



# FDA Office of Hematology and Oncology Products (OHOP)— 2011 Review



# OHOP

- 130 total employees
- 55 oncologists including 9 pediatric oncologists
- 25 PhDs in Pharmacology/Toxicology
- 24 Regulatory Project Managers
- Support staff



# Prior Organization Structure

- Division of Drug Oncology Products
- Division of Biologic Oncology
- Division of Hematology Products
- Pharm/Tox reviewers located in clinical divisions
- Matrix organization—statisticians, clinical pharmacology, chemistry/manufacturing located in separate offices



## New Divisions and Therapeutic Areas

- **Division of Oncology Products 1 (DOP 1):** Breast, Gynecologic & Supportive care, Genitourinary
- **Division of Oncology Products 2 (DOP 2):** Lung/H&N; Gastrointestinal; Melanoma/Sarcoma; Neuro-oncology, Rare cancers, Pediatric Solid Tumors
- **Division of Hematology Products (DHP):** Benign Heme, Heme Malignancy, Heme Support
- **Division of Hematology Oncology Toxicology (DHOT)**



# Principles Behind Re-organization

- Consistency of advice to sponsors
- Workload more efficient and balanced
- Coordinated understanding of specific diseases and all protocols within disease → efficient review of drug applications
- Staff expertise recognized by external entities
- Formation of Division of Hematology Oncology Toxicology (DHOT) → increased opportunities for review of broader classes of molecules and development of specialized expertise



## Oncology Program—located in OHOP

- Coordinates external oncology activities—monthly teleconference with EMA, Health Canada, professional groups, advocacy groups
- Coordinates internal FDA activities—meetings with CDRH and CBER to discuss applications, guidances, programs



# 2011 New Molecular Entity (NME) Approvals



## CDER 2011 NMEs

Datscan (ioflupane I-123)	Zytiga (abiraterone)	Brilinta (ticagrelor)
Natroba (spinosad)	Tradjenta (linagliptin)	Zelboraf (vemurafenib)
Viibryd (vilazodone HCl)	Victrelis (boceprevir)	Adcetris (brentuximab)
Edarbi (azilsartan)	Edurant (rilpivirine)	Firazyr (icatibant)
Daliresp (roflumilast)	Incivek (telaprevir)	Xalkori (crizotinib)
Benlysta (belimumab)	Dificid (fidaxomicin)	Ferriprox (deferiprone)
Gadavist (gadobutrol)	Potiga (ezogabine)	Onfi (clobazam)
Yervoy (ipilimumab)	Nulojix (belatacept)	Jakafi (ruxolitinib)
Horizant (gabapentin enacarbil)	Arcapta (indacaterol)	Erwinaze (asparaginase <i>Erwinia chrysanthemi</i> )
Caprelsa (vandetanib)	Xarelto (rivaroxaban)	Eylea (aflibercept)



## OHOP 2011 NMEs/Original BLAs

Drug	Indication	Study	Endpoint
<b>Yervoy</b> (ipilimumab)	Unresect/met. melanoma	Randomized, double-blind; 676 pts	OS
<b>Zelboraf</b> (vemurafenib) <i>-Diagnostic</i>	Unresect/met. melanoma BRAFV600E mutation	Randomized, open-label; 675 pts	OS & PFS
<b>Xalkori</b> (crizotinib) <i>-Diagnostic</i> <i>-Accelerated</i>	Local adv/met. ALK+ NSCLC	2 multicenter, single-arm trials; 255 pts	ORR
<b>Zytiga</b> (abiraterone)	Met. castration-resistant prostate cancer	Randomized, plac-controlled; 1,195 pts	OS
<b>Xarelto</b> (rivaroxaban)	DVT prophylaxis, which may lead to PE in knee/hip replacement surgery	3 randomized, double-blind; over 6000 pts	Occurrence of VTE



