Health Canada International Symposium on
Drug, Food and Natural Health Product Interactions
February 9, 2006
Gatineau, Quebec

Risk of Drug Interactions Involving Herbal and Citrus Products

Shiew-Mei Huang, PhD
Deputy Director for Science
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
Food and Drug Administration
Shiewmei.huang@fda.hhs.gov

Adverse Drug Reactions-Marketed Drugs

- **2,000,000**

  number of serious ADRs yearly

- **100,000**

  annual number of ADR-related deaths

- **4-6**

  ranking of serious ADRs as causes of death

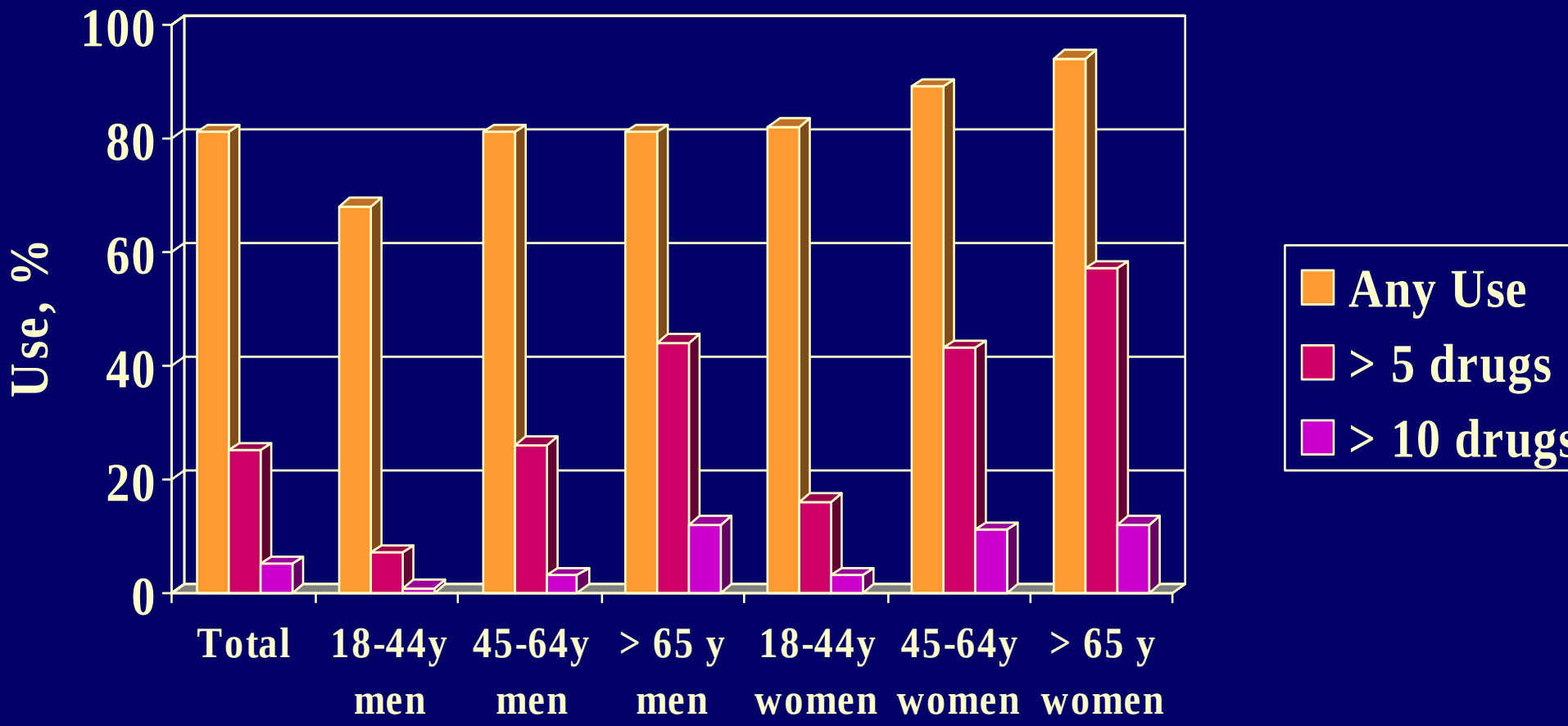
- **136,000,000,000**

  annual cost in dollars associated with ADRs

< JAMA 1998;279:1200–1205; Arch Intern Med 1995;155(18):1949–1956>

Why are there so many ADRs?

Use of Medications by Sex and Age



< JAMA 2002;287:337-344 >

- Use of botanicals has increased

- One in five Americans (18.4%) take prescription medications concurrent with at least 1 herbal product, a high-dose vitamin, or both
- 15 millions are at risk for potential adverse interactions (including 3 millions 65 years or older)

< Eisenberg DM et al., JAMA 280 (18): 1569, 1998>

Evaluation of Drug-Drug Interactions?
-When are they significant-

Tools available

- **Draft Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling (expected publication: 1Q 2006)**
- **Reviewer Guide: Good Review Practices (April 2004)**
- **"Drug Interactions in Drug Development" website (expected one-line 1Q 2006)**
  <http://www.fda.gov/cder/drug/drugInteractions/default.htm>

< http://www.fda.gov/cder/guidance/index.htm; http://www.fda.gov/cder/mapp/4000.4.pdf; http://www.fda.gov/cder/drug/drugInteractions/default.htm>

Key messages:

