Considerations for Integration of CDRH and CDER Regulations- A Case Study: Irinotecan and UGT1A1"

Atiqur Rahman, Ph.D
Division of Clinical Pharmacology 5
Office of Clinical Pharmacology
CDER, FDA

March 16, 2006

Personalized Medicine

A Scientific approach to Personalized Medicine is a reality which requires an adequate test to identify specific subpopulation for selection and dosage of therapeutics for safe and effective treatment.

Overview

- Process and Evidence for Camptosar Label Update
- Process and Evidence for the Clearance of the Invader UGT1A1 Molecular Assay
- CDER/CDRH Regulations to Help Drug/Biologics and Test Development
- Conclusions

Overview
Camptosar® Package Insert Update

- Scientific and Clinical Evidence
- Advisory Committee Presentation
- Label Negotiation

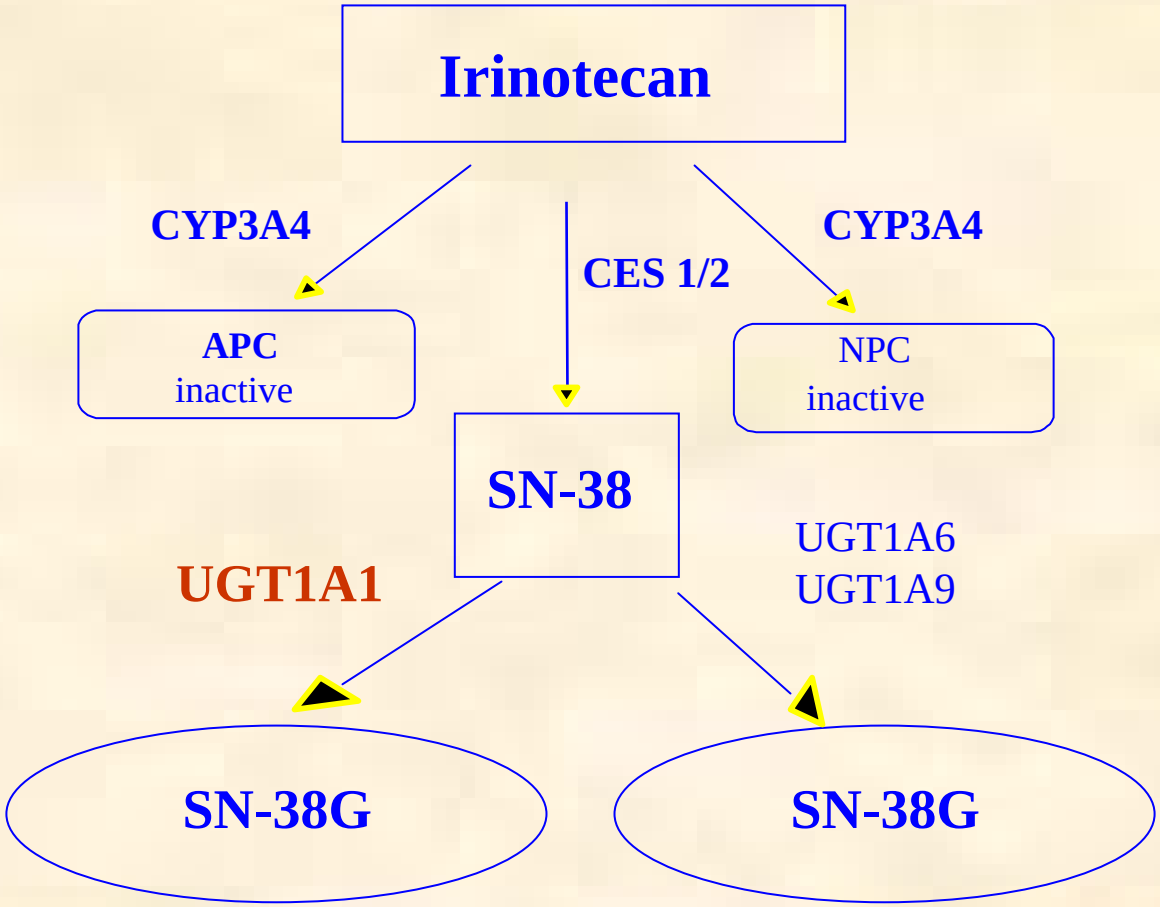
Important Statistics

- Colorectal cancer is the 4th most commonly diagnosed cancer in the United States
- 145,000 new cases per year in United States and over 1,000,000 worldwide

