Topic 1_A: Background information

LABELING RECOMMENDATIONS FOR DRUGS/BIOLOGICS AND DEVICE RELATED TO PHARMACOGENOMIC DATA AND TEST

1. Drugs and Biologics Labeling

All clinically relevant information on the effect of polymorphic variation in drug metabolizing enzymes, transporters, receptors and/or other proteins on pharmacokinetics, pharmacodynamics, clinical responses (both safety and efficacy) should be included in the CLINICAL PHARMACOLOGY or CLINICAL STUDIES sections of the labeling of drugs and biologics. Where the information has important implications for safe and effective use, the consequences of the genetic differences and/or recommendations may be placed in INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, PRECAUTIONS/WARNINGS, CONTRAINDICATIONS, BOXED WARNING, CLINICAL STUDIES and/or ADVERSE REACTIONS sections, as appropriate. Clinically relevant genetic information should not be included in detail and/or repeated in more than one section, but rather referenced from one section to other sections as needed. When the genetic differences result in recommendations for dosage adjustments, contraindications, or warnings, that were included in the BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, or DOSAGE AND ADMINISTRATION sections, these recommendations should also be included in "HIGHLIGHTS." Refer to the guidance for industry "*Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements"* for more information.

Examples of appropriate labeling language are provided in italic below.

A. INDICATIONS AND USAGE

- If the drug is indicated only for a population with a certain genetic makeup, and a genotypic or phenotypic test needs to be conducted prior to drug prescription and administration….

(Drug) is indicated for the treatment of patients with _____ genotypes. (See CLINICAL STUDIES)Clinically beneficial effects are limited to patients with _____ genotypes). (Drug) should be used only in patients with _____ genotypes.

(Drug) is indicated for the treatment of _____ expressing patients..

(Drug) is indicated for the treatment of patients with _____ positive _____ cancer. (See CLINICAL STUDIES : _____ cancer)

(Drug) is indicated for patients with ____ receptor positive or _____receptor unknown locally confined _____cancer. …. Patients with _____receptor negative disease

……..rarely responded to (Drug). (See CLINICAL STUDIES : _____ protein expression for information regarding protein testing)

B. DOSAGE AND ADMINISTRATION

- If the dose recommendations are different for subgroups of patients with different genetic makeup…..

The dosage for patients with two non-functional enzyme alleles may be ____% of the regular dose.

C. PRECAUTIONS/WARNINGS

- If individuals with certain genetic makeup are more sensitive to one of the severe adverse events

There are individuals with an inherited deficiency of the_____ enzyme who may be unusually sensitive to the (adverse event) of (Drug) and prone to developing (adverse event) following the initiation of treatment. Substantial dosage reductions may be required to avoid the development of (adverse event) in these patients.

D. CONTRAINDICATIONS

- If individuals with certain genetic makeup are more sensitive to one of the life threatening adverse events that may not be managed via dose reduction. .

(Drug) should not be given to patients with the following genetic makeup: _____. Patients should be tested for their genotypes prior to administration of drug _____.

E. CLINICAL PHARMACOLOGY

- If the drug is metabolized by a polymorphically distributed enzyme and individuals with different genotypes have different dose-concentration-response relationships.

(Drug) is metabolized by _____enzyme to an inactive metabolite. _____enzyme varies tremendously among patients, because of a common inherited genetic defect in _____enzyme . ___, ___, and ____% of the Caucasian, African American, and Asian American populations, respectively, are completely deficient and ___, ___, and ____% of the above populations, respectively, are moderately deficient in _____enzyme activity because they have inherited one variant (non-functional) _____enzyme allele (i.e., heterozygotes). Patients with low _____enzyme activity have higher concentrations of the (Drug) and are more susceptible to ___adverse event.

F. CLINICAL STUDIES

- If the drug shows differential clinical benefit or adverse events in patients with different genetic makeup.

Clinical beneficial effects of (Drug) are limited to patients with _____ genotypes. (Drug) should be used only in patients with _____ genotypes.

(Drug) shows a higher rate of (adverse reactions) in patients with _____ genotypes. (Drug) should not be given to patients with the following genetic makeup: _____.

The ree of ___protein overexpression was a predictor of treatment effect. (See CLINICAL STUDIES : _____protein overexpression.)

- The receptor values were used to recruit patient in clinical trials.

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive _____ expression. Primary tumor or tumor from a metastatic site was tested with the brand _____ test kit. Specimens were scored based the percentage of cells expressing ___ and intensity (barely/faint, weak to moderate, and strong). Response rate correlate (or not correlate) with either the percentage of positive cells or the intensity of ____ expression.

G. ADVERSE REACTIONS

- If the drug is metabolized by a polymorphically distributed enzyme and individuals lacking this enzyme had a higher rate of adverse reactions.

Among patients with (indicated disease), as many as ___% of those with ____toxicity while taking (Drug) may have a defect in _____enzyme activity.

H. LABORATORY TESTING

- If the drug is metabolized by a polymorphically distributed enzyme and individuals lacking this enzyme had a higher rate of adverse reactions. The following information may be included.