## OHOP 2011 NMEs/Original BLAs (con't)

Drug	Indication	Study	Endpoint
<b>Adcetris</b> (brentuximab) <i>-Accelerated</i>	HL & ALCL	<ul style="list-style-type: none"><li>• <u>HL</u>: open-label, single-arm; 102 pts</li><li>• <u>ALCL</u>: open-label, single-arm; 58 pts</li></ul>	ORR
<b>Jakafi</b> (ruxolitinib)	Intermediate or high-risk myelofibrosis	2 randomized, Phase 3; 528 pts	% Pts w/ 35% or greater ↓ in spleen vol
<b>Ferriprox</b> (deferiprone)	Transfusional iron overload due to thalassemia	Prospective, planned, pooled analysis of studies; 236 pts	20% ↓ serum ferritin
<b>Caprelsa</b> (vandetanib)	Symp./prog. Medullary Thyroid Cancer	Randomized, double-blind; 331 pts	PFS
<b>Erwinaze</b> (asparaginase <i>Erwinia chrysanthemi</i> )	ALL in pts hypersensitive to <i>E.coli</i> -derived asparaginase	Single-arm, open-label, safety & clinpharm study; 58 pts	Sustained Asparaginase Activity



## 2011 OHOP Approval Highlights

- Two drugs (Zelboraf, Crizotinib) approved concurrently with companion diagnostics
- Two drugs (Zelboraf, Yervoy) for melanoma
- First drug (Adcetris) in decades for Hodgkins
- First drug (Jakafi) for myelofibrosis—use of patient reported outcome



## 2011 OHOP Approval Highlights (con't)

- Flexibility with 3 NME approvals based on single-arm trials and 1 NME approval based on prospectively pooled analysis
- Two NME approvals were accelerated approval and 8 were regular approval
- Continued drug development in prostate cancer with approval of Zytiga (abiraterone)
- Pediatric drug approval (Erwinase)
- Rare diseases—Vandetanib for medullary thyroid cancer
- Variety of endpoints-OS, PFS, PROs, decreased serum ferritin level, spleen size, asparaginase activity



# Accelerated Approval ODAC



# Types of Approval

- Regular approval
  - Direct evidence of clinical benefit (e.g., improved survival or reduction in symptoms)
  - Improvement in established surrogate for clinical benefit (e.g., durable CR's in acute leukemia)
- Accelerated approval
  - Surrogate endpoint reasonably likely to predict clinical benefit (e.g., ORR)



# Accelerated Approval

- For serious or life-threatening diseases
- Drug appears to provide benefit over available therapy
- Approval based on a surrogate that is reasonably likely to predict clinical benefit
- Applicant must verify and describe benefit
- Post-marketing studies usually underway
- The applicant must carry out such studies with due diligence

