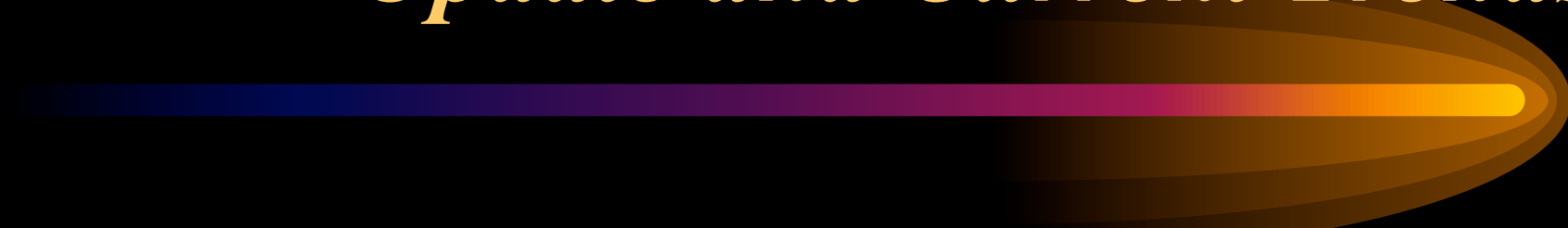


Black Box Warnings: Update and Current Trends



Joyce Generali, MS, RPh, FASHP
Kansas University Medical Center
Drug Information Center



CAFERGOT

(ergotamine tartrate and caffeine)
SUPPOSITORIES, USP

Rx Only

WARNING

Serious and/or life threatening peripheral ischemia has been associated with the coadministration of CAFERGOT with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of CAFERGOT, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated (*See also CONTRAINDICATIONS and WARNINGS section*)

Boxed Warnings

21 CFR 201.57 (e)

Labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug: a causal relationship need not have been proved....

Boxed Warnings

21 CFR 201.57 (e)

Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displaced box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.

Black Box Facts



- Intended to provide alert regarding high risks associated with drug.
- Can only be issued following an FDA mandate.
- Black Box warnings emphasize significant and serious safety data regarding prescription drugs.
- Warnings may include: potential adverse events, drug interactions, dosing information, monitoring and administration requirements, and at-risk populations

Black Box Facts

- New Black Box data available at marketing or may be added post-marketing (reflecting the dynamic nature of a safety profile post-marketing)
- Safety profile of a NCE is limited by premarketing data
 - number of patients (~3,000)
 - homogeneous population
 - concurrent pharmacotherapy
 - latent side effects