Poor metabolizers (PM) of CYP2D6 exhibit 10-fold higher plasma levels (AUC). Laboratory tests are available to identify CYP2D6 PMs ….…higher blood levels in PMs lead to higher rate of some adverse effects of (Drug).

- When a specific laboratory test is developed and used in pivotal clinical trials of the drug or biologic and additional tests become available after marketing of the drug/biologic.

- Both the generic and brand names of the tests may be mentioned in the drug/biologic's labeling.

Detection of _____ overexpression is necessary for selection of patients appropriate for _____ therapy. Overexpression of _____ by tumors was an entry criterion of the two clinical studies described above. In those studies, a_____ assay (referred to as the Clinical Trial Assay, CTA) was used.

The commercial assays _____ (brand), _____ (brand), and _____ (brand) are appropriate assays to aid in the selection of patients for ____ therapy (see CLINICAL STUDIES: ___ detection: ___ protein overexpression detection methods)

2. Device Labeling

Examples of appropriate labeling language are provided in italic below. Detailed information on specific regulatory items required in labeling of in vitro diagnostic devices (IVDs) can be found in 21 CFR 809.10(b).

A. Intended Use

For device labeling, the intended use/indications for use would explain what is being measured and why.

This device is intended for in vitro diagnostic use.

This device is a ___(type)___ assay to determine__(marker)__ (over) expression in ____(matrix)____ routinely processed for histological evaluation. ___(Device) is indicated as an aid in the assessment of patients for whom ___(drug)___ treatment is being considered (see drug or biologics package insert)

__(Device)___ is a genotyping assay to determine alleles of _____ (enzyme) . Individuals with _____ (alleles) may be poor metabolizers and may be unusually sensitive to adverse events of certain drugs metabolized by this enzyme. These patients may be prone to developing adverse events following the initiation of drug treatment. Substantial dosage reductions may be required to avoid the development of adverse events in these patients

B. Summary and Explanation of the Test

This section includes a discussion of the clinical utility of the test which summarizes the safety of the drug/test combination. For tests to be used with a specified drug(s), language such as the following may be appropriate:

If the test gives a false positive result, the patient will receive unnecessary drug treatment with the following possible adverse effects: _____, _____, _____. If the test gives a false negative result, the patient will not receive the potential benefits of therapy with _____ drug.

C. Test Procedure Section

This section describes the procedures for running the test and including sample acquisition and handling, appropriate quality control procedures, sample testing protocols, and the interpretation of results. If applicable, any criteria used to distinguish the cut-off of positive from negative and, possibly, indeterminate results should be clearly stated.

Clinical interpretation of results should also be described where applicable. For example:

The combination of the activity of the enzymes encoded by the two [enzyme] alleles determines the overall metabolic activity for an individual. These combinations are shown [below]. There are four phenotypic types: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers. The predicted phenotypes, based on the genotype call for the [gene] are provided in the test result report.

D. Limitations Section

This section states any test limitations (e.g., known extrinsic and intrinsic factors or interfering substances affecting results) that are necessary to assure correct interpretation and usage of the test. If further testing, either more specific or more sensitive, is indicated in all cases where certain results are obtained, the need for the additional test will also be stated in this section. Some examples of limitations that may be found in device labeling for use with therapeutics are below.

All of the patients in the Herceptin® clinical trials were selected using a clinical trial assay. None of the patients in those trials were selected using _____ test. The _____test was compared to _____test on an independent sample and found to provide acceptably concordant results. The actual correlation of _____test to clinical outcome has not been established.

Some rare alleles are not reported by the test. These alleles are _____. New alleles not identified at the time of release of test will not be correctly detected. In that case, a _____ result will be obtained for the relevant gene.

Depending upon the significance of the limitation, it may be placed in the vicinity of the Intended Use at the beginning of the package insert.

E. Summary of Expected Results or Performance Characteristics

This section describes the expected results for the populations of patients that are expected to receive the diagnostic test and how the test results affect the clinical applications. This section may also contain the protocol for the studies used to determine the cut-off between positive and negative and, possibly, indeterminate results. When the test has been used during the clinical trials to establish the safety and efficacy of the drug

in certain populations, the clinical and analytical data are described. For tests developed after market approval of the drug, comparison data with the original test are presented here.

When there is a sufficient literature base to establish the clinical validity of a certain test or type of test, this section will contain analytical validation (reproducibility, limit of detection, linearity, analytical specificity, and accuracy, usually established by method comparison).

Inter-run reproducibility was tested…. Excellent reproducibility (____%) was seen.

In the pivotal trial, patients with ____ (brand) positive test results were treated with ___ drug. ___ (number) tumor specimens were tested. There was ____(or no) correlation between the degree of tumor response and the percentage of _____-positive cells or ____-staining intensity. (See Table 1)

Table 1: ___drug Pivotal Trial Response Rates

	Total number of patients tested	*Response Rate[#] of cases treated with _____*
_____ positive		*__%, (95% CI =_%,_%)*
_____ negative		*None treated*

In an additional supportive study, a ___ kit was used to enroll patients. ___ % of patients had a positive test result.

Table 4: Summary of ____ Percent Positivity in _____Patients

Study ID	*Positive Ratio (# positive/# tested)*	*% Positive*	*95% Confidence Intervals*
Pivotal Trial			
Supportive Study			