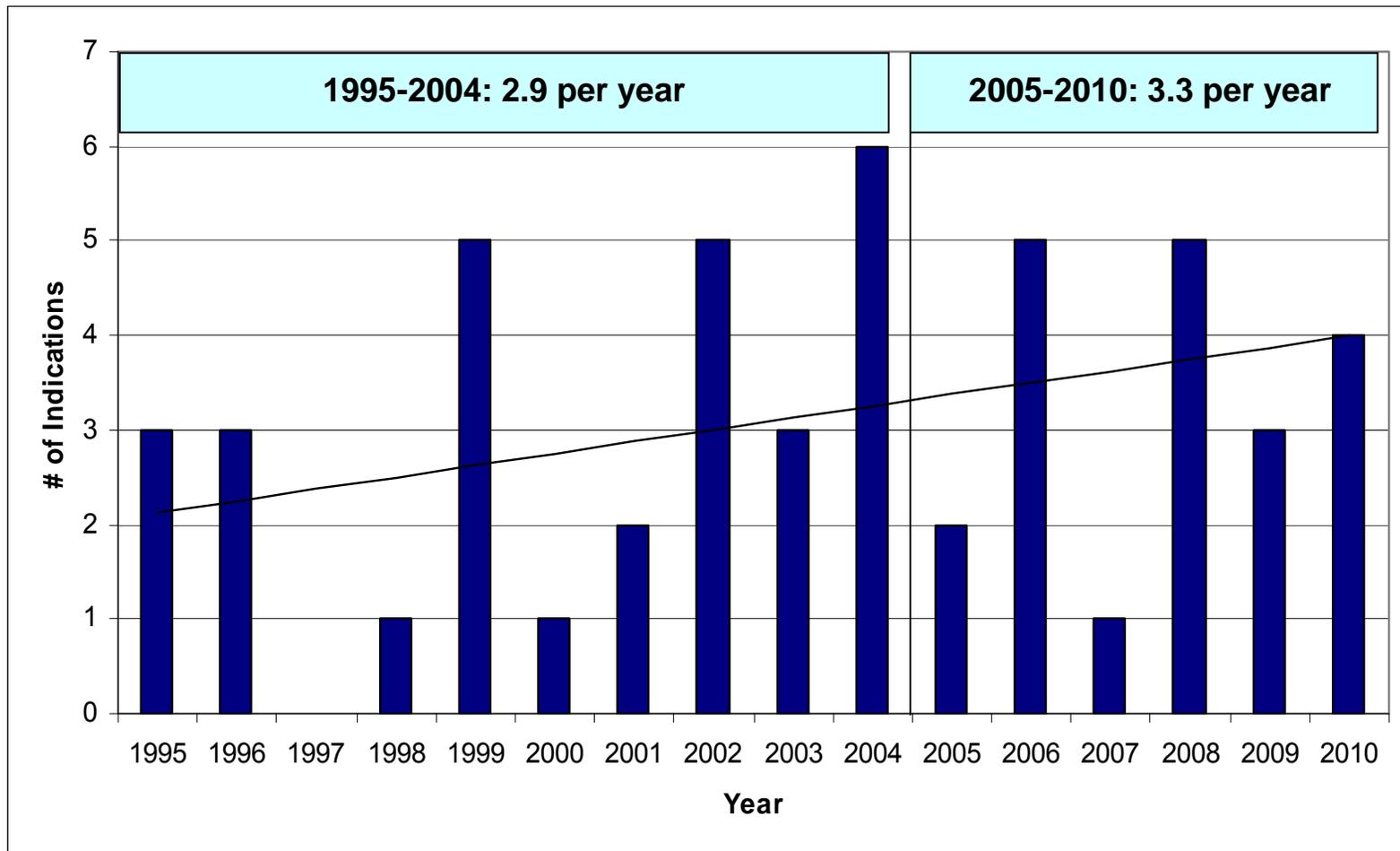


## 2011 ODAC on Accelerated Approval

- 49 new indications, 37 oncology products
  - 55% (27/49) completed PMRs verifying benefit
  - 14.3% (7/49) AA < 24 months
  - 10.2% (5/49) have failed to confirm a benefit
    - Amifostine, celecoxib, gemtuzumab, gefitinib, bevacizumab