Black Box Facts



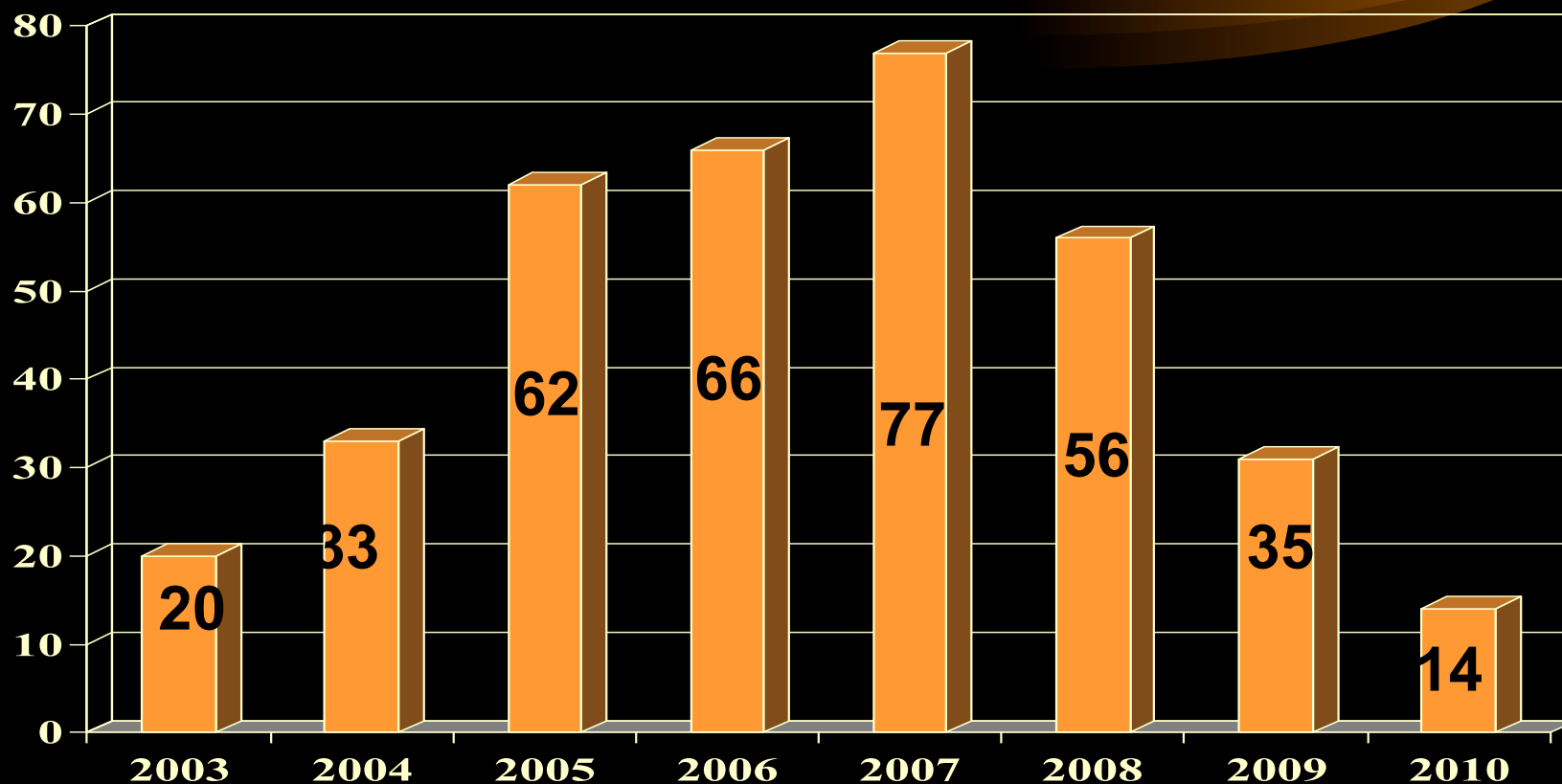
- Must be cited in all advertising and included in package inserts
- Distribution of medication guides
- Impact on prescribing

