Drug Safety and Post-Approval Adverse Event Reporting*

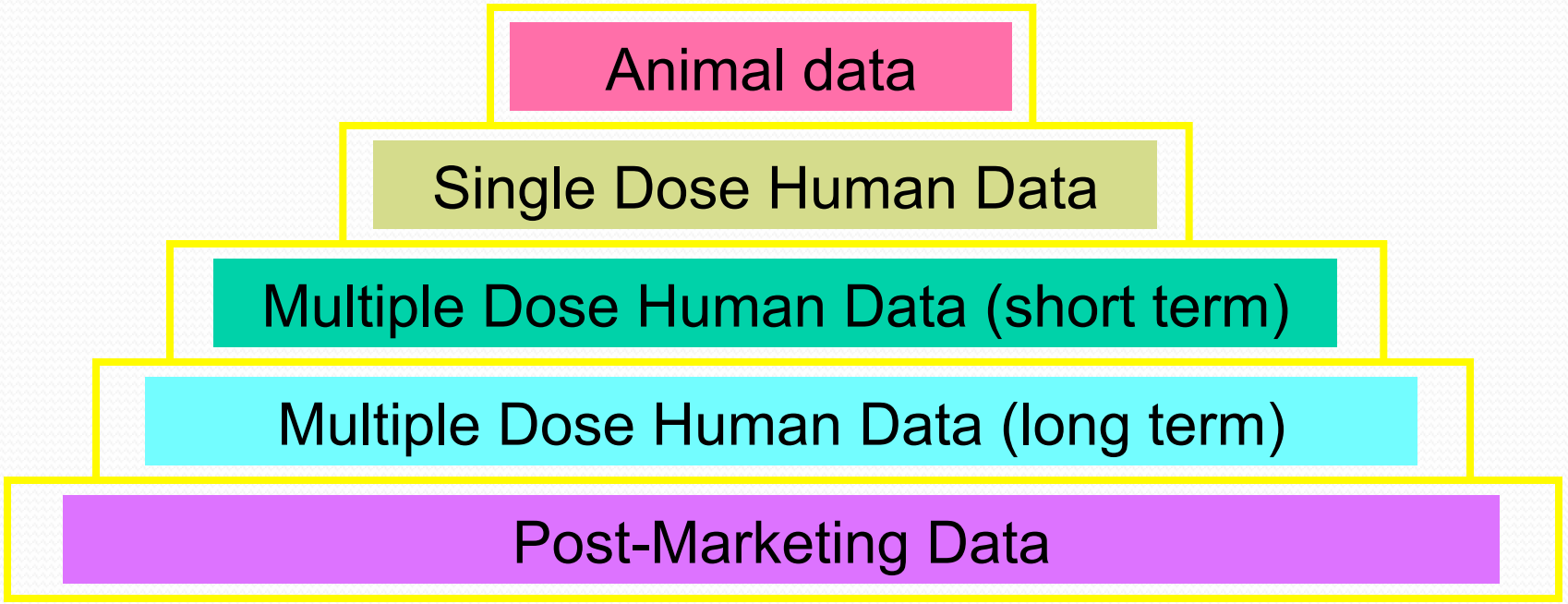
Kenneth L. Hastings, Dr.P.H., D.A.B.T., F.A.T.S.
Associate Vice President for Regulatory Policy
Sanofi SA, Bethesda, MD USA

* The content of this presentation do not represent the opinions of Sanofi SA

Safety

- Safety assessment is an ongoing process (i.e. does not end at time of drug approval)
  - Premarketing safety data
  - Postmarketing safety data

FDA Reviews Safety Data In All Phases of Development



Detection of Adverse Events

Pre-Approval

- Frequent (>1-2%)
- Events not expected in the general population
- Temporal Association
- Abrupt/acute presentation
- Typical Drug Reactions
- Expected (animals)

Post-Approval

- Infrequent or rare
- Increase in common condition
- Late occurring
- Indolent process
- Atypical presentation
- Susceptible subgroup

Premarketing Safety Data- source

- Non-clinical data
- Safety profile of other drugs in the class
- Safety database from clinical trials

  (phase 1-3)
  - Annual Reports
  - Clinical Study Reports
  - Integrated summaries at each stage of development
  - Individual (IND) safety reports