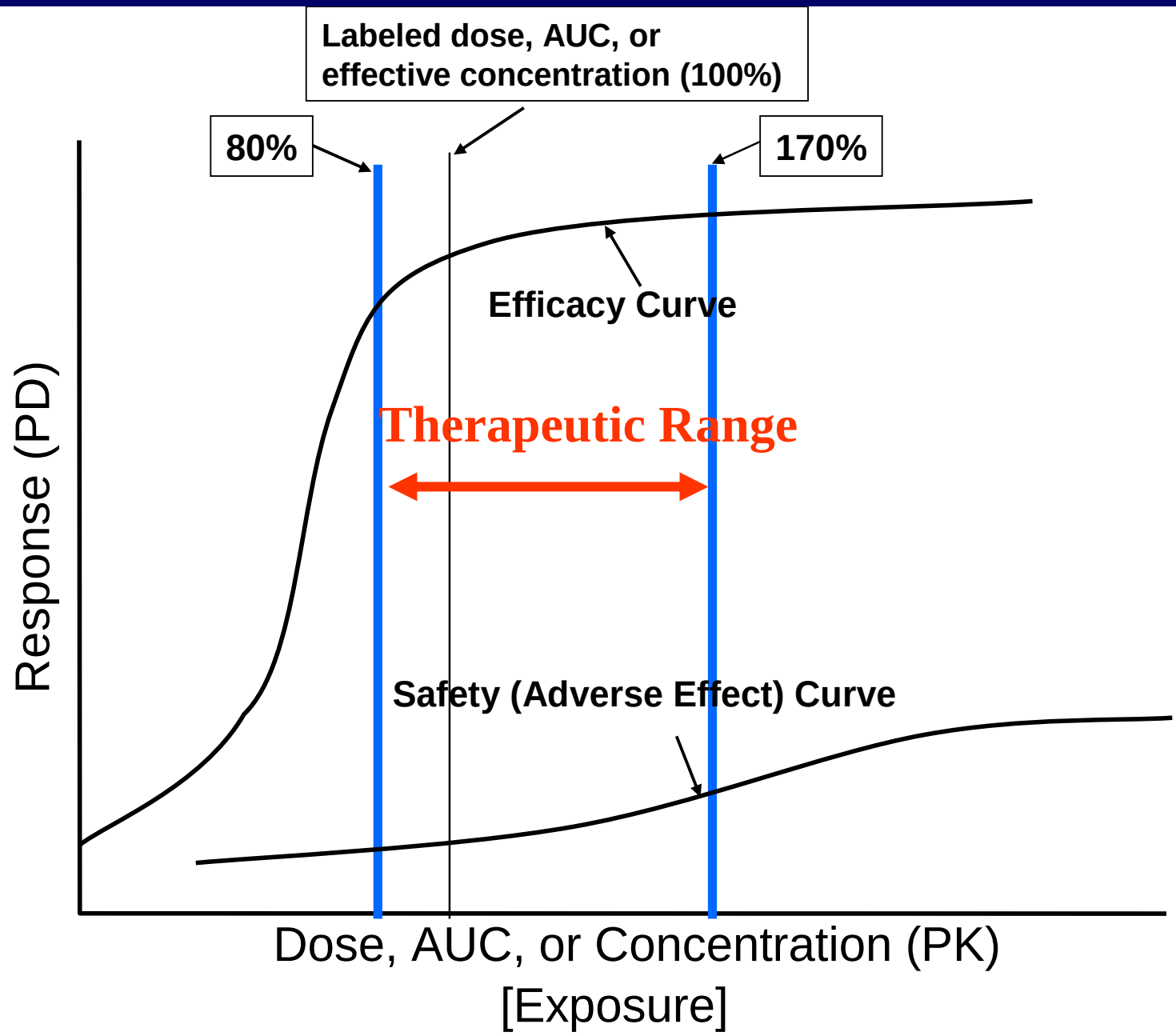
1. Metabolism, drug-interaction info key to benefit/risk assessment
2. Integrated approach may reduce number of unnecessary studies and optimize knowledge
3. Study design/data analysis key to important information for proper labeling
4. Need to establish “Therapeutic equivalence boundaries” (no effect boundaries)
5. Labeling language needs to be useful and consistent

Key Questions To Ask On Drug-Drug Interactions:

1. Will an NME alter exposure to other drugs

2. Will other drugs alter exposure to the NME?

3. Are these alterations in exposure significant enough to warrant dose adjustment?



Adapted from Huang SM, Lesko, LJ, Williams RL, J Clin Pharmacol, 39 :1006-1014, 1999

Labeling Impact
- Drug-Drug Interactions -

- **Concomitant Medications: The dosage of LEVITRA may require adjustment in patients receiving certain CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, indinavir, and erythromycin) (see WARNINGS , PRECAUTIONS , Drug Interactions).**

Labeling Impact
- Drug-Drug Interactions (2) -

- **For ritonavir, a single dose of 2.5 mg LEVITRA should not be exceeded in a 72-hour period.**
- **For indinavir, ketoconazole 400 mg daily, and itraconazole 400 mg daily, a single dose of 2.5 mg LEVITRA should not be exceeded in a *24-hour* period.**
- **For ketoconazole 200 mg daily, itraconazole 200 mg daily, and erythromycin, a single dose of *5 mg* LEVITRA should not be exceeded in a 24-hour period.**

Evaluation of Drug-Herb Interactions?
-When are they significant-

Key Questions To Ask On Drug-Drug Interactions:

1. Will an NME alter exposure to other drugs

2. Will other drugs alter exposure to the NME?

3. Are these alterations in exposure significant enough to warrant dose adjustment?

} Questions on Drug-Botanical Interactions

Evaluation of Drug-Herb Interactions? -Which herbs-

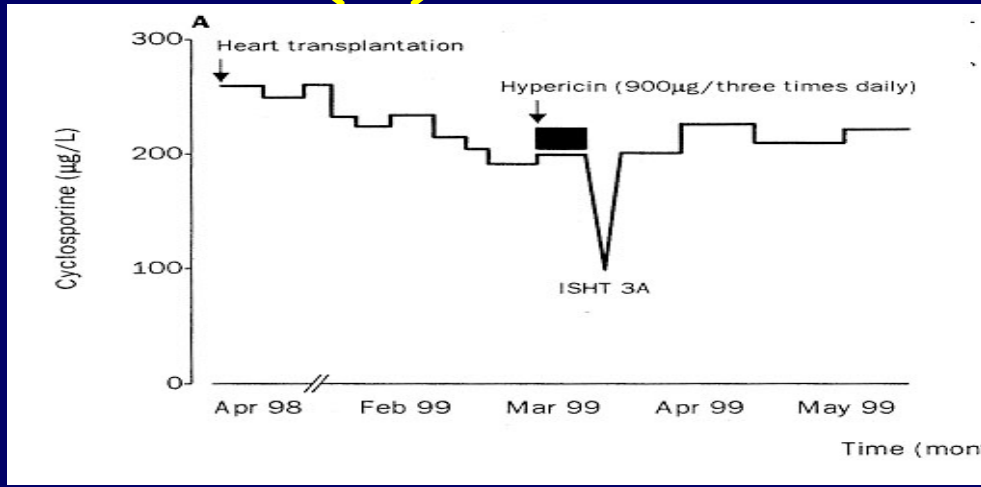
- **Case reports**
  - systematic evaluation of reports
- **Specific studies to understand mechanisms of interactions**
  - herb's effects on specific drugs
  - herb's effects on specific probes for enzymes and transporters

    <in vitro and in vivo studies>

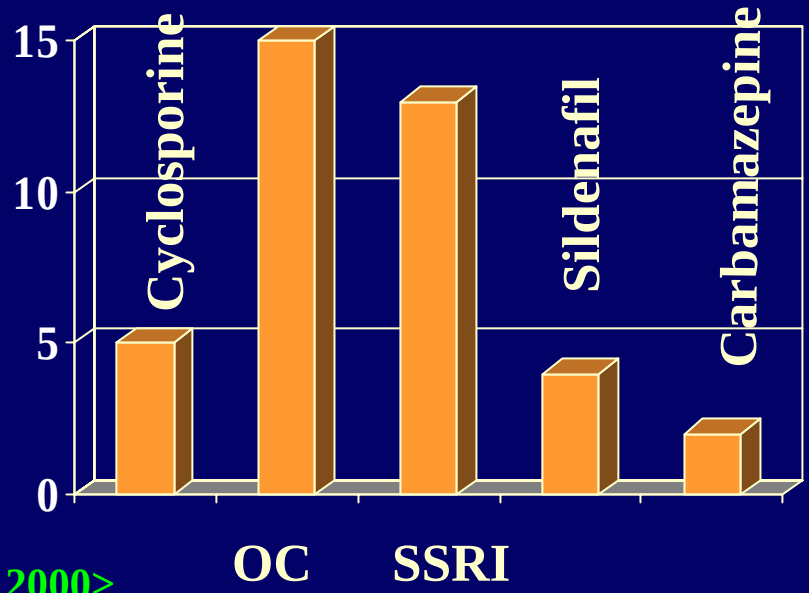
St John's Wort

St John's wort (2)