The Imperfect Nature of BBWs

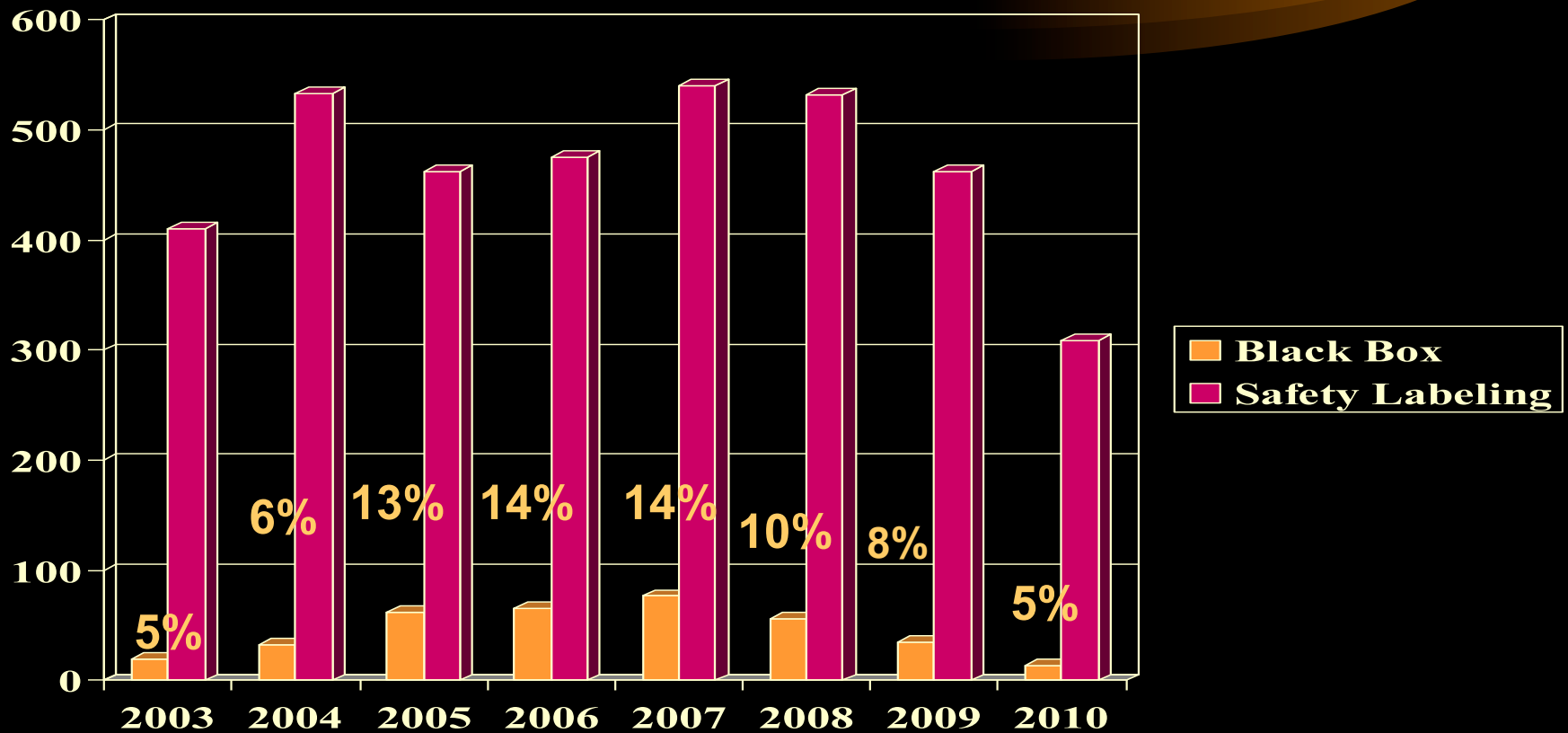


- Criteria for development
- Supportive evidence
- Efficacy as risk communication tool
- Inconsistent presentation
- Adherence
- Resources for keeping current
- Prescriber notification
- Patient notification/materials
- Market Withdrawals