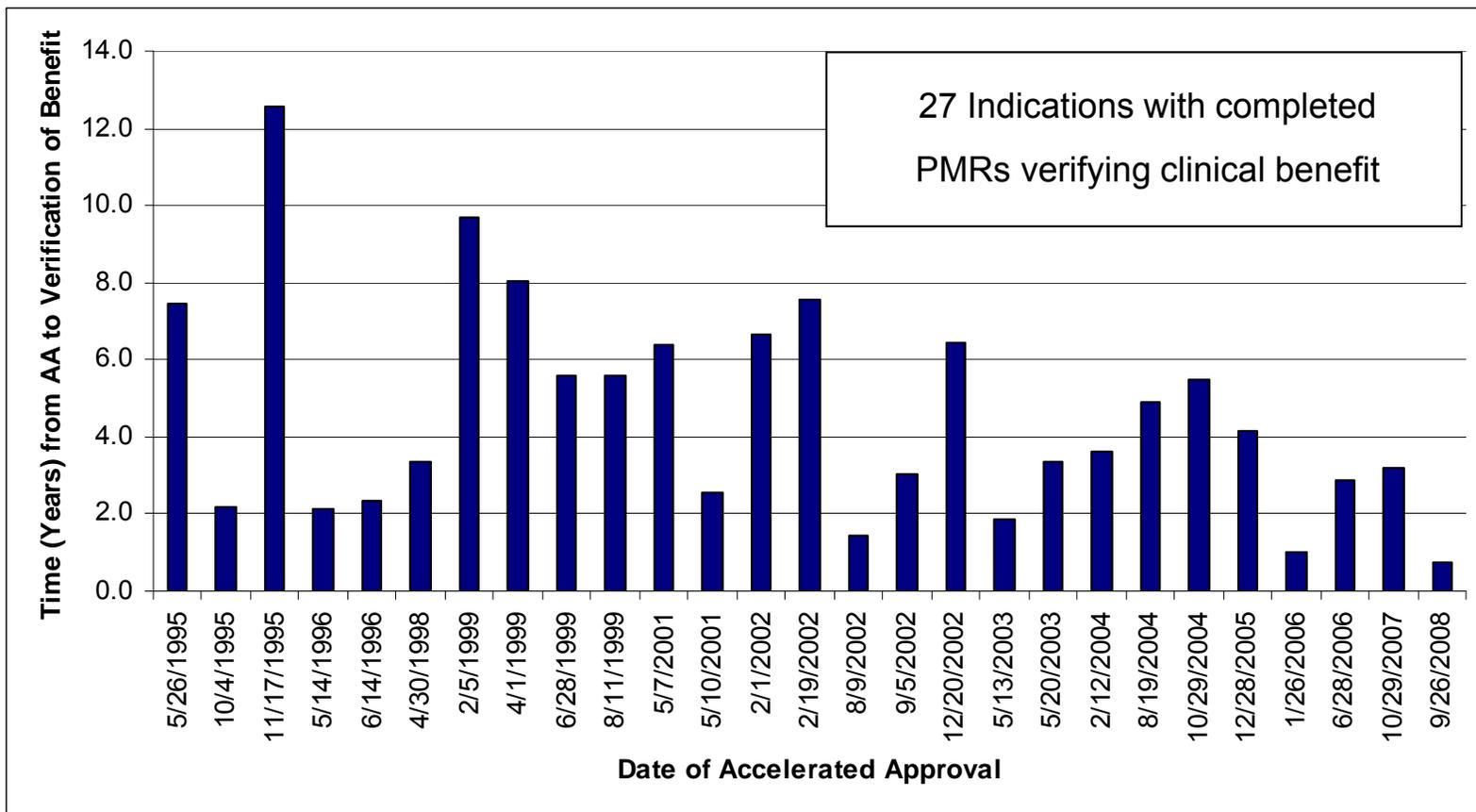
# Accelerated Approvals over Time





## Time from AA to completed trials confirming clinical benefit

Median 3.6 years (0.8 – 12.6)





# Due Diligence

- AA indications that **have not completed confirmatory trials:**
  - The 5 longest times since AA: 11.0, 6.9, 6.0, 6.0 and 5.2 years
  - Celecoxib, Cetuximab, Tositumumab 131, Clofarabine and Nelarabine respectively
- AA indications with **completed trials verifying clinical benefit:**
  - 5 longest times since AA: 12.6, 9.7, 8.1, 7.5 and 7.4 years
  - Liposomal Doxorubicin, Denileukin, Lipo-cytarabine, Ibritumomab and Dexrazoxane respectively
- This represents a suboptimal period of time for a drug to be marketed prior to verification of clinical benefit.



## Indications failing to demonstrate a benefit

AA Date	Drug	Abbreviated Indication	Outcome	Years on Market
3/15/1996	Amifostine	Cisplatin-Induced renal toxicity in NSCLC	Voluntarily Withdrawn 3/28/2006	10.0
12/23/1999	Celecoxib	Reduction in colonic polyps FAP	Voluntarily Withdrawn	11.0
5/17/2000	Gemtuzumab	2 <sup>nd</sup> line AML in patients >60	Voluntarily Withdrawn 6/21/2010	10.1
5/5/2003	Gefitinib	3 <sup>rd</sup> line NSCLC	Voluntarily Withdrawn 7/1/2011	2.1
2/22/2008	Bevacizumab	1 <sup>st</sup> line metastatic HER-2 neg Breast Ca	Withdrawal	2.9