- Cases of rejection of heart transplant patients on St John's wort



- Up to 2001, FDA's Adverse Event Reporting System (AERS) in CDER indicated up to 39 case reports



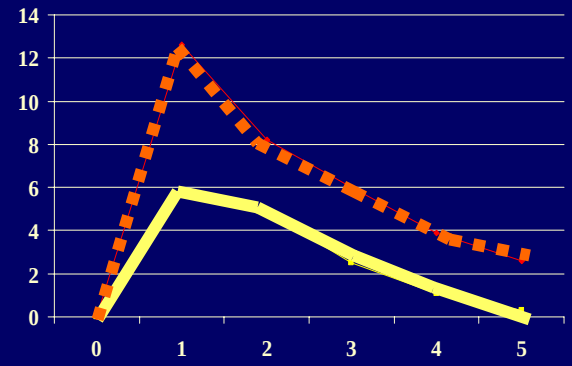
<Ruschitzka F, et al, Lancet 355: 548-549, February 12, 2000>

<Chen M, Drug-Herb Interactions, Eds. Lam, Huang, Hall, Taylor & Francis, in press>

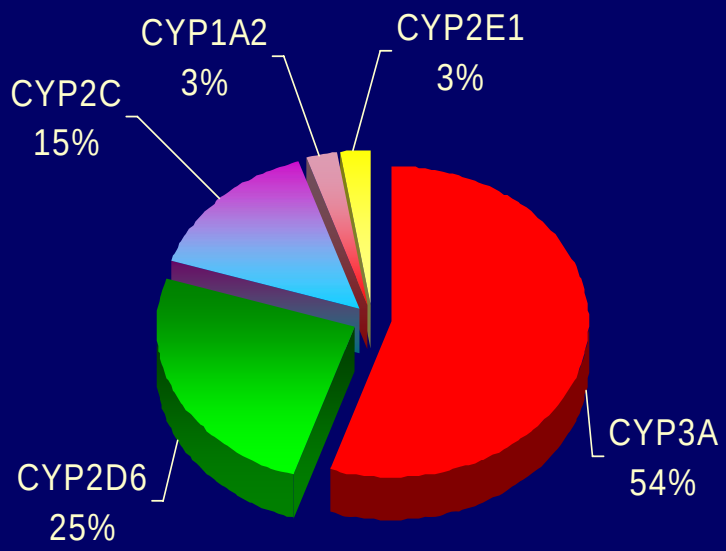
St John's wort (3)
-effect on CYPs-

- St John's wort decreased indinavir plasma levels

<Piscitelli S, et al, Lancet, Feb 2000>



- Acute St John's wort had little effects on major CYPs (CYP1A2, 2D6, 2C9, 3A)
- Chronic St John's Wort induced CYP3A



<Wang Z, et al, Clin Pharmacol Ther 2001;70:317-26; Clin Pharmacol Ther 2002;71:414-20>

St John's wort (4)
- Effect on P-gp -

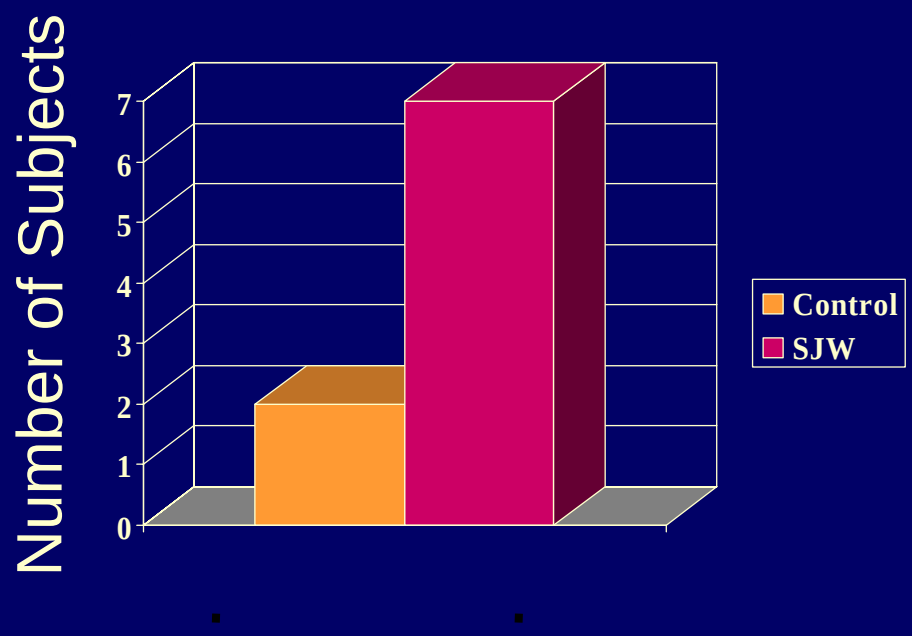
- **Fexofenadine levels were *slightly increased* by acute St John wort dosing and *reduced* during chronic dosing**

- **Consistent with an increase in immunodetectable CYP3A4 and P-gp in intestinal biopsies following 14 days treatment with St John's wort (Dürr et al., CPT 68, 598, 2000).**

Wang Z, et al, Clin Pharmacol Ther 2001;70:317-26; Clin Pharmacol Ther 2002;71:414-20

St John's wort (5)
- Effect on OC -

- 8 weeks of St John's Wort *decreased* norethindrone levels and ethinyl estradiol t1/2
- More breakthrough bleeding occurred in St John's Wort phase
- Higher midazolam clearance for those with breakthrough bleeding
  (216+ 67 vs. 98 +37)



< Gorski JC, et al, Clin Pharmacol Ther 2003 Dec;74(6):525-35 >

St John's wort (6)

- **Case reports**
  - systematic evaluation of reports
- **Specific studies to understand mechanisms of interactions**
  - herb's effects on specific drugs
  - herb's effects on specific probes for enzymes and transporters

    <in vitro and in vivo studies>

St John's wort (7)
- Regulatory Impact-

- FDA Health Advisory on "concomitant use with protease inhibitors or NNRTI is not recommended"
<http://www.fda.gov/cder/drug/advisory/stjwort.htm>

- Labeling revision of marketed drug products

- Labeling of newly approved drugs

St John's wort (8)
- Regulatory Impact-

When do we include St. John's Wort in the drug labeling?