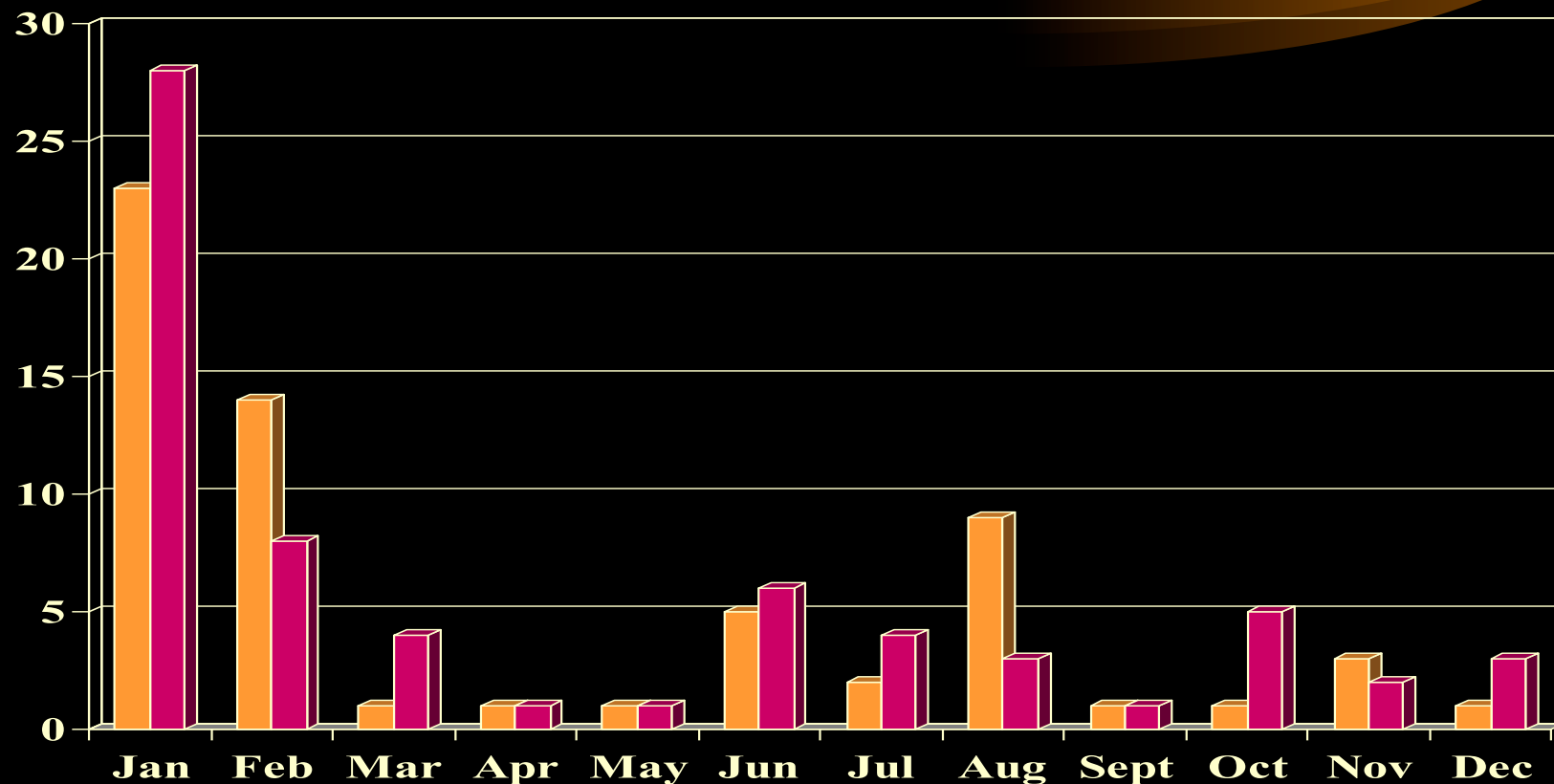
Safety Labeling Changes Approved by FDA: Black Box Warnings