Premarketing Safety Data – Evaluation

- Safety evaluation include:
  - Adverse events collection- can be subjective
    - Definitions and classification
    - Reporting
    - Causality, severity assessment
  - Laboratory toxicities
  - Exposure- response relationship
  - Other (VS, ECG)
  - Pharmacogenomics (e.g. hypersensitivity and HLA-B*5071 for abacavir)

Premarketing Safety Data- Limitations

- Several factors determine the likelihood of observing an AE:
  - Number of subjects exposed to study drug
  - Length of treatment
- Per ICH[1] recommendation (minimum)

  If chronically administered
  - 1500 people total
  - 300-600 people for 6 months
  - 100 people for one year
  - At clinically relevant doses

[1] International Conference on Harmonisation (ICH-E1A). ICH E1A: Guideline for Industry. The extent of population exposure to assess Clinical Safety. For drugs intended for long-term treatment of non-life-threatening conditions. http://www.fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/ucm073083

Premarketing Safety Data - Limitations(2)

- Safety database is not expected to detect rare AEs (e.g., those occurring in < 1 in 1,000 patients)
- Power of database: 95% confident that we will detect at least one event if the true incidence is 1% (1/100) --rule of three
- Events occurring over longer duration or in vulnerable subgroups not identified

Rule of Three

Number Needed for > 95% Chance of Observing at Least One Adverse Event

True Incidence	Number Needed
1 in 10	30
1 in 100	300
1 in 1,000	3,000
1 in 10,000	30,000

NDA Safety Review

- Clinical Review Template
  - promotes consistency of clinical reviews across FDA
  - focuses evaluation on common events, deaths, serious adverse events, laboratory abnormalities, outliers
- Extensive safety evaluation via electronic datasets
  - FDA does independent evaluation of “raw” data
  - reproduce sponsors assessments/findings
  - conduct exploratory and additional analyses to better understand data

NDA Safety Review Example
Abacavir Hypersensitivity Reaction (HSR)

- Original accelerated approval 1998
- Based on data in treatment-naïve subjects
- Approximately 5% of subject developed ABC HSR during clinical trials

Accelerated Approval Risk-Benefit Analysis

- Although different from typical hypersensitivity, clinical signs recognizable and manageable (knowledge about rechallenge- ↑ risk death)
- Latency defined (usually within 6 wks)
- Consideration of indicated population
- Efficacy data through 16-24 wks, and some supportive 48 wk data found ABC superior to active control
- Adequate labeling and plan for Drug Interactions and safety monitoring
- Final Decision = Approval

How to communicate safety to Providers?

- Labeling
- Advisory Committee Meetings
- Early Safety Communications
- Health Care Provider Sheets
- Dear Health Care Provider Letters
- Press Releases
- Seasonal Drug Safety Newsletter
- Drug Safety Podcasts
- All available on web: www.fda.gov

Label Development and Negotiations

- Labels are written by manufactures and submitted to FDA for review
- Labeling negotiations occur during review cycle.
- Examples:
  - Outcome numbers (efficacy, adverse events)

Drug Labels

- Prescribing Information (USPI)
- Patient Labeling:
  - Patient Package Insert (PPI)
  - Medication Guide (MG)

USPI

- Objective:
  - Contains necessary information for safe and effective use of a drug
  - Makes information easier to access for healthcare providers
  - Reduces medication error
- Audience: Healthcare professionals
- 3 major parts:
  - Highlights for Prescribing Information (HL)
  - Table of Contents
  - Full Prescribing Information (FPI)

Highlights
Concise summary of information in FPI

- Limitations Statement
- Product Names and Date of Initial US Approval
- Boxed Warning
- Major Recent Changes
- Indications and Usage
- Dosage & Administration
- Dosage Forms & Strengths
- Contraindications
- Warnings & Precautions
- Adverse Reactions (listing of most common ARs)
- Drug Interactions
- Use in Specific Populations
- Patient Counseling Information Statement

Contents of FPI

- Boxed Warning
- 1 Indications & Usage
- 2 Dosage & Administration
- 3 Dosage Forms & Strengths
- 4 Contraindications
- 5 Warnings & Precautions
- 6 Adverse Reactions
- 7 Drug Interactions
- 8 Use in Specific Populations
- 9 Drug Abuse & Dependence
- 10 Overdosage
- 11 Description
- 12 Clinical Pharmacology
- 13 Nonclinical Toxicology
- 14 Clinical Studies
- 16 How Supplied/Storage & Handling
- 17 Patient Counseling Information