Cytochrome P450 3A and/or P-gp substrates and where the products' effectiveness may be reduced upon co-administration of St. John's Wort

Current Labeling
- St John's wort -

- 55 drug products with St John's wort in the labeling
  - 2 based on actual clinical studies
  - others based on reports and/or mechanistic reasons
  - 2 not related to the products (concurrent OC use)

< As summarized in Huang S-M, Lesko, LJ, Temple R, in "Herb-drug interactions", eds, Lam, Huang, Hall, Taylor & Francis, in press>

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/57300800.htm

Current Labeling
- St John's wort and OC -

PRECAUTIONS: Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
http://www.fda.gov/cder/guidance/5197dft.pdf

Other botanical products?

Echinacea

- Echinacea selectively modulates the catalytic activity of CYP3A at hepatic and intestinal sites
- The type of drug interaction observed between echinacea and other CYP3A substrates will be dependent on the relative extraction of drugs at hepatic and intestinal sites.
- Study to evaluate the effects on OC ongoing

<Gorski, Huang, Pinto, Hamman, Hilligoss, Zaheer, Desai, Miller, Hall, Clin Pharmacol 2004 Jan;75(1):89-100. >

Other botanical products?

- **Ginkgo Biloba extract induced CYP2C19**

- **AUC ratio (omeprazole/5-OH omeprazole) decreased by 68%; the extent of interactions appear to be CYP2C19 genotype-dependent**

<Yin OQ et al, Pharmacogenetics, 2004 Dec;14(12):841-50>

Protocol Design

How do we address possible drug dietary supplement interactions?

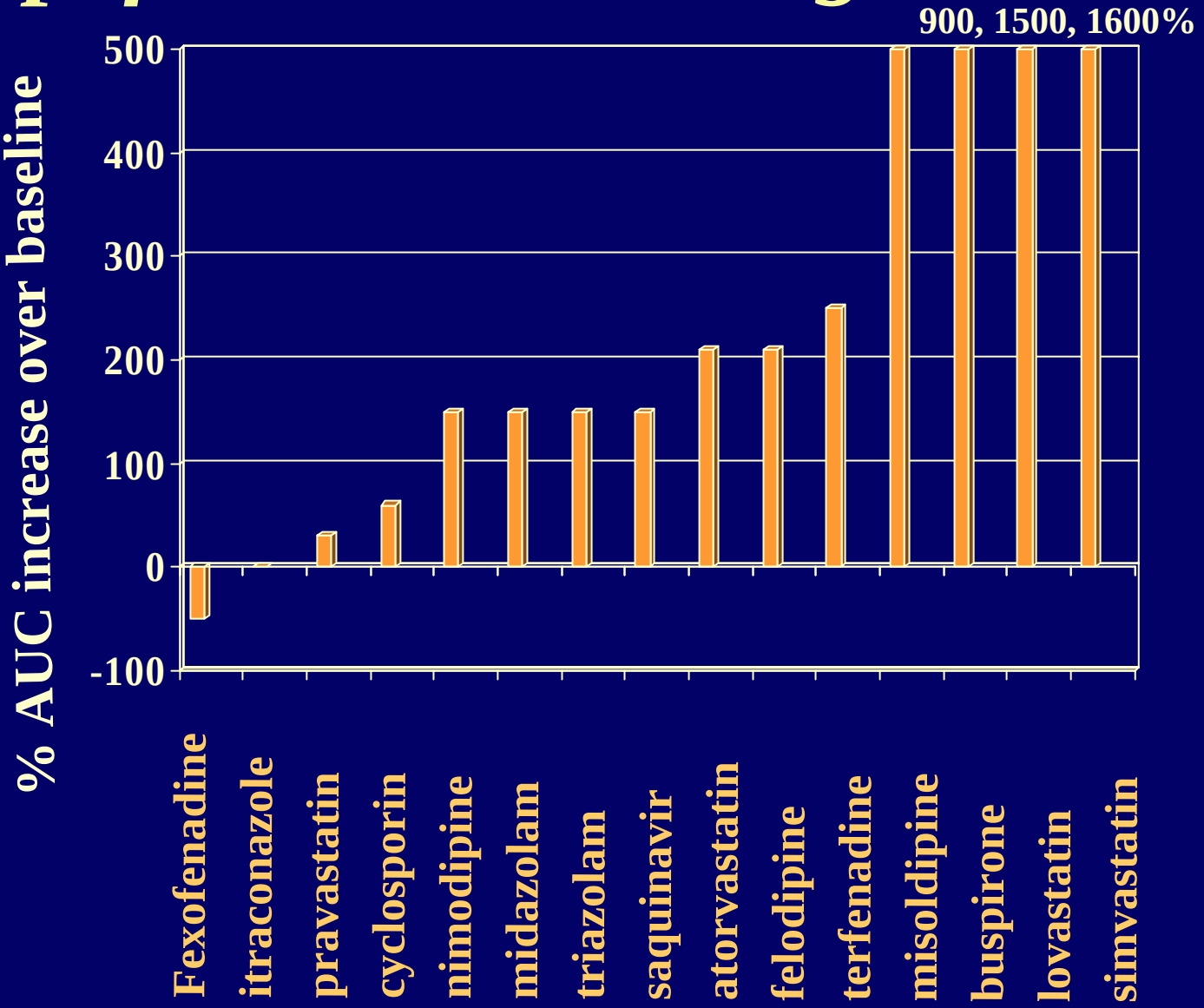
Clinical protocol- Participants will be excluded for the following reasons:
….. use of prescription or over-the-counter medications, *including herbal products*, or alcohol within two weeks prior to enrollment;

<Protocol for FDA/Indiana echinacea- cytochrome P450 interaction study; results in Clin Pharmacol 2004 Jan;75(1):89-100 >

Interactions with Citrus Fruit/Juices

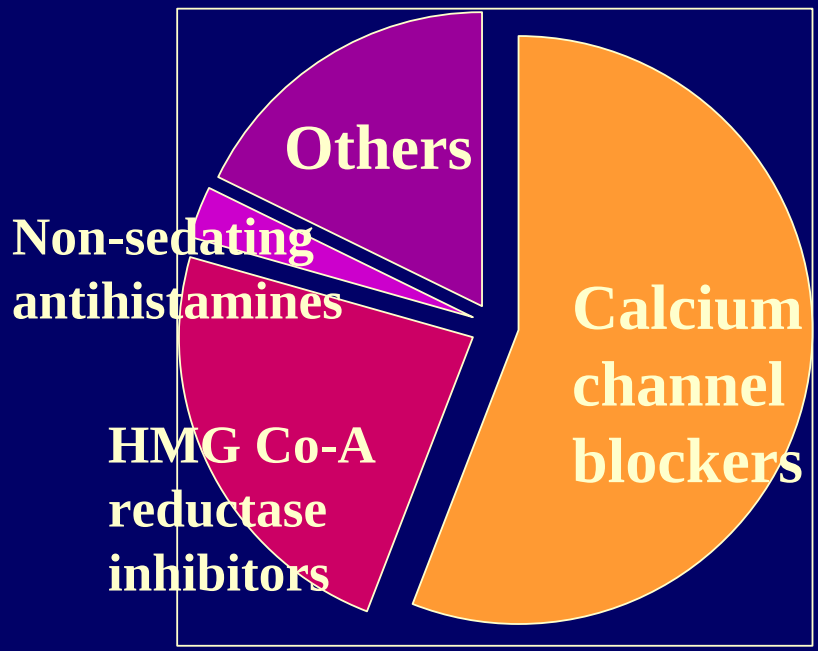
Grape fruit juice

Grapefruit Juice - Drug Interactions



Grapefruit Juice
Post-marketing reports (FDA)