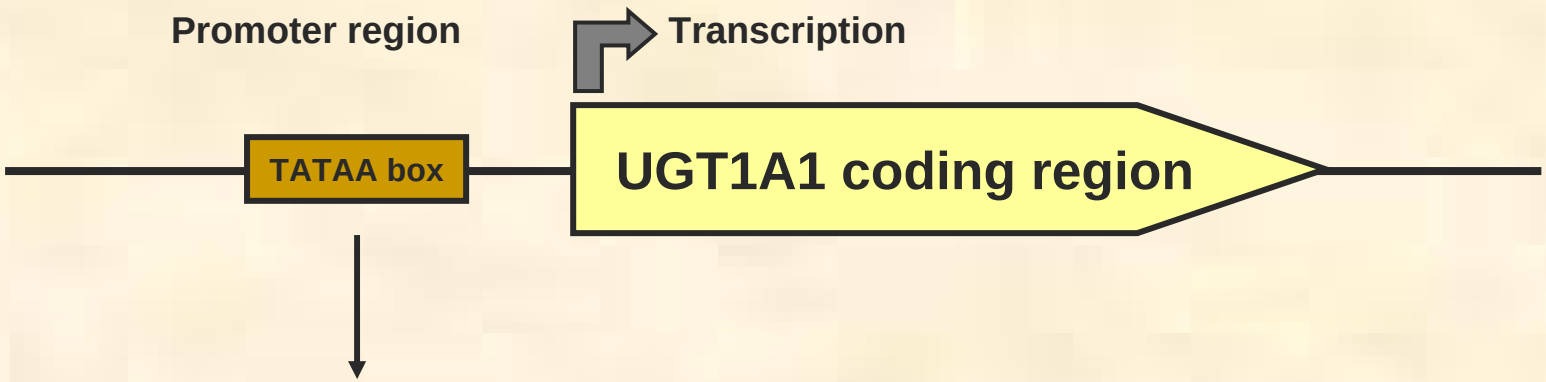
Scientific and Clinical Evidence: Camptosar Indications

- Indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum.
- Indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.
- Indicated with Erbitux for patients with advanced metastatic colon cancer

Scientific and Clinical Evidence: Metabolic Pathways



Scientific and Clinical Evidence: UGT1A1 Pharmacogenetics



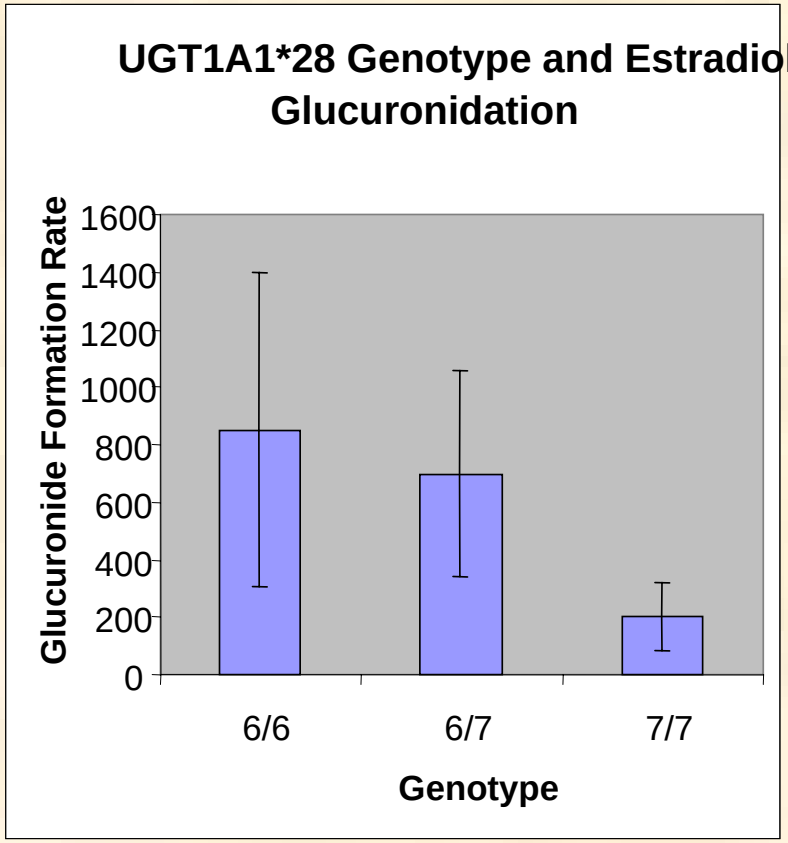
DNA sequence of TATAA box region	Common name	Allele designation	Effect on gene expression
GGTGTATCGATTGGTTTTTGCCATATATATATATAAGTAGGAGAGGGCGAACC	TA_5	UGT1A1*36	Increased
GGTGTATCGATTGGTTTTTGCCATATATATATATATAAGTAGGAGAGGGCGAACC	TA_6	UGT1A1*1	Wildtype
GGTGTATCGATTGGTTTTTGCCATATATATATATATATAAGTAGGAGAGGGCGAACC	TA_7	UGT1A1*28	Reduced
GGTGTATCGATTGGTTTTTGCCATATATATATATATATATAAGTAGGAGAGGGCGAACC	TA_8	UGT1A1*37	Reduced

Scientific and Clinical evidence: Genotype Versus Phenotype

Genotype and Phenotype

Genotype	Glucuronidation
6/6	851±545
6/7	699±361
7/7	199±118

Mean ± Standard Deviation



Fisher et al. Pharmacogenetics, 2000

Scientific and Clinical Evidence: Genotype and Safety

Incidence of Grade 4 Neutropenia					
Genotype	Patients No.	ANC nadir	Percent	SN-38 AUC	Total Bilirubin
7/7	6	3	50	542±195	0.8±12
6/7	24	3	12.5	458±380	0.48±0.03
6/6	29	0	0	336±168	
The relative risk of grade 4 neutropenia was 9.3 for the 7/7 genotype patients.					