# Withdrawal Procedures

## CFR 21 314.53 and 601.43

- AA indications may be withdrawn by FDA if:
  - Postmarketing study(s) fails to confirm a benefit
  - Failure to perform PMR with due diligence
- Until recently, products that failed to confirm benefit were withdrawn voluntarily by sponsor
- 12/16/2010 FDA initiated withdrawal proceedings for bevacizumab for treatment of HER-2 negative metastatic breast cancer.
  - The first FDA-initiated withdrawal for an accelerated approval oncologic drug indication



## Accelerated Approval ODAC Conclusions

- **FDA remains committed to the accelerated approval pathway**
  - 49 new oncology indications since 1995
  - 3.3 oncology indications per year since 2005
- **AA has provided early access to clinically beneficial cancer therapies**
  - 27 oncology indications have confirmed benefit in post-marketing trials
  - Made available a median of 3.6 years prior to the verification of their clinical benefit



# Draft Guidance: *In Vitro* Companion Diagnostic Devices

[www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf)



# Diagnostic Tests

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- Drugs approved for a target-selected sub-population need an assay that is
  - linked to assay used in clinical trials
  - reliable
  - widely available
- Assays are regulated by CDRH
- Involving CDRH:
  - by sponsor and/or diagnostic partner directly
  - by CDER during Pre-IND and EOP2 meetings



# Draft Guidance

- Identify patients who are most likely to benefit from drug
- Identify patients likely to be at increased risk for serious adverse reactions
- Monitor response to treatment for purpose of adjusting treatment (schedule, dose, discontinuation) to achieve improved safety or effectiveness



## IVD Guidance

- Novel Drug—If IVD is *essential* to safety and efficacy, then FDA does not believe drug can be approved without approval (clearance) of IVD
- Exceptions: *Life-threatening diseases*—if benefits from drug outweigh risks of not having IVD approved. *Already approved drugs--safety issues*



# Guidance: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination

<http://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/UCM236669.pdf>



## Codevelopment is Appropriate?

- Intention is to treat serious disease
- Compelling biological rationale (e.g., drugs inhibit distinct targets)
- Preclinical model (*in vivo* or *in vitro*) or short term clinical study suggests that combination has substantial activity and provides greater than additive activity or more durable response
- Compelling reason why agent cannot be developed individually—i.e. drugs have limited activity when used as monotherapy
  - Example: two investigational drugs target different pathways



# Phase 1

- Safety profile for individual drugs should be characterized in phase 1 studies, including DLT, PK parameters, effect on biomarker
- If not possible to characterize safety of individual drugs, nonclinical studies of combination should support initial dosing of combination
- Safety/dosing of combination could use sequential testing in same patient—subjects receive A, then B, then AB



# Clinical Pharmacology

- Same pharmacology studies for each drug in combination as if drugs developed separately
- Drug interaction potential follows same sequence as in other development program—results of *in vitro* metabolism studies inform need for *in vivo* drug interaction studies
- Dose response should be evaluated for each drug of the combination. If one drug has no activity alone, dose response should be assessed when the drugs are administered in combination



# Proof of Concept Studies

- Demonstrate the contribution of each component of the combination to extent possible and needed (given nonclinical/pharmacological data)
- Provide evidence of effectiveness of combination
- Optimize dose/doses of combination for phase 3 trials



## Confirmatory Trials: Phase 3

- If findings from preclinical models and/or phase 2 trials adequately demonstrate contribution of each drug, phase 3 trials comparing the combination to SOC will be sufficient to establish efficacy
- Unexpected toxicity attributed to one drug combination may use lower dose of drug



# 2012 Projects

- Draft Guidance: Path CR in the neoadjuvant treatment of breast cancer
- Joint workshops with professional groups: Minimal Residual Disease as a registration endpoint in pediatric ALL, adult CLL, AML
- PFS: Role of Independent Radiographic Review of scans
- Draft Guidance: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations: public comment February 2012