- **Up to 2004, FDA's Adverse Event Reporting System (AERS) in CDER indicated up to 40 case reports**



Case Report

Lovastatin and Grapefruit Juice (1)

- 60 yo male with hypertension, chronic lower extremity venous stasis/edema, renal insufficienty, non-insulin dependent diabetes mellitus and familial history of hyperlipidemia
- taking lovastatin concurrent with gemfibrozil, amlodipine, metoprolol, glyburide, trovafloxacin, vitamine E, metformin, aspirin, ciprofloxacin
- changed his usual orange juice to grapefruit juice
- muscle pain and high CPK (>40, ooo U/L)

<Piazza-Hepp, T, in ""Herb-drug interactions", eds, Lam, Huang, Hall, Taylor & Francis, in press>

Case Report
Lovastatin and Grapefruit Juice (2)

- ICU for rhabdomyolysis with acute renal failure, overlapping with chronic renal failure
- started IV fluid; d/c lovastatin and gemfibrozil; creatinine (5 mg/dL); gradually back on other meds
- CPK to 1,017; improved on muscle weakness
- Physician concluded drug interactions between grapefruit and lovastatin and gemfibrozil
  => told the patient to avoid grapefruit juice

Case Report

Nifedipine and Grapefruit Juice

- 92 yo female with hypertension took nifedipine 30 mg daily for 4 years
- while traveling in Florida, took nifedipine with grapefruit juice: experiences extreme fatigue, dizziness, vertigo, decreased appetite, disorientation
- hospitalized, juice stopped, recovered
- Back home, took nifedipine with grapefruit juice again, experiences a similar but milder grapefruit and lovastatin and gemfibrozil

=> pharmacist suspected an interaction between nifedipine and grapefruit juice

Current Labeling
- Grapefruit juice -

- 35 drug products with grapefruit juice in the labeling
  - 50% reported clinical data
  - others based on reports and/or mechanistic reasons
  - grapefruit juice considered “moderate CYP3A inhibitor”- CYP class labeling

< As summarized in Huang S-M, Lesko, LJ, Temple R, in “herbal-drug interactions”, eds, Lam, Huang, Hall, Taylor & Francis, in press>

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/57300800.htm

Regulatory Impact

When do we include grapefruit juice in the drug labeling?

Cytochrome P450 3A substrates with low oral bioavailability (due to enteric first pass)

Dosage and Administration:
Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of *cyclosporine (Neoral)* , thus should be avoided

Warnings/Precautions:
To avoid possible serious side effects, avoid drinking large quantities of grapefruit juice (more than on quart daily) while on *simvastatin (ZOCOR)* (see ….Muscle)

<http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/57301293.htm#PDRCON01, 11/99 update>

Health Canada on GFJ

- **Certain drugs and health products used in the treatment of the following medical conditions are known to cause this effect:Angina; Anxiety; Cancer; Convulsions; Depression; Erectile dysfunction; Gastrointestinal reflux; High blood pressure; High lipid (cholesterol) levels; HIV/AIDS; Infections; Irregular heart rhythms; Organ graft rejections; Psychotic problems**
- **if you are taking medication for any of the conditions listed above, DO NOT drink grapefruit juice or eat grapefruit in any form, until you have talked to your doctor and your pharmacist about the potential for an adverse reaction.**
- **Avoid taking any drug with grapefruit juice until you have asked your doctor or pharmacist if it is safe to do so.**

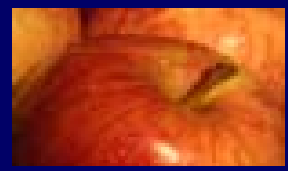
<http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2002/2002_49_e.html

<http://www.hc-sc.gc.ca/iyh-vsv/food-aliment/grapefruit-pamplemousse_e.html; last update: Jan 2006>