Example of Contents for a Fictitious Drug

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

When to Use a Boxed Warning

- Adverse reaction so serious in proportion to the potential benefit from drug (e.g., fatal, life-threatening, permanently disabling) OR
- Serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of drug (e.g. patient selection, careful monitoring, avoiding certain concomitant therapy, etc) OR
- Restricted distribution
- More likely based on observed adverse reactions

Contraindications

- Only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities must be listed
  - Likely clinical situation examples
    - Underlying conditions (existing kidney or liver disease, pregnancy, etc)
    - Demographic risk factor (age, sex, race, genetic vulnerability)
    - Never use in selected subset of the larger population with a disease
    - drug- interactions with serious outcomes

WARNING and PRECAUTIONS

Clinically significant adverse reactions observed in association with drug and reasonable evidence of a causal association

Adverse reaction that:

- requires discontinuation, dosage regimen adjustment or addition of another drug
- Could be prevented or managed with appropriate patient selection or avoidance of concomitant therapy
- Significantly affect patient compliance

OR

- Interferes with a laboratory test

Reactions expected to occur but not yet observed

- Based on known pharmacology, chemistry, or class of drug
- Animal data raise concern (teratogenic effects)

Patient labeling

- Patient Package Insert (PPI)
- Medication Guide (Med Guide)
- Consumer Medicine Information (CMI)
- PPIs and Med. Guides are written by manufacturers and approved by FDA
- CMIs are provided by pharmacies/pharmacists; usually one to two pages in length and provide patients with a summary of their medication

Differences Between Med Guide and PPI

Patient Package Insert

- convey directions and safety information in patient friendly language.
- Written by manufacturers and FDA approved
- Do not have to be dispensed

Difference between a Med Guide and a PPI (2)

Medication Guide:

- Paper handouts required for certain prescription medicines
- Contain FDA-approved information necessary for patients' safe and effective use of the drug product
- Healthcare professionals (HCP) distribute a Med Guide if the patient will be using the product without direct supervision by a HCP
- The drug product is one
  - for which patient labeling could help prevent serious adverse effects,
  - directions for use is crucial for the drug's effectiveness
  - that has serious risks (relative to benefits) of which the patients should be made aware because information concerning the risk(s) could affect patients decision to use, or continue to use the product

Postmarketing Safety Data-Monitoring/Pharmacovigilance

- Goal is to detect previously unknown adverse drug effects
  - Looking for signals

Postmarketing Safety Data Source- spontaneous reporting

- Spontaneous reporting from FDA Adverse Event Reporting System (AERS)
- Spontaneous reporting from other regulatory agencies and World Health Organization

Postmarketing Safety- Limitations

- Difficulty estimating denominator
  - How many people taking the drug
- Unreliable numerator
  - Under-reporting
- Incomplete information
- Difficulty obtaining follow-up
- Uncontrolled
- Data quality
- Concomitant medications
- Events may be similar to natural disease processes

Postmarketing Safety Data Source-postmarketing studies

- FDA, sponsors, academia or investigators
  - Formal studies/trials to refute or confirm drug safety risks, quantify
  - observational studies, Cohort studies
  - registries, meta-analyses
  - Medical Databases—Kaiser, VA

