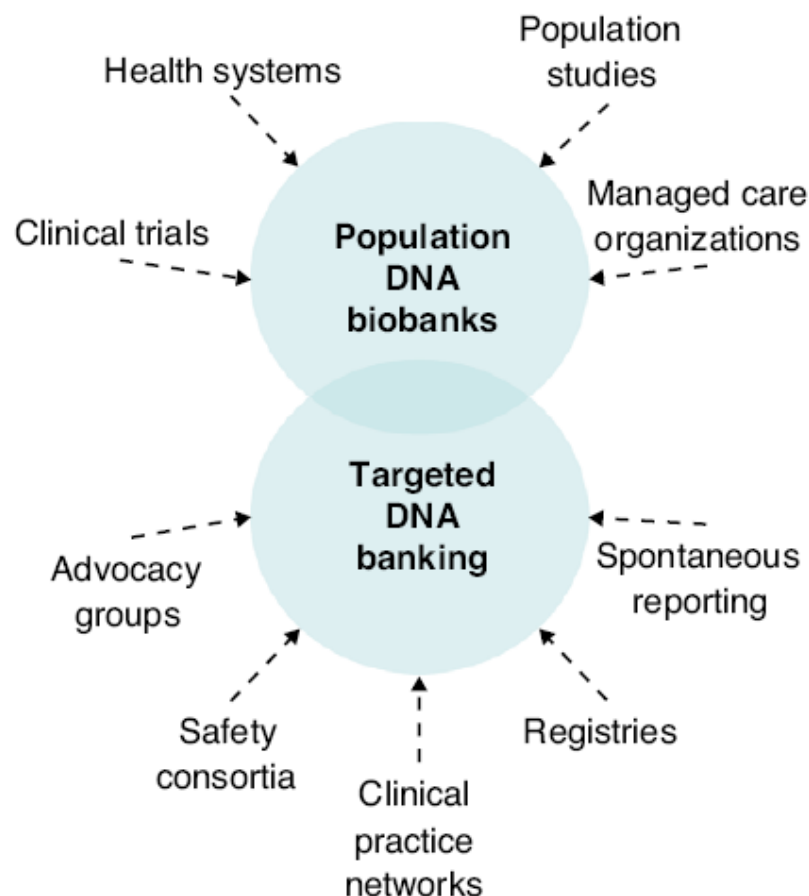
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## Review Considerations

- Risk/benefit of alternative treatments
- Testing recommendations in the context of event rate
- Generalizability to diverse populations and the spectrum of adverse events
- Validity of the signal and qualities of research methods (e.g., breadth and depth of HLA typing, phenotype definition)
- Availability of robust experimental models to support causal inference

# Academic Research, Public-Private Partnerships



## Selected N.A. efforts:

- **SAEC: Pharma, HMORN, et al.**
- **eMERGE: Vanderbilt, Marshfield, Mayo, et al.**
- **Kaiser Permanente RPGEH**
- **Canadian Pharmacogenomics Network for Drug Safety (PMID 20860467)**

# Premarket Review

- Clinical Pharmacogenomics Guidance
  - Collection and storage of DNA from a large number of clinical trial participants, all arms, all phases, is a prerequisite for genetic studies
  - **If** known factors are likely to influence efficacy, safety, or dosing of investigational drug, comparator, or background, **then** collect DNA from all subjects specify objective
  - **If** concentrations or responses are highly variable or exhibit ethnic differences, or serious toxicities are observed, **then** collect DNA from as many subjects as possible for future use in exploratory studies



# Post-Marketing Studies

<b><i>Validation</i></b>	
<b>Clopidogrel</b>	<b>CYP2C19 effects on PK/PD</b>
<b>Ipilimumab</b>	<b>CD86 effects on immune-related AEs</b>
<b>Prasugrel</b>	<b>CYP450 genotype effects on outcomes</b>
<b>Belinostat</b>	<b>Safety and PK by UGT genotype</b>
<b><i>Discovery</i></b>	
<b>Telaprevir</b>	<b>Exploratory GWAS for skin reactions</b>
<b>Deferiprone</b>	<b>DNA banking for agranulocytosis</b>
<b>Infliximab</b>	<b>DNA banking for HSTCL</b>
<b>Agalsidase alfa</b>	<b>Mutation effects on renal disease</b>
<b>Eslicarbazepine</b>	<b>DNA banking for skin reactions</b>

## Additional FDA Efforts

- Funding research to discover and validate risk factors
  - Identify rare adverse event cases through administrative claims data and obtain genetic samples
  - Leverage existing biobanks to assess “common” events for widely prescribed drugs
- Measuring risk management
  - Passive surveillance (FAERS): Low reporting of test results overall, test-negative cases over-reported, testing may be ex poste facto
  - Active surveillance: Insensitivity of ICD codes for tests precludes assessment of testing patterns

## Research Directions

- Establish infrastructure
  - Capture cases, specimens; interoperable repositories
  - Implementation, dynamic clinical decision support
  - Evaluate post-SJS/TEN treatments/outcomes
- Promote consistency and quality in research methods
  - Case adjudication and genotyping
  - EHR study methods
- Strengthen experimental models
  - Predict possible risks and validate signals
- Develop efficacy biomarkers to
  - Shift risk-benefit of culprit drugs

# Summary

- FDA has been proactive about incorporating genomic risk factors for serious adverse events in labeling
- Myriad challenges exist with respect to interpreting evidence, communicating risks, and formulating testing recommendations
- Integrating distributed databases/biobanks could enable biomarker discovery/validation, test monitoring/utility