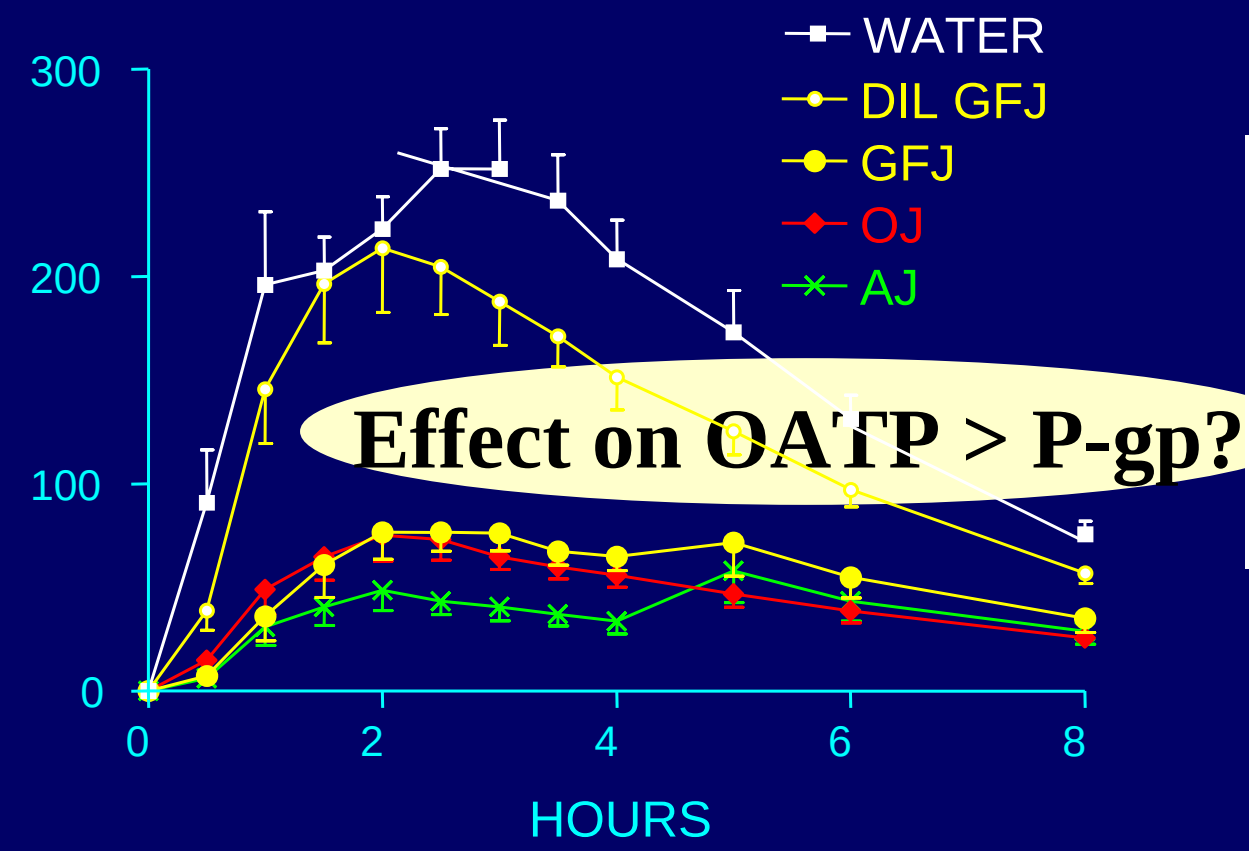
Interactions with Citrus Fruit/Juices

- Effects on *transporters*

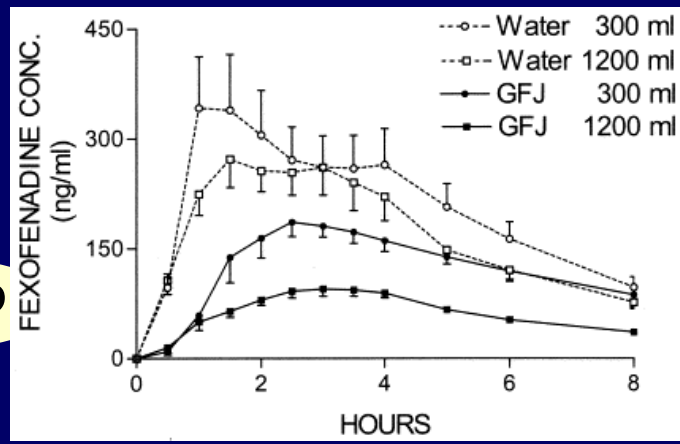
Grapefruit juice/
Apple juice/
Orange juice



Effect of various juices on fexofenadine (n=10)



Effect on OATP > P-gp?

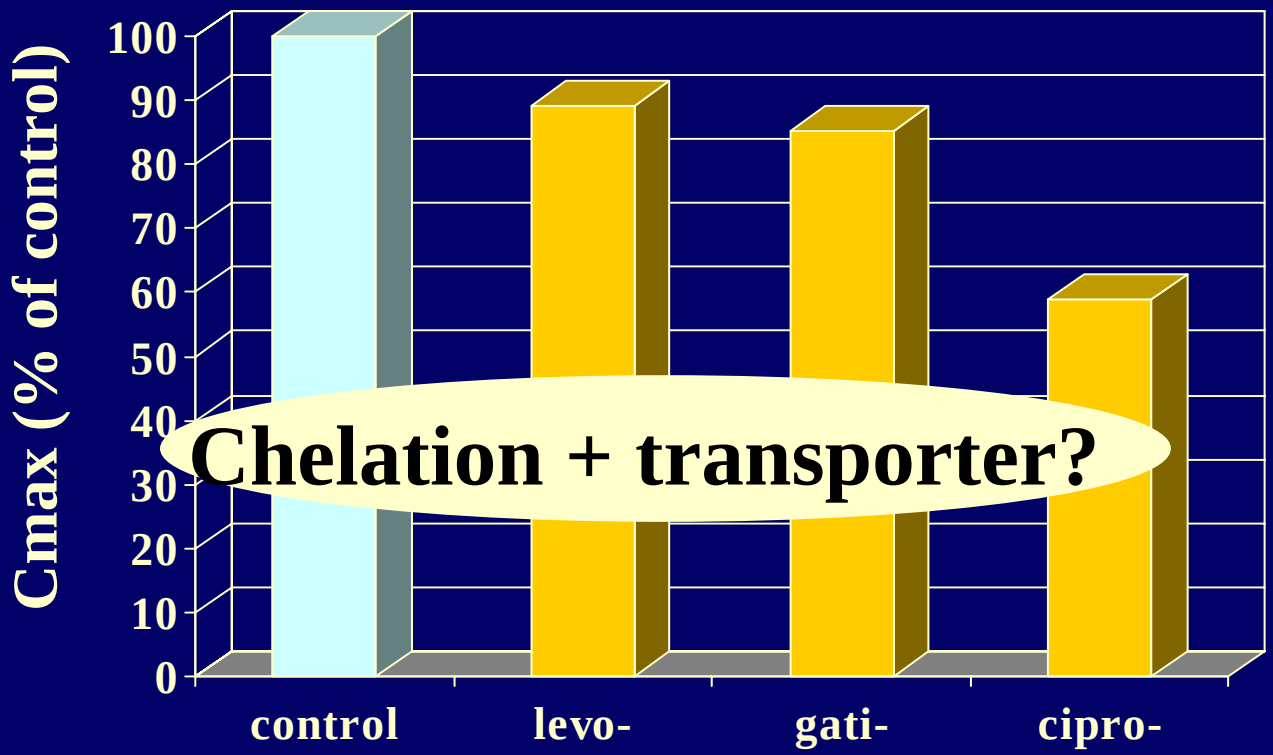


(1.2 L over 3 hours) in a randomized 5-way crossover

<Bailey D, et al, ASCPT presentation, 2001; Dresser GK et al, Clin pharmacol Ther, 2002 Jan; 71(1):11-20; 2005 Mar;77(3):170-7 >

Other interactions with citrus fruit

Calcium-fortified Orange juice



Evaluation of -floxacins from various studies (n=15-16)

<Neuhofel AL, et al ,J Clin Pharmacol. April 2002; Wallace AW, et al, J Clin Pharmacol. Jan and May 2003>

Other interactions with Cranberry Juice

September 2003, "Current Problems in Pharmacovigilance“ by British Committee on Safety of Medicines

- patients taking warfarin *should limit or avoid* drinking cranberry juice

- five reports; one fatal-- involved a man whose INR >50 six weeks after starting cranberry juice

Effect on CYP2C9?

http://www.mca.gov.uk/ourwork/monitorsafequalmed/currentproblems/cpsept2003.pdf

Protocol Design

How do we address possible drug-juice interactions?