Innocenti et al. J. Clin. Oncol. 2004; 22(8); 1382-1388.

Scientific and Clinical Evidence

Test Performance: Clinical Perspective

ANC	Parameters	Numbers	Percent
Presence of grade 4 neutropenia	**Sensitivity**	**3/6**	**50**
	Specificity	**56/59**	**95**
Absence of grade 4 neutropenia	**Sensitivity**	**29/29**	**100**
	Specificity	**29/29**	**100**

Scientific and Clinical Evidence: Clinical Utility

Genotype	Total Numbers	Patients with Neutropenia	Percent	Fever Percent
7/7	7	5	71	60 (3/5)
6/7	35	14	40	36 (5/14)
6/6	31	3	10	0 (0/3)

Grade 3 and 4

Genotype	No. of Patients	Delayed Therapy	Hospitalization
7/7	7	71% (5/7)	100% (5/5)
6/7	35	60% (21/35)	14% (3/21)
6/6	31	32% (10/31)	0% (0/31)

Rouits et al. Clinical Cancer Research 2004; 10:5151-5159.

Overview
Camptosar® Package Insert Update

Advisory Committee Presentation

- Presentation of the Evidence
- Discussion
- Recommendation

Questions to the Committee

1. **Is the scientific and the clinical evidence presented sufficient to demonstrate that homozygous UGT1A1*28 genotypes (7/7 genotype) are at significantly greater risk for developing :**

   a) **Neutropenia,**
      Yes: 12
      No: 0

   b) **Acute and delayed diarrhea from irinotecan therapy?**
      Yes: 0
      No: 11
      Abstain: 1

Questions to the Committee

4. **Is the measurement of UGT1A1*28 sufficiently robust in terms of sensitivity and specificity to be used as a response predictor test for irinotecan therapy?**

Yes: 9
No: 0
Abstain: 3

Discussion: The measurement of UGT1A1*28 is sufficiently a robust predictive test based on Clinical judgment but not statistics given the clinical consequences of Grade 4 neutropenia.

The test should not be used in isolation but coupled with other information….

Overall Recommendation

- **The evidence presented suggest an association between the UGT1A1*28 allele and neutropenia.**
- **There is clinical utility for inclusion of UGT1A1 polymorphism information in the package insert of Camptosar in absence of any FDA approved test for genotyping patients.**
- **The Clinical Utility is not based on statistics but based on the clinical consequences of grade 4 neutropenia.**

Overview
Camptosar® Package Insert Update

Label Negotiation with the Sponsor

- Label Update
- Communication

Camptosar Package Insert Dosage and Administration

Dosage in Patients with Reduced UGT1A1 Activity

- **Starting dose reduction administered either as a single agent or in combination**
- **Precise dose is not recommended for UGT1A1*28 genotype patients**
- **Subsequent dose is based on patient's tolerance**

Camptosar Package Insert. July 21, 2005.

Camptosar Package Insert Warnings

Patients with Reduced UGT1A1 Activity

- **Increased risk for neutropenia**
- **A reduced initial dose should be considered**
- **Heterozygous patients may be at increased risk for neutropenia**

Camptosar Package Insert. July 21, 2005.

Camptosar Package Insert Clinical Pharmacology

Metabolism and Excretion

- Role of UGT1A1 in deactivation of Irinotecan
- Polymorphism of UGT1A1
- Ethnic distribution of UGT1A1 Polymorphism

Camptosar Package Insert. July 21, 2005.

Camptosar Package Insert
What we could do better?

- **Scientific approach to dose reduction**
  - **Toxicity based dose reduction?**
  - **AUC or Cmax based dosing?**
- **Provide dose recommendation for 6/7 genotype patients.**
- **Include information about TA5 and TA8 alleles.**

Labeling Negotiations: Challenges

- **Requirement versus Recommendation**
- **Availability of a Test**
- **Brand name versus Generic Drugs**
- **Timing Issues**

Communication

- Label update sent to the members of the American Society of Clinical Oncology (ASCO)
- Various presentations by the OCP members at the National and International forums
- Presenting FDA position to the media

Communication

- Discussion with academic experts on the impact of the updated package insert
- Publication on the package insert update process and the evaluated data
- Possible update of FDA website with Physician Education Materials

Overview
Invader UGT1A1 Molecular Assay

- IDE at CDRH
- Device Label
- CDER/CDRH Interaction

Invader UGT1A1 Molecular Assay

- **Pre-IDE Package Submission:** **April 13, 2005**
- **Pre-IDE Meeting:** **April 29,2005**
- **IDE Submission (a):** **July 5, 2005**
- **IDE Submission (b):** **July 25, 2005**
- **Review Issues Resolved:** **August 18, 2005**

Invader UGT1A1 Molecular Assay

Intended Use

The Invader UGT1A1 Molecular Assay is an *in vitro* diagnostic test for the detection and genotyping of the *1 (TA6) and *28 (TA7) alleles of the UGT1A1 gene in genomic DNA from whole peripheral blood as an aid in the identification of patients with greater risk for decreased UGT activity.