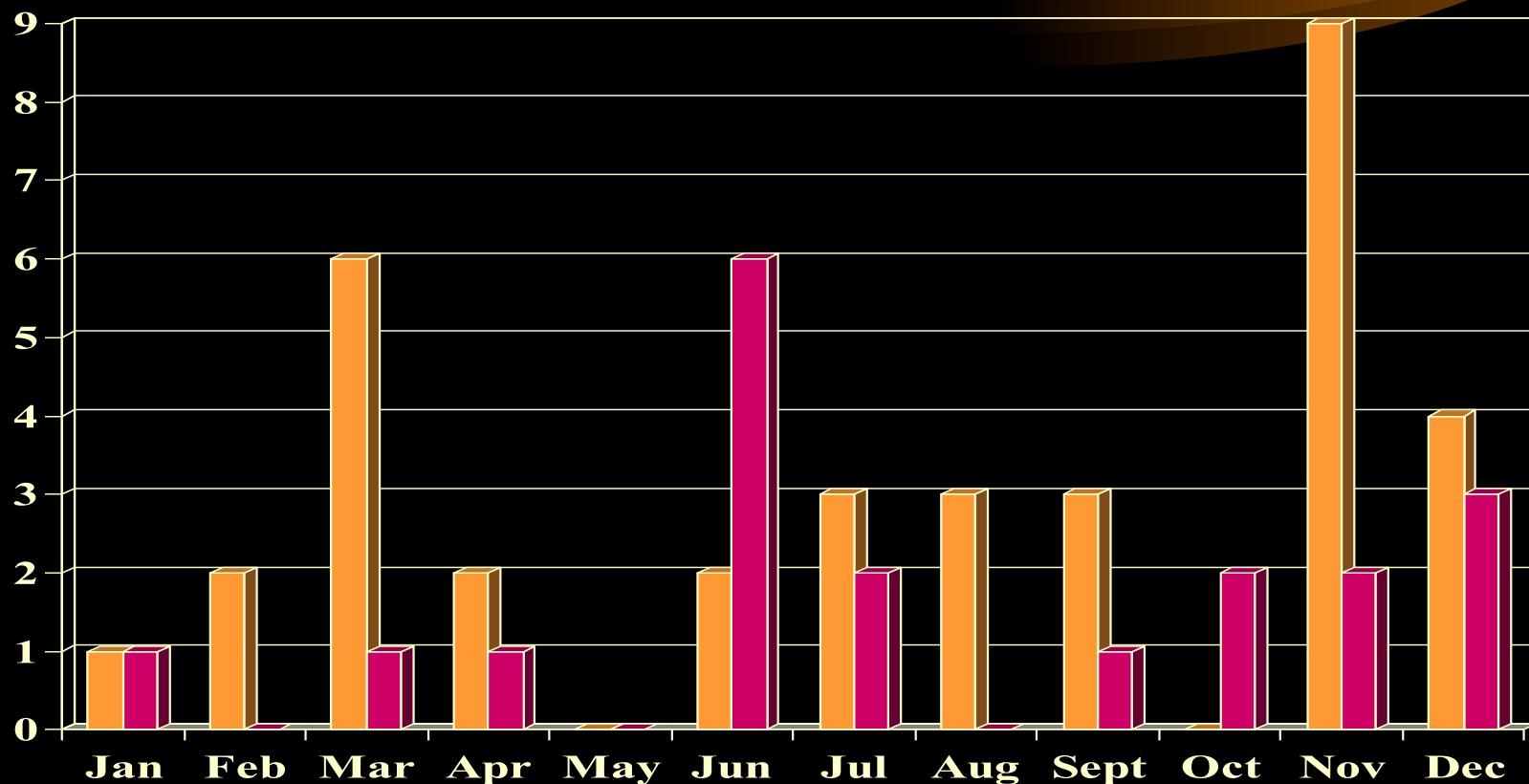
Safety Labeling Changes Approved by FDA: Total vs Black Box Warnings