"For at least two weeks prior to the start of the study until its conclusion, volunteers will not be allowed to eat any food or drink any beverage containing *alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family* (e.g., kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard) and *charbroiled meats.*"

Related to Drug- Natural Product Interactions:

1. Metabolism, drug-interaction info key to benefit/risk assessment
2. Integrated approach may reduce number of unnecessary studies and optimize knowledge
3. Study design/data analysis key to important information for proper labeling
4. Need to establish "Therapeutic equivalence boundaries" (no effect boundaries)
5. Labeling language needs to be useful and consistent

NME's clearance pathway needs to be well-defined

Studies may not be needed- from known info

NME's exposure-response needs to be well-defined

Drug Interactions working group

Sophia Abraham	Sayed Al-Habet	Raman Baweja
Sang Chung	Philip Colangelo	Paul Hepp
Shiew-Mei Huang	Ron Kavanagh	Lawrence Lesko
Patrick Marroum	Srikanth Nallani	Wei Qiu
Nam Atik Rahman	Kellie Reynolds	Xiaoxiong Wei
Lei K Zhang	Jenny H Zheng	

Jerry Collins	Soloman Sobel	John Strong
David M Green	David Frucht	
Hon Sum Ko	Toni Stifano	
Robert Temple	Janet Norden	

Questions?

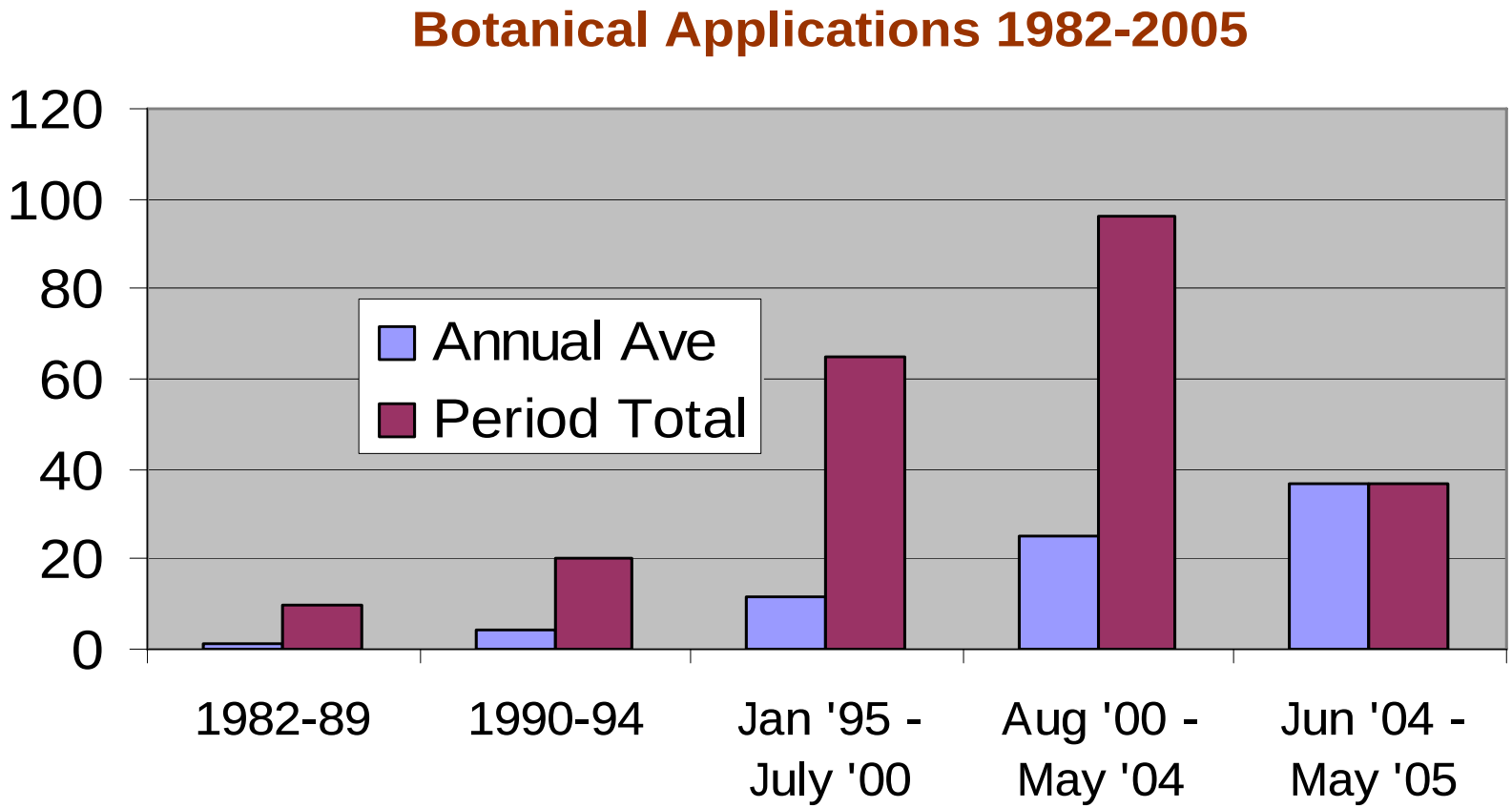
Update on Botanical IND's

Botanical Applications in FDA (as of June 1, 2005)

- Total of 242 Applications
- 192 INDs (2/3 active); 50 pre-INDs
- 50 in‘’90-’98, 192 in‘’99-’05
- 2~3 new subm/month in recent yrs
- 40% commercial, 60% research
- 2/3 single herb, 1/3 multiple herbs