Invader UGT1A1 Molecular Assay Package Insert. August 18, 2005.

UGT1A1 Allele Frequency

Table 1: UGT1A1 Allele Frequency			
Allele	**Caucasian N=71**	**Asian N=47**	**African N=101**
6	**61.3%**	**84%**	**47%**
7	**38.7%**	**16%**	**42.6%**

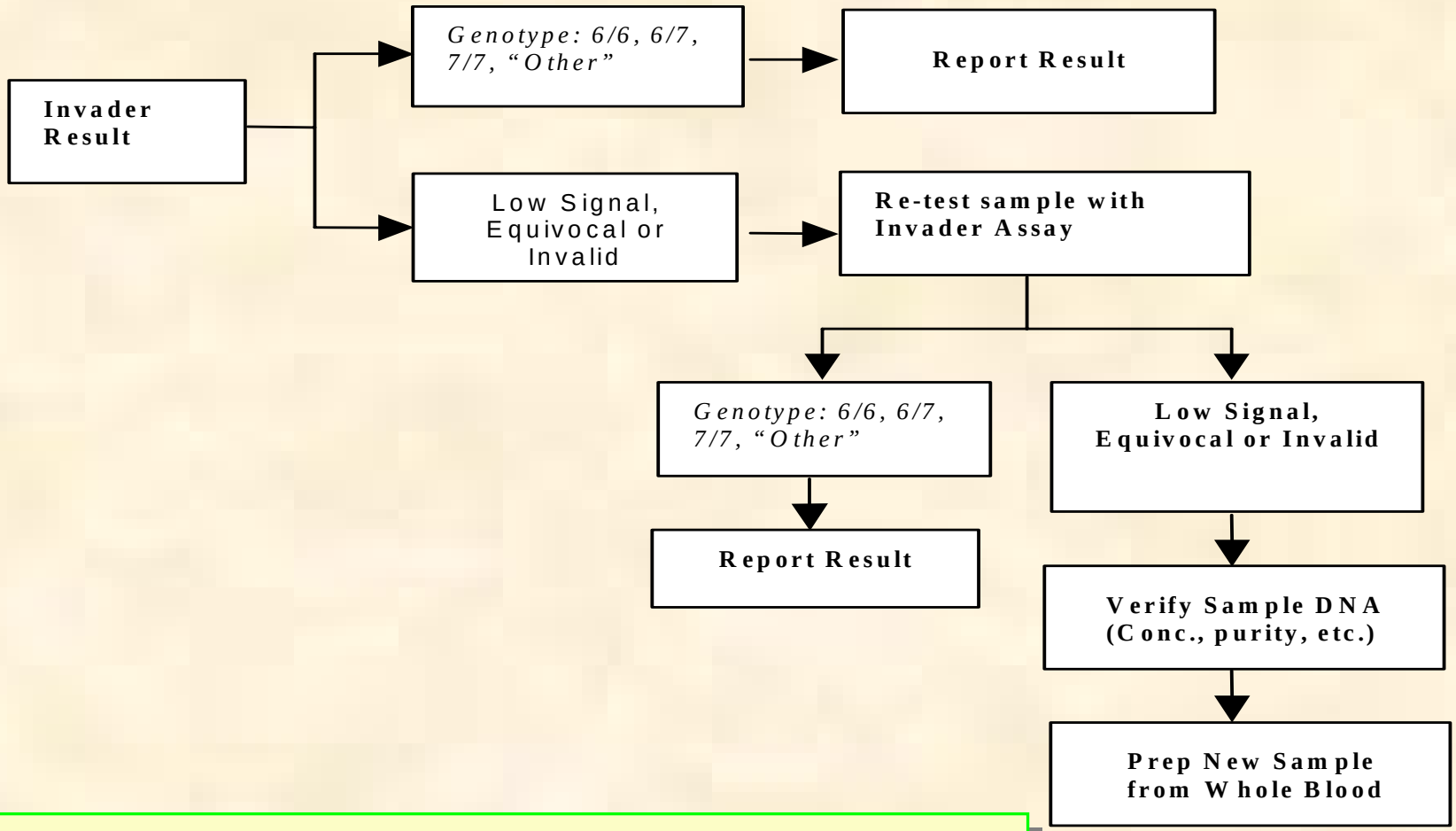
Invader UGT1A1 Molecular Assay Package Insert. August 18, 2005.

Summary of Allele Prevalence and Risk of Toxicity

Group	Prevalence	Risk of Toxicity
All Patients (N=66)	----	10%
Patients that are 7/7	10%	50%
Patients that are 6/7	40%	12.5%
Patients that are 6/6	50%	0%

Innocenti et al. J. Clin. Oncol. 2004; 22(8); 1382-1388.