Safety Labeling Changes Approved by FDA: Black Box Warnings 2005-2006



Safety Labeling Changes Approved by FDA: Black Box Warnings 2009-2010



Black Box Warnings Class Labeling 2005-2010



- Fluoroquinolones
- NSAIDs: cardiovascular
- Antipsychotics : mortality risk in dementia
- Antidepressants : suicidal ideation
- Estrogens : WHI updates
- TNF Blockers
- Botulinum Toxins
- LABAs

Black Box Warnings

2009

- Abacavir/Lamivudine/Zidovudin
- Bupropion
- Certolizumab
- Dalteparin
- Efalizumab
- Enoxaparin
- Fentanyl citrate
- Fludarabine
- Fonaparinux
- Icodextrin
- Infliximab
- Iron dextran
- Itraconazole
- Metoclopramide
- Mitoxantrone
- Nilotinib
- Progesterone
- Sirolimus
- Sodium Phosphate Monobasic monohydrate/ anhydrous
- Testosterone (gel)
- Tinzaparin
- Varenicline

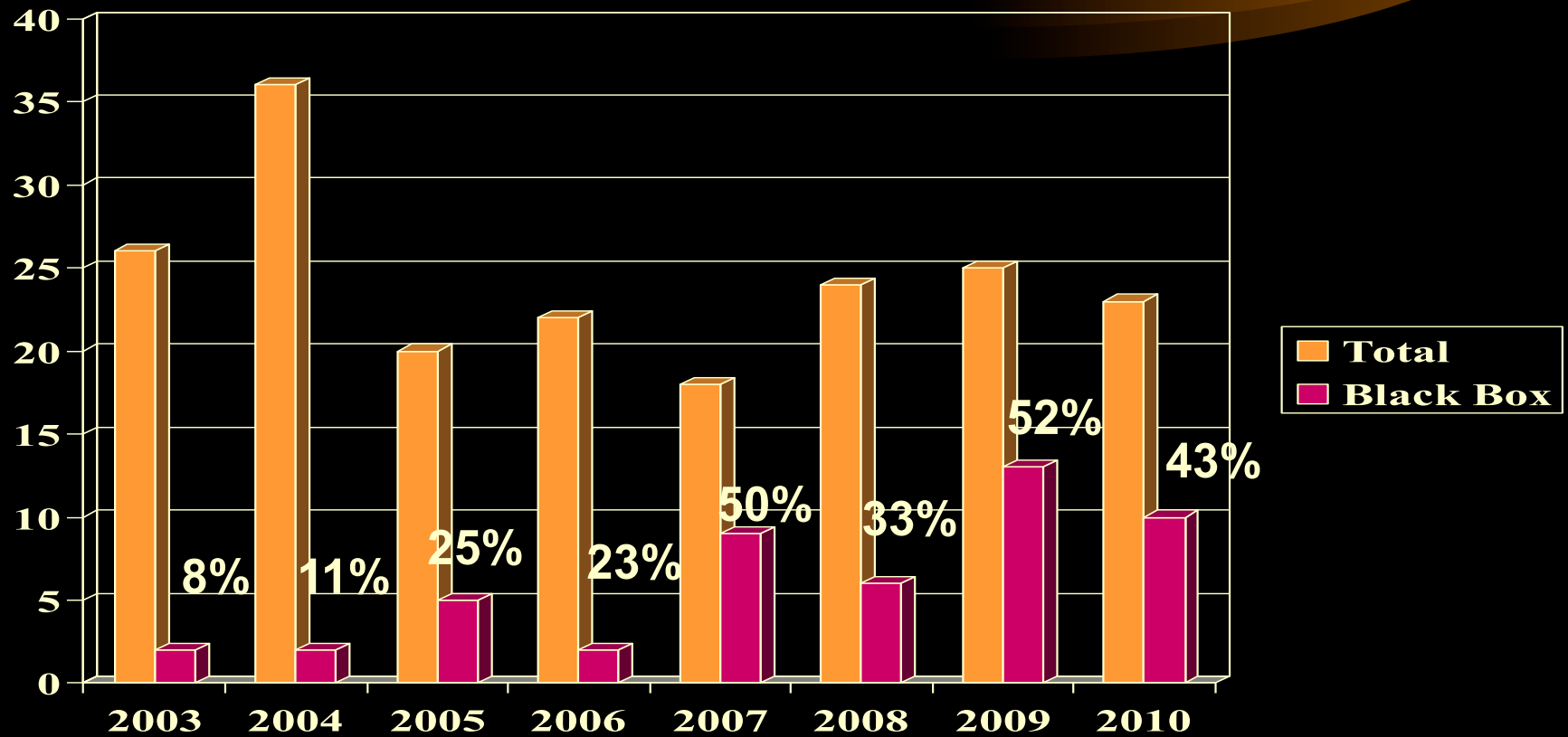
Black Box Warnings

2010

- Ambrisentan
- Clopidogrel
- Conivaptan
- Deferasirox
- LABAs (6)
- Leflunomide
- Maraviroc
- Mirtazapine
- Mitoxantrone
- Nevirapine
- Propylthiouracil
- Ramipril
- Repaglinide/metformin
- Sunitinib
- Tranylcypromine

Drug Approvals

Total vs Black Box Warnings



Implications for Prescribing & Patient Safety

- Postmarketing surveillance is essential to optimize safety during early market life of drug (e.g., ADRs, off-label use) due to limited premarketing data
- Liability related to prescribing outside of PI for safety reasons
- Notification of new BBW data and changes (FDA website, e-lists, Dear health professional letters)

Policies Addressing BBx Warnings



- Drug Listing
- Education
- ADR Reporting
- Review and Maintenance
- Embedded Alerts
- Patient Care Plans Regarding Safety

Patient Care Plans



- Drug Name
- Formulary Restriction
- Summary of Warning
- Physician Actions to Consider
- Nursing Actions to Consider
- Pharmacist Actions to Consider

BBWs: What's Next?



- New labeling modifications
 - Highlights of Prescribing Information
 - Prescriber friendly (bullet summaries)
 - Examples : [Zolinza](#) [Januvia](#)
- Class labeling

BBW Information Resources

- FDA Medication Safety Sites
 - <http://www.fda.gov/medwatch/safety.htm>
- FDA E-mail notification
 - <http://www.fda.gov/medwatch/elist.htm>
- Black Box List
 - <http://blackboxrx.com>