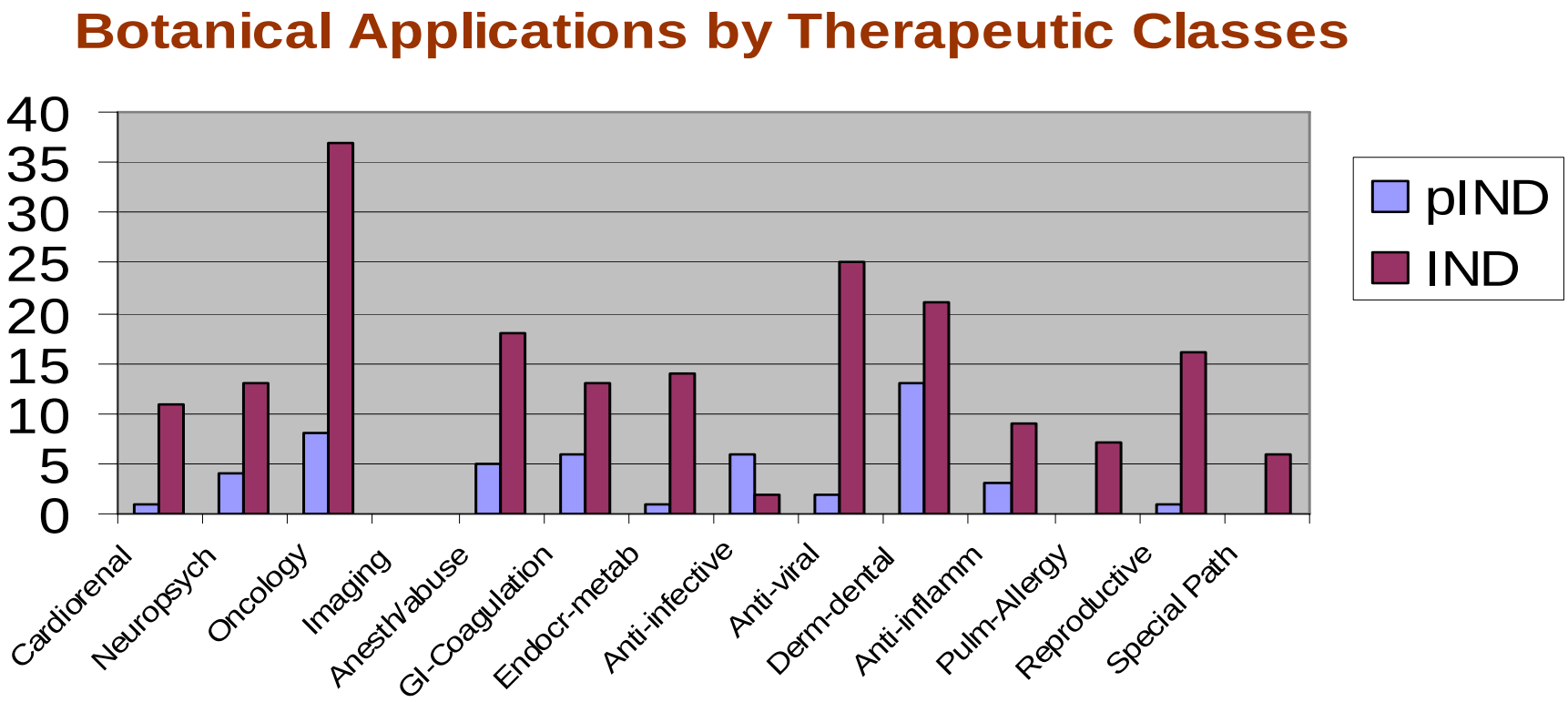
<Shaw Chen, CDER, FDA, November 2005>

Botanical Applications at FDA
Growing over the Years



<Shaw Chen, CDER, FDA, November 2005>

Botanical Applications in FDA



<Shaw Chen, CDER, FDA, November 2005>

Drug-Drug Interactions
- Labeling Implications -

- **All relevant information…. should be included in the PHARMACOKINETICS subsection of the CLINICAL PHARMACOLOGY section of the labeling.**

- **The clinical consequences …. should be placed in DRUG INTERACTIONS, WARNINGS AND PRECAUTIONS, BOXED WARNINGS, CONTRAINDICATIONS, or DOSAGE AND ADMINISTRATION sections, as appropriate.**

- **When the data resulted in recommendations for dosage adjustments, contraindications, warnings, <u>these recommendations should also be included in "HIGHLIGHTS."</u>**

Drug- Natural Product Interactions
- Current Labeling examples -

Physicians' Desk Reference at http://pdrel.thomsonhc.com/pdrel/librarian
A catalog of FDA approved drug products, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
CDER New and Generic Drug Approvals: 1998-2004, http://www.fda.gov/cder/approval/index.htm

Cyclosporine

DOSAGE & ADMINSTRATION

Grapefruit and grapefruit juice **affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.**

Fexofenadine

Interactions with Fruit Juices

Fruit juices such as grapefruit, orange and apple **may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. …… Therefore, to maximize the effects of fexofenadine, it is recommended that ALLEGRA-D 24 HOUR *should be taken with water***

http://www.fda.gov/cder/foi/label/2004/21704lbl.pdf

Levonorgestrel and Ethinyl Estradiol

Herbal products containing *St. John's wort (Hypericum perforatum)* may induce hepatic enzymes (cytochrome P 450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding .

http://pdrel.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.IndexSearchTranslator#PDRPRE01el/2004/21704lbl.pdf

Isotretinoin

CONTRAINDICATIONS and WARNING

Patients should be prospectively cautioned not to self-medicate with the *herbal supplement St. John's wort* because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's wort (see PRECAUTIONS).*1

Warfarin

PRECAUTIONS

Caution should be exercised when *botanical medicines (botanicals)* are taken concomitantly with COUMADIN. Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and COUMADIN. Due to a lack of manufacturing standardization with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to *monitor the patient's response with additional PT/INR determinations when initiating or discontinuing botanicals.*

http://www.fda.gov/cder/foi/label/2005/009218s101lbl.pdf

Warfarin (2)

Information for Patients

Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g., aspirin and topical analgesics), other over-the-counter medications, and *botanical (herbal) products (e.g., bromelains, coenzyme Q10, danshen, dong quai, garlic, Ginkgo biloba, ginseng, and St. John's wort)* except on advice of the physician

http://www.fda.gov/cder/foi/label/2005/009218s101lbl.pdf

St John's wort Products

WARNING: St. John's Wort can have potentially dangerous interactions with some prescription drugs. *Consult your physician* before taking St. John's Wort if you are currently taking *anticoagulants, oral contraceptives, antidepressants, anti-seizure medications, drugs to treat HIV or prevent transplant rejection, or any other prescription drug*.

FTC Warning ON Herbal Outlook or similar product (Panda), St. John's Kava Kava (ForMor), http://www.ftc.gov/opa/2001/06/cureall.htm

References for Draft Guidance on Drug Interactions

- Guidance for industry: In vivo metabolism/drug interactions: Study design, data analysis and recommendation for dosing and labeling (Issued 11/24/1999, Posted 11/24/1999); http://www.fda.gov/cder/guidance/index.htm; http://www.fda.gov/cder/guidance/2635fnl.pdf
- Tucker, Houston and Huang, Clin Pharm Ther August 2001; 70(2):103
- Bjornsson, Callaghan, Einolf, et al, J Clin Pharmacol, May 2003; 43(5):443
- Yuan, Madani, Wei, Reynolds, Huang, Drug Metab Disp, December 2002; 30(12) 1311
- Labeling guidance: http://www.fda.gov/cder/guidance/6005dft.pdf (Jan 2006)
- FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues and challenges in the evaluation and labeling of drug interaction potentials of NME. Rockville, MD. April 23, 2003; http://www.fda.gov/ohrms/dockets/ac/03/slides/3947s2.htm; http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3947T2.htm
- FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004; http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm; http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4079T1.htm
- Huang S-M, Lesko LJ, J Clin Pharmacology, June 2004
- Huang S-M, Hall S, Watkins P, et al, Clin Pharmacol Ther, Jan 2004
- Huang S-M, Temple R, Lesko LJ, in “Botanical – Drug Interactions, Scientific and Regulatory Challenges”, Ed, Lam F, Huang S-M, Hall S, Taylor and Francis, in press
- CDER Drug Interactions Website (available 1Q; http://www.fda.gov/cder/drug/drugInteractions/default.htm)