Testing Algorithm



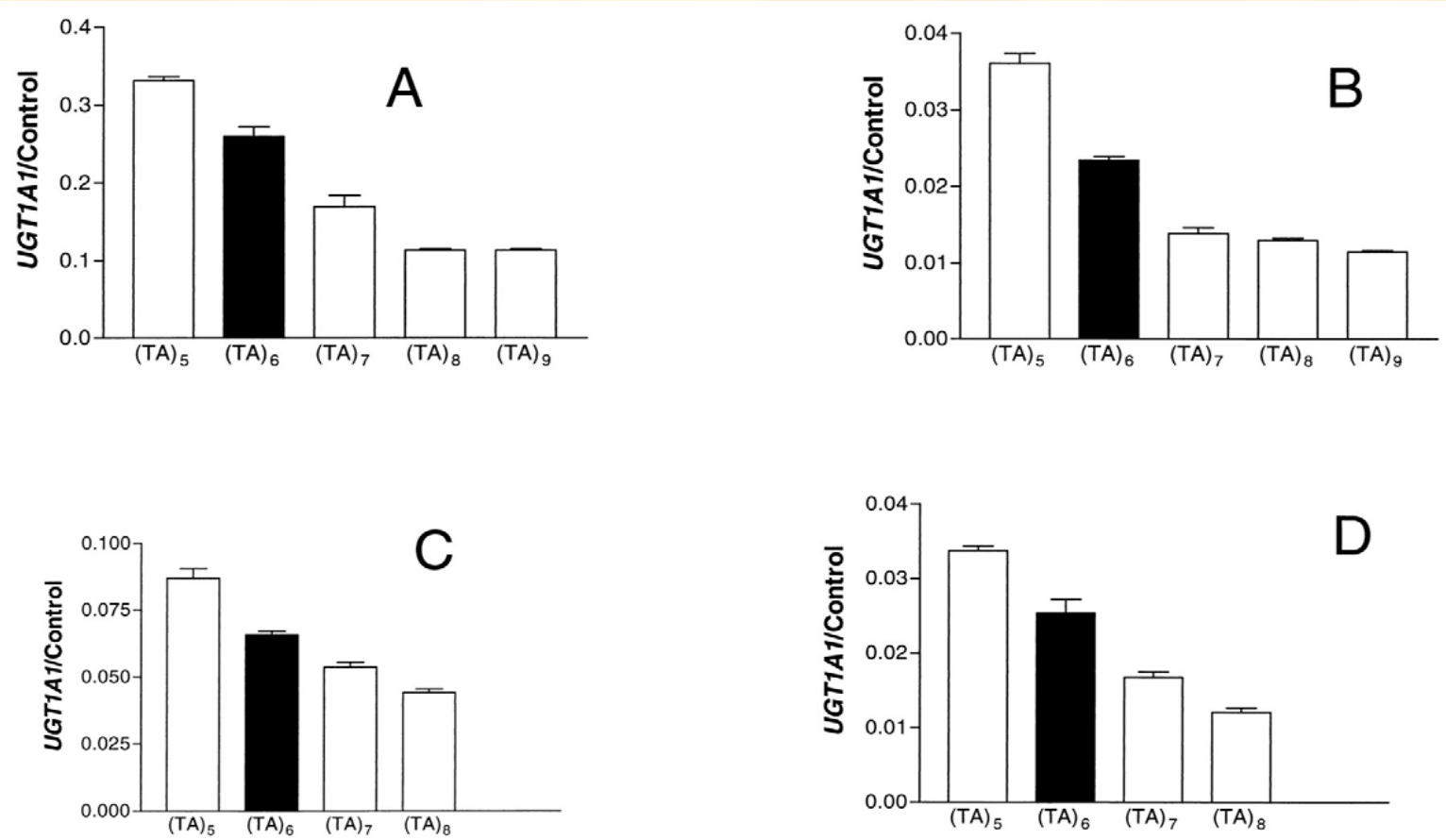
Invader UGT1A1 Molecular Assay Package Insert. August 18, 2005.

CDER/CDRH INTERACTION

Table 3. *UGT1A1* promoter gene frequencies (number of chromosomes) in three different ethnic groups			
Allele	**European (N=71)**	**Asian (N=47)**	**African (N=101)**
5	**0 (0)**	**0 (0)**	**0.035 (7)**
6	**0.613 (87)**	**0.840 (79)**	**0.470 (95)**
7	**0.387 (55)**	**0.160 (15)**	**0.426 (86)**
8	**0 (0)**	**0 (0)**	**0.069 (14)**

Beutler et al. Proc. Natl. Acad. Sci. 1998; 95:8170-8174.

Activity of UGT1A1 Promoter



Beutler et al. Proc. Natl. Acad. Sci. 1998; 95:8170-8174.