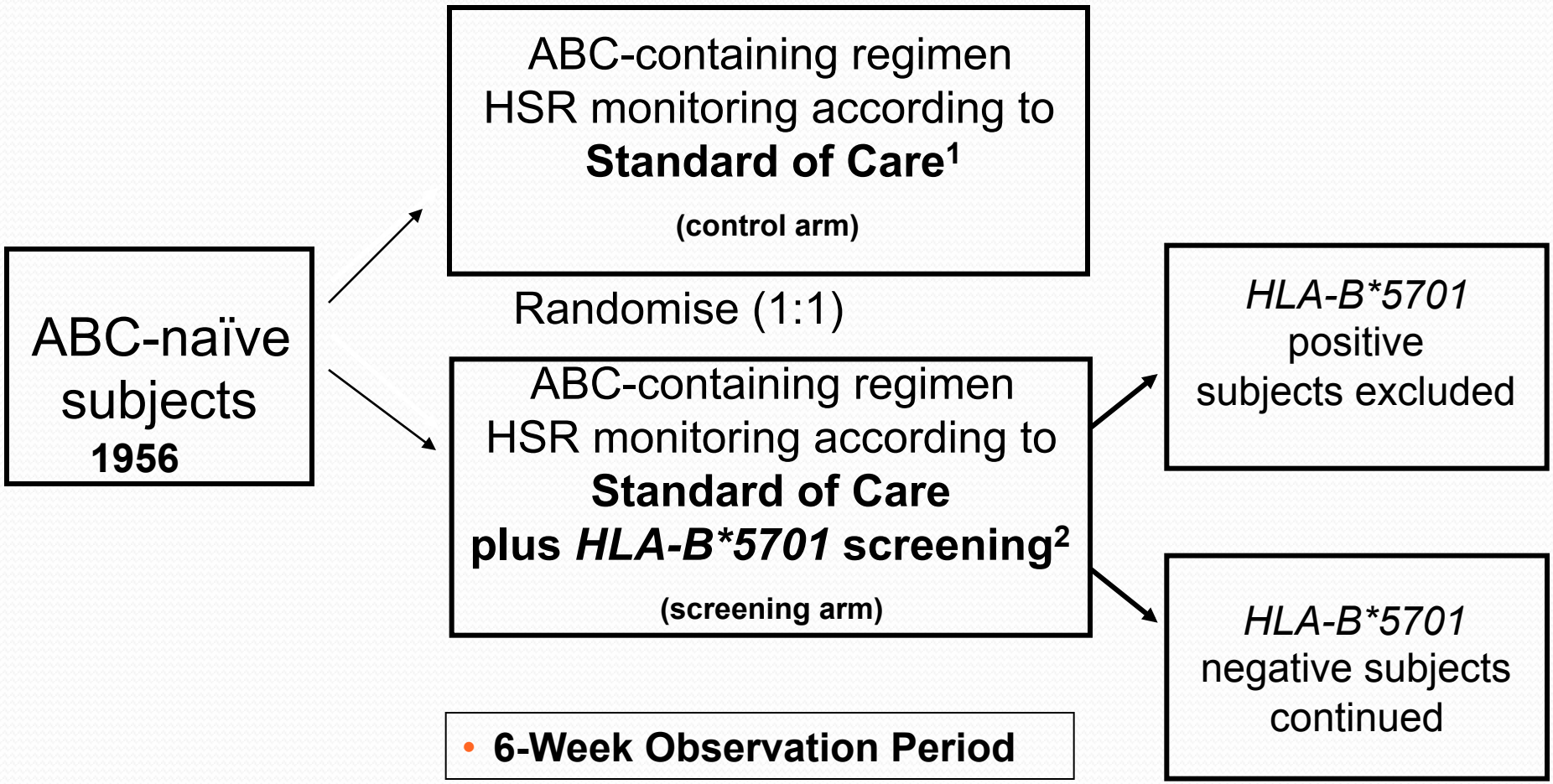
What are PMR/PMC?

- Postmarketing requirement (PMR) and Postmarketing commitment (PMC) are:
- Clinical trials or studies *required of* or *agreed to* by a sponsor
- Trials may be ongoing at time of approval or conducted after FDA has approved a product for marketing
- Provide additional information about safety
- May also be an efficacy study (e.g. pediatric studies); clinical pharmacology; CMC (e.g. stability)