UGT1A1 Genotype in Different Ethnic Groups

Genotype	Caucasian	Asian	African
6/6	33.8%	70.2%	25.7%
6/7	54.9%	27.7%	36.6%
7/7	11.3%	2.1%	18.8%
7/8	0.0%	0.0%	5.9%
8/8	0.0%	0.0%	2.0%
6/8	0.0%	0.0%	4.0%
7/5	0.0%	0.0%	5.0%
6/5	0.0%	0.0%	2.0%

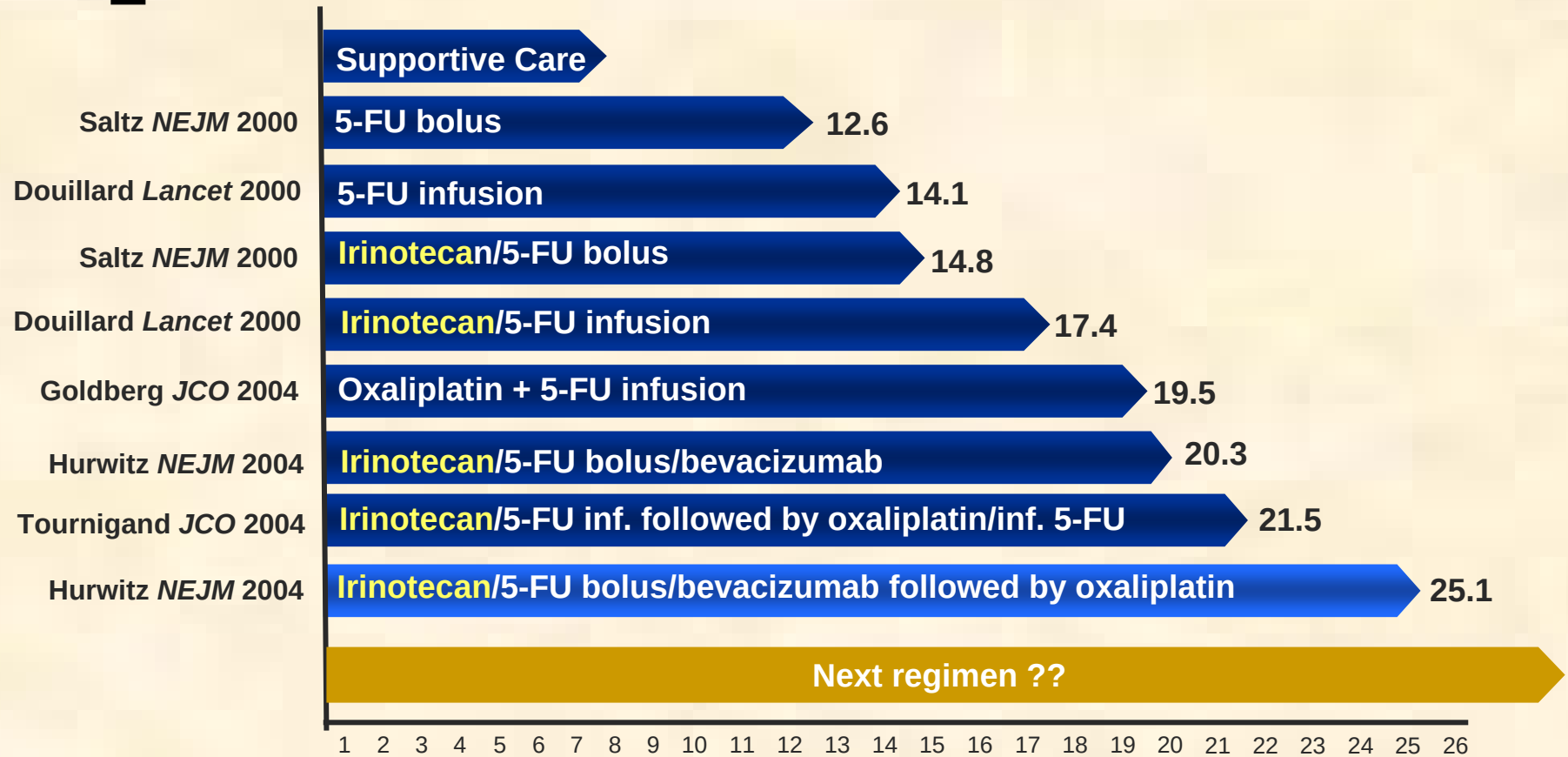
19% unaccounted in AA

OCPB PROPOSED TABLE

CDER/CDRH Regulations to Help Drug/Biologics and Test Development

- Current Reality
- Relevant Questions
- Potential Solutions

Increasing Survival Benefit for Metastatic CRC



Median overall survival (months)

Luis Parodi, Pfizer Inc. October 2005

Important Statistics

- Prescription sales for Camptosar in the United States was estimated $476 million in the year 2005.
- Eight-week regimen of Camptosar can cost approximately $10,000.
- Approximate cost of treating a patient with febrile neutropenia ranges from $14,000 to $62,000 per episode.
- UGT1A1 test cost ranges from $300 to $750.