Postmarketing Commitment Example- ABC HSR

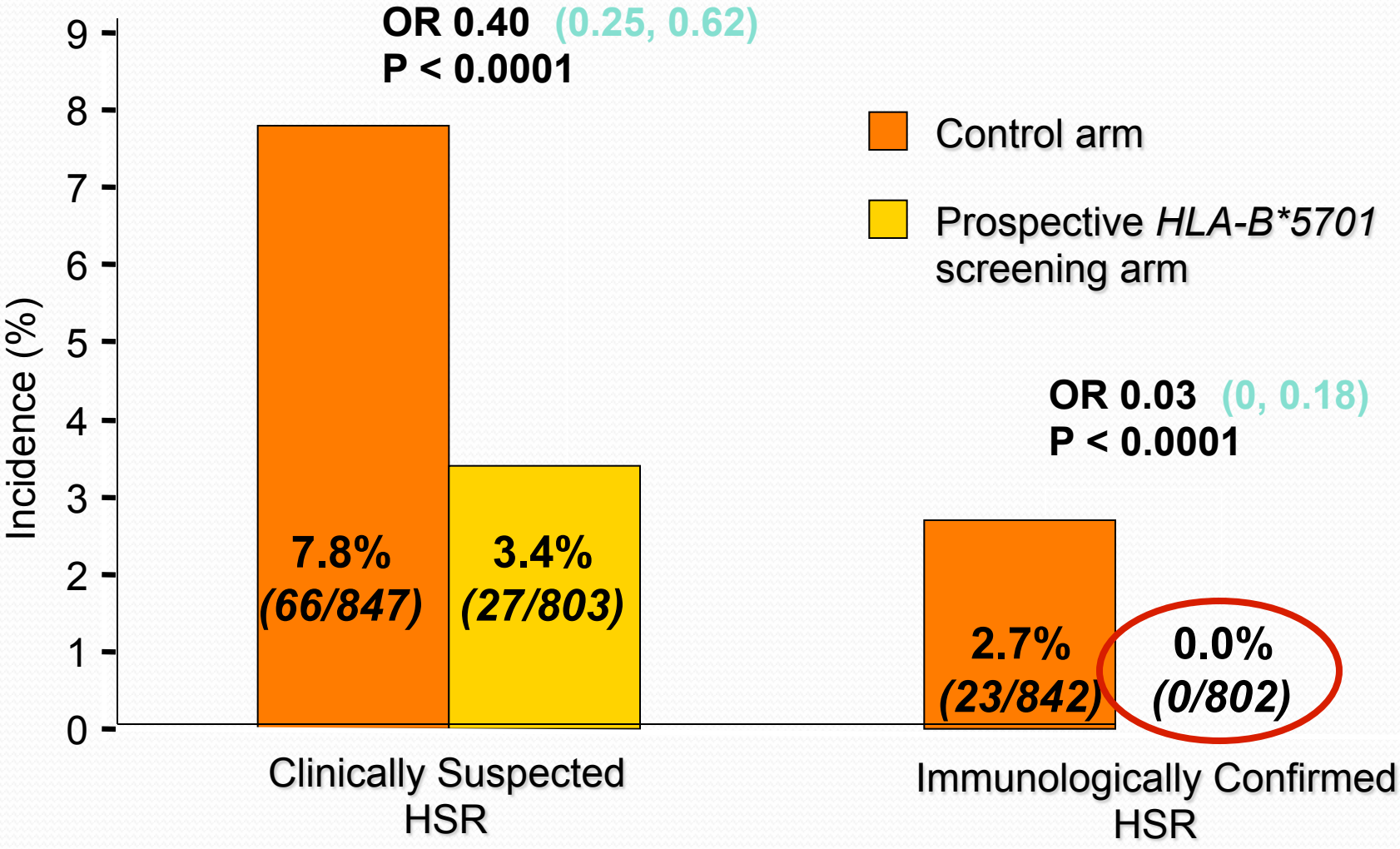
- PMCs for ABC to study and characterize ABC HSR
- Studies observed familial susceptibility and lower incidence in some ethnic groups
- GSK began pharmacogenomic evaluation:
  - Prospective Study: showed reduction in ABC-HSRs due to genetic pre-screening
  - Retrospective study; also supported above conclusion

Confirmatory Prospective Double-Blind Study



1. retrospective high resolution typing
2. prospective high resolution typing

Prospective Double-Blind Study - PREDICT-I



Hughes et al., Pharmacogenomics J. 8:365-374

Prevalence of HLA-B*5701 in the world

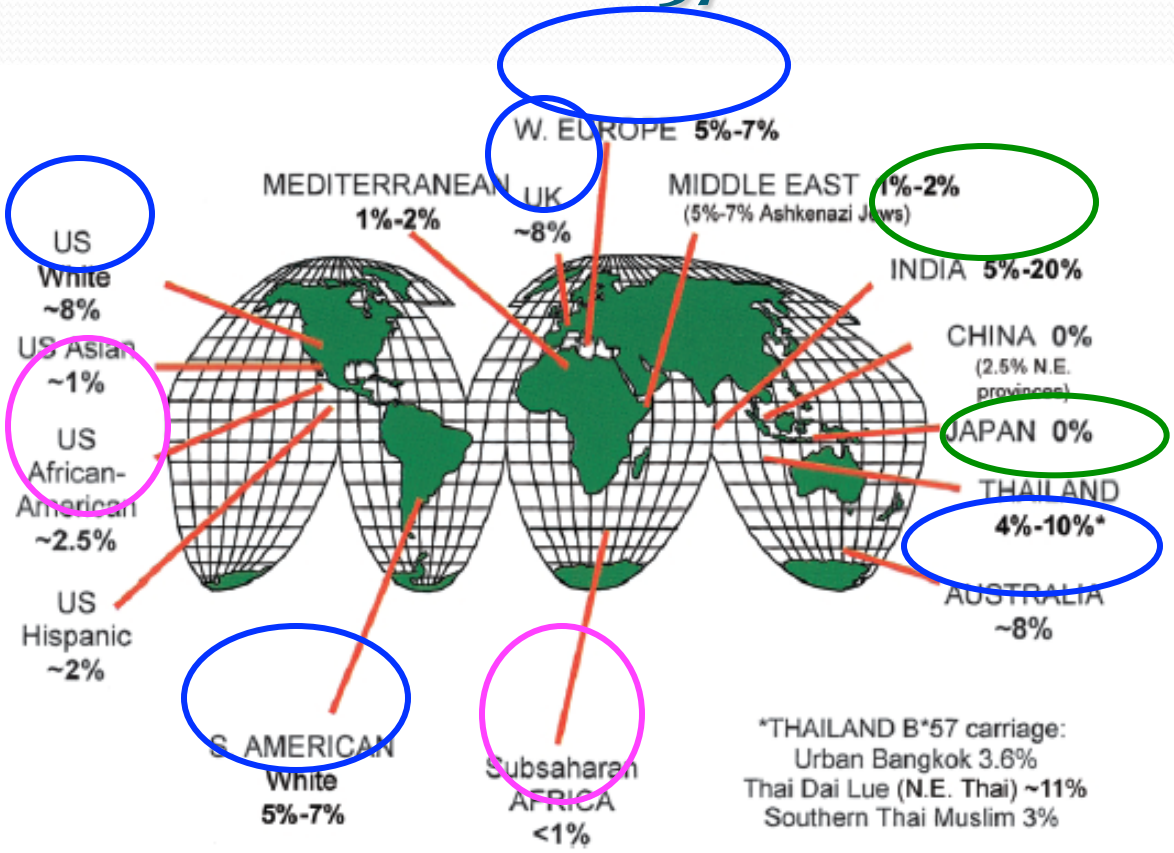


Figure 1. The prevalence of *HLA-B*5701* in different parts of the world. These carriage frequencies mirror the incidence of abacavir hypersensitivity in exposed individuals. Adapted from [7].

Phillips EJ (2006) Clin.Infect.Dis. 43:103-105

Retrospective, case-control study to evaluate sensitivity and specificity of HLA-B*5701 and ABC HSR within Black and White subjects in the US-ABC107442 (SHAPE)

Study Design

- No study drugs given, no blinding
- All subjects identified with CS-HSR underwent skin patch test (SPT)
- To be identified as a case, subjects had to meet clinical criteria for ABC HSR & have a positive SPT (CS-SPT pos)
- Controls were identified as those who tolerated ABC for 12 weeks (no SPT done)