UGT1A1 Testing for Gr 4 Neutropenia After CPT-11 (350 mg/m^2 q 3 wks)

- Without testing, 100% of pts are treated and 10% have Gr 4 neutropenia
- With testing, 90% of pts are treated and 5% have Gr 4 neutropenia
- 5% absolute reduction
  - Test 20 to protect 1

Mark Ratain, Advisory Committee Presentation. Nov 3, 2004

Efficacy Enhancement

- **Genotyping will lead to less inadvertent decrease in dose intensity in 7/7 patients and reduce the risk of loss of efficacy**
- **Genotyping may assist in the decision to increased dose for the 6/6 genotype**
  - **Camptosar label allows for dose increment from 125 mg/m^2 to 150 mg/m^2 weekly dose in absence of any toxicity.**
  - **Based on PGx testing, 6/6 genotype patients may start at 150 mg/m^2 dose?**

CDER/CDRH Regulations to Help Drug/Biologics and Test Development

- Current Reality
- **Relevant Questions**
- Potential Solutions

Relevant Questions

- What type and how much scientific and clinical evidence we need for Drug/Biologics label update with Pharmacogenomics information?
- What type and how much scientific and clinical evidence we need to include rare alleles in a test label?
- When do we require versus recommend a test for approved drug/biologics use?

Relevant Questions

- Can we have conditional approval for device with paucity of data for rare alleles with strong mechanism of action?
- What type of clinical studies be required to approve a test containing a rare allele?

Relevant Questions

- How device regulations help assess the safety and effectiveness of genetic tests?

- How drug/biologics regulations help inclusion of genetic information in the package insert?

CDER/CDRH Regulations to Help Drug/Biologics and Test Development

- Current Reality
- Relevant Questions
- **Potential Solutions**

Determination of Safety and Effectiveness Sec.860.7

(c)(1) Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective.

Determination of Safety and Effectiveness

(c)(2) Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

Determination of Safety and Effectiveness

(d)(2) Among the types of evidence that may be required, when appropriate, to determine that there is reasonable assurance that a device is safe are investigations using laboratory animals, investigations involving human subjects, and non-clinical investigations including in vitro studies.

Regulation Helps…

CDRH regulations promotes test development for specific subpopulation

Labeling Regulations

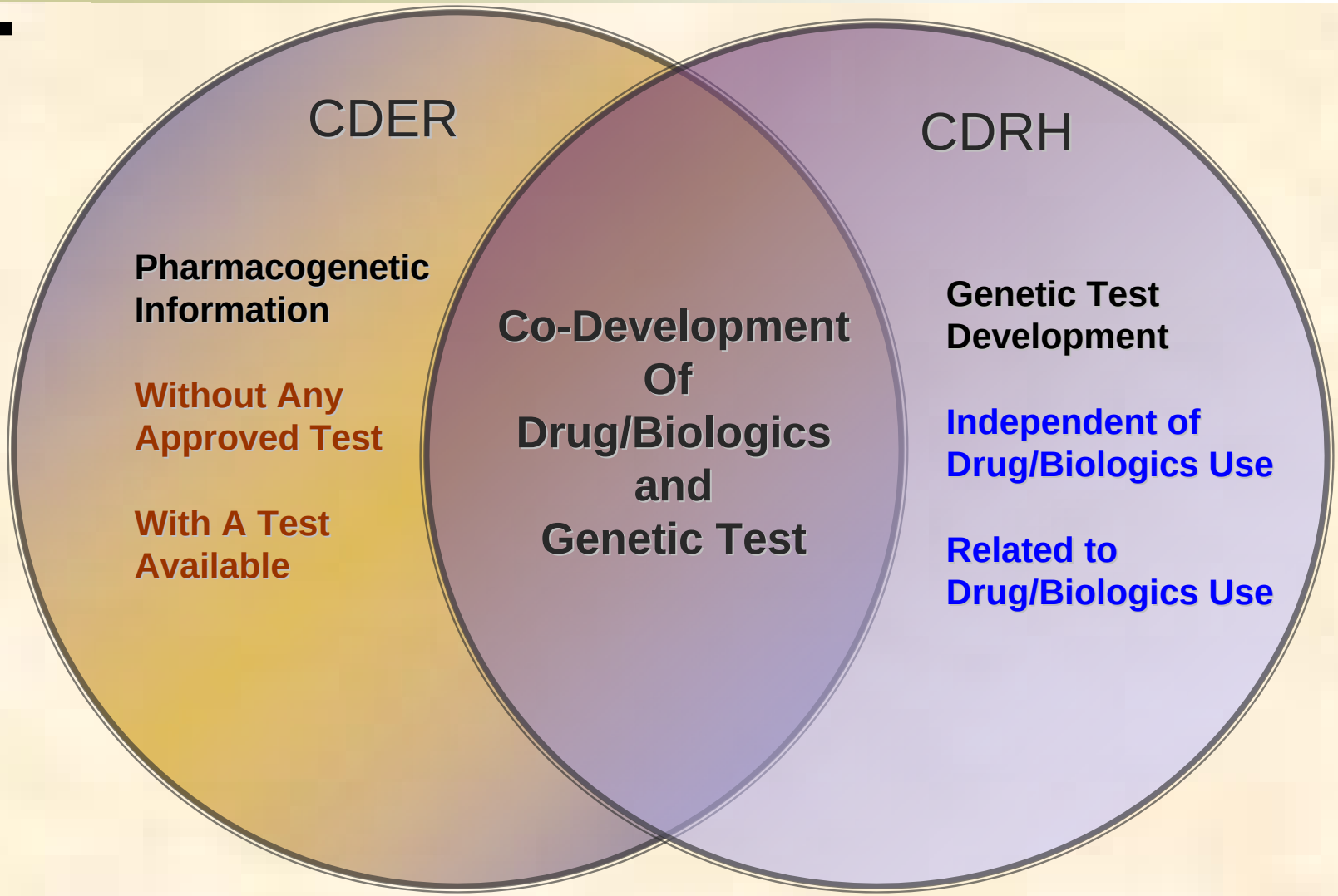
"If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug."

- 21 CFR 201.57(a)(3)(i)

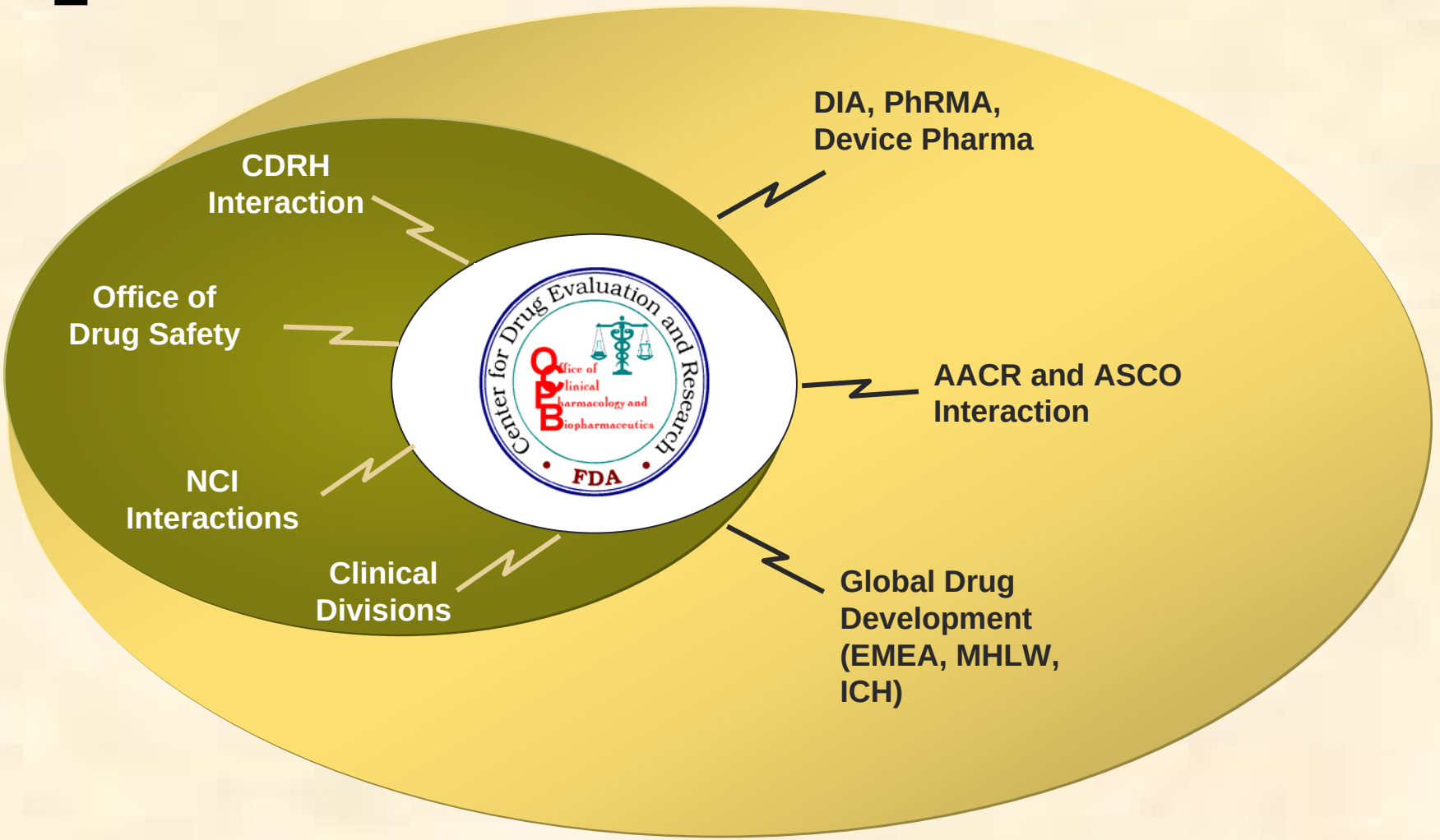
Regulation Helps…

- No barriers to including Pharmacogenomics information in product labels.
- CDRH regulations promotes test development for specific subpopulation.

Critical Path Opportunity



Shared Responsibilities



Acknowledgement

Larry Lesko
Felix Frueh
Shiew-Mei Huang
Mehul Mehta

Brian Booth
Roshni Ramchandani
Joga Gobburu

Rick Pazdur
John Johnson
Amna Ibrahim
Grant Williams
Brenda Atkins

Mark Ratain
Federico Innocenti

Uwe Scherf
Steve Gutman

THANK YOU