Result

- consistent with PREDICT-1

Reduction in cases of ABC-HSR due to genetic screening

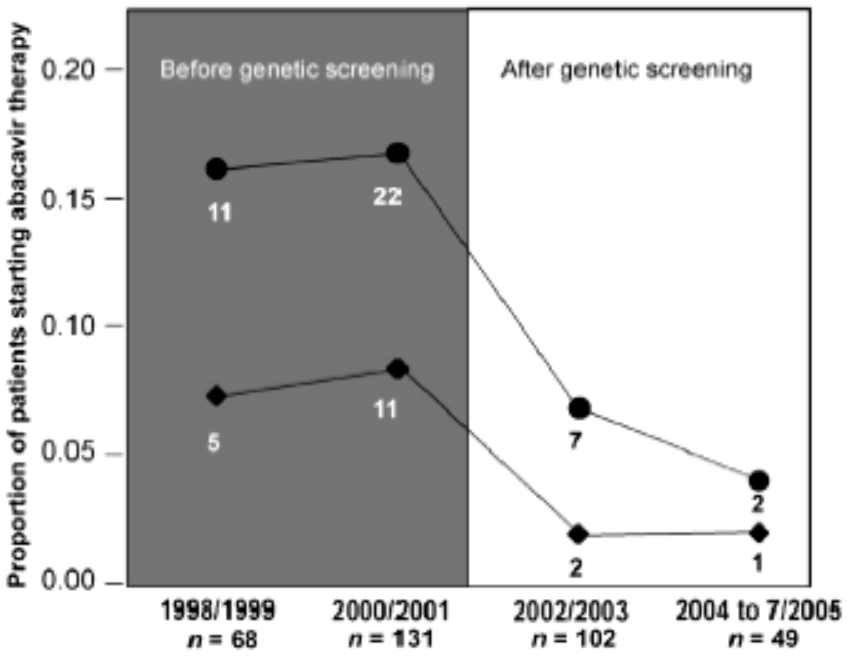


Figure 1. Proportion of patients stopping abacavir therapy in the first 6 weeks of treatment before and after introduction of prospective genetic screening. The numbers below the time periods indicate the number of abacavir-naive individuals starting abacavir therapy. The upper line (●) indicates the proportion of patients who stopped abacavir therapy because of any symptoms in the first 6 weeks of therapy; the number of patients indicated below the circle indicates the total number of patients with "minor" symptoms (abacavir hypersensitivity not excluded) plus the number of patients with definitive abacavir hypersensitivity reactions. The bottom line (◆) indicates the proportion of patients with definitive abacavir hypersensitivity reactions; the number of patients in the respective time period is indicated below the diamonds.

8% to 0.4% in Australia

6.2% to 0.5% in UK

12% to 0% in France

Updated Abacavir Label

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZIAGEN safely and effectively. See full prescribing information for ZIAGEN.

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution
Initial U.S. Approval: 1998

WARNING: HYPERSENSITIVITY REACTIONS/LACTIC ACIDOSI AND SEVERE HEPATOMEGALY

See full prescribing information for complete boxed warning.

- Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)
- Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogue (5.2)

----------RECENT MAJOR CHANGES ----------
Warnings and Precautions (5.1, 5.5) July 2008

----------INDICATIONS AND USAGE----------
ZIAGEN, a nucleoside analogue, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Adults: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.1)
- Pediatric (≥3 Months)/Adolescent Patients: Dose should be calculated on body weight (kg) and should not exceed 300 mg twice daily. (2.2)
- Patients With Hepatic Impairment: Mild hepatic impairment – 200 mg twice daily; moderate/severe hepatic impairment – contraindicated. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 300 mg; Oral Solution: 20 mg/mL (3)

----------CONTRAINDICATIONS----------

- Previously demonstrated hypersensitivity to abacavir. (4, 5.1)

FULL PRESCRIBING INFORMATION

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate).

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Regardless of HLA-B*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Advertisement

- The FDA regulates advertising only for prescription drugs.
- In most cases, federal law does not allow the FDA to require that drug companies submit ads for approval before the ads are used. FDA sees many ads at about the same time the public sees them.
- Division of Drug Marketing, Advertising and Communications (DDMAC) evaluates information (with consultation from primary review division) and provides recommendations to Sponsor
- Many drug companies voluntarily seek advice from us before they release TV ads. However, if FDA believes that an ad violates the law, FDA sends a letter to the drug company asking that the ads be stopped right away

Conclusions

- Drug safety is an integral component of new drug development
- Non-clinical data important to enable clinical trials
- Ultimately, most drug safety information obtained in clinical trials
- However, the reality is drug safety can only be thoroughly assessed once the drug is marketed: pharmacovigilance and PMR/PMC

ANDA/PAS

- ANDA (Abbreviated NDA)
- PAS (Prior Approval Supplement)
- GDUFA (Generic Drug User Fee Amendments of 2012)
- Fees are calculated yearly , methodology published in FR, available on FDA website
- Includes other fees (DMF, DS/DP Facility Fees)
- For 2014: ANDA Fee ($68,860), PAS Fee (31,930)
- Fees due at application submission
- Up to 75% may be refunded depending on circumstance

GDUFA Fees

- Application complete with payment of fees, receipt date when this is done
- If re-submission: full fees apply
- API inspection fees apply to every new site, but paid once
- Fee structure is complex, published formula apply (www.fda.gov/CDER)
- PAS: labelling changes (pre-approval)
- CBE: labelling changes (after approval)