Accelerated Approval (AA) for Oncology Drug Products: An Update and Regulatory Overview

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Outline

- **Regulatory Background**
- Accelerated Approvals Update
- Conclusions
- ODAC Agenda

Regulatory Background

- Regular approval – substantial evidence of clinical benefit demonstrated prior to approval based on prolongation of life, a better life or an established surrogate for either of the above.

- AA regulations 1992
  - 21 CFR Part 314, Subpart H (for drugs)
  - 21 CFR Part 601, Subpart E (for biologics)

- Accelerated approval (AA) - designed to hasten the delivery of products appearing to provide a benefit for serious or life-threatening illnesses lacking satisfactory treatments.

Accelerated Approval

- "…a **surrogate endpoint** that is **reasonably likely**…to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."
- "Approval… subject to the requirement that the applicant **study the drug further**, to verify and describe its clinical benefit…"
- "…Postmarketing studies would usually be **studies already underway**."
- "…such studies must also be **adequate and well-controlled**."
- "…The applicant shall carry out any such studies with **due diligence**."

Critical Elements of Accelerated Approval:

- Serious or life threatening diseases
- Provides a benefit over existing therapies
- A surrogate reasonably likely to predict clinical benefit
- Subject to the requirement to verify benefit
- Post-marketing trials would usually be underway
- Applicant should carry out studies with due diligence

If post-marketing studies fail to demonstrate clinical benefit or applicant fails to perform required post-marketing studies with due diligence, FDA may withdraw approval, following an open public hearing.

Guidance: “Available Therapy”

- Available therapy (and the terms existing treatments and existing therapy) should be interpreted as therapy that is **specified in the approved labeling of regulated products, with only rare exceptions.**
  - Exceptions may include established oncologic treatments.

http://www.fda.gov/downloads/RegulatoryInformation/Guidances

Uncertainty

- Post-marketing trials to confirm clinical benefit needed when there is uncertainty
  - Relationship of the surrogate endpoint to clinical benefit
    - Response rate, Progression free survival
  - Observed clinical benefit to ultimate outcome.
    - Dexrazoxane decreased cardiac toxicity, but there was concern regarding tumor-protective effect and thus uncertainty with respect to ultimate outcome.

1996 Presidential Communication

- Established objective tumor shrinkage (including partial response) as a surrogate endpoint reasonably likely to predict a benefit
- Objective response and its frequency and duration should outweigh the associated toxicity and risk
- Post-approval studies will be required to further define the benefit

Facilitating Accelerated Approval

- Post-marketing studies need not be carried out in the same population for which the drug was approved
- An indication approved under accelerated approval **which has not yet verified clinical benefit with its post-marketing trials** is NOT considered existing therapy.
  - Does not preclude the approval of additional therapies for that indication under AA.

EMA – Conditional Marketing Authorization 4/2/2006

- Approval types
  - Normal, Exceptional, Conditional
- Conditional Marketing Authorization
  - Demonstrates positive benefit:risk based on preliminary evidence
  - “Specific Obligations” to provide further data necessary to become a Normal approval.
  - Authorization valid for ONE YEAR (renewable)
  - Clear information to patients and providers on the conditional nature of the approval
  - Financial penalties if fail to observe obligations

Food and Drug Administration Amendments Act of 2007 (FDAAA)

- Purpose:
  - To amend the Federal Food, Drug, and Cosmetic Act to enhance the post-marketing authorities of the Food and Drug Administration
- Under FDAAA, failure to conduct a post-marketing study under the accelerated approval regulations is deemed to be a violation.
- Violations under FDAAA are subject to financial penalties

ODAC on Accelerated Approval

- First held in 2003 with the goal to:
  - Identify applications that were delayed in fulfilling their post-marketing requirements
  - Discuss challenges unique to those applications
  - Solicit input for improving the AA process

2003 ODAC on Accelerated Approval

- 19 indications for 16 drugs
  - 7/19 (37%) less than 18mo old
  - 4/19 (21%) completed trials verifying benefit
  - 8/19 (42%) presentations
- Early integration of accelerated approval planning into a comprehensive drug development plan is critical

2005 ODAC on Accelerated Approval

- 28 indications for 24 drugs
  - 10/28 (35.7%) AA < 36 months
  - 10/28 (35.7%) completed PMRs verifying benefit
  - 2/28 (7.1%) restricted distribution or withdrawn
    - Amifostine-withdrawn
    - Gefitinib-restricted distribution
  - 6/28 (21.4%) presentations

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2011 ODAC on Accelerated Approval

- 49 new indications, 37 oncology products
  - 27 of 49 (55%) completed PMRs verifying benefit
  - 7/49 (14.3%) AA < 24 months
  - 5/49 (10.2%) have failed to confirm a benefit or have or are in the process of withdrawing their indication after not completing their confirmatory trials
    - Amifostine, celecoxib, gemtuzumab, gefitinib, bevacizumab
  - 6/49 indications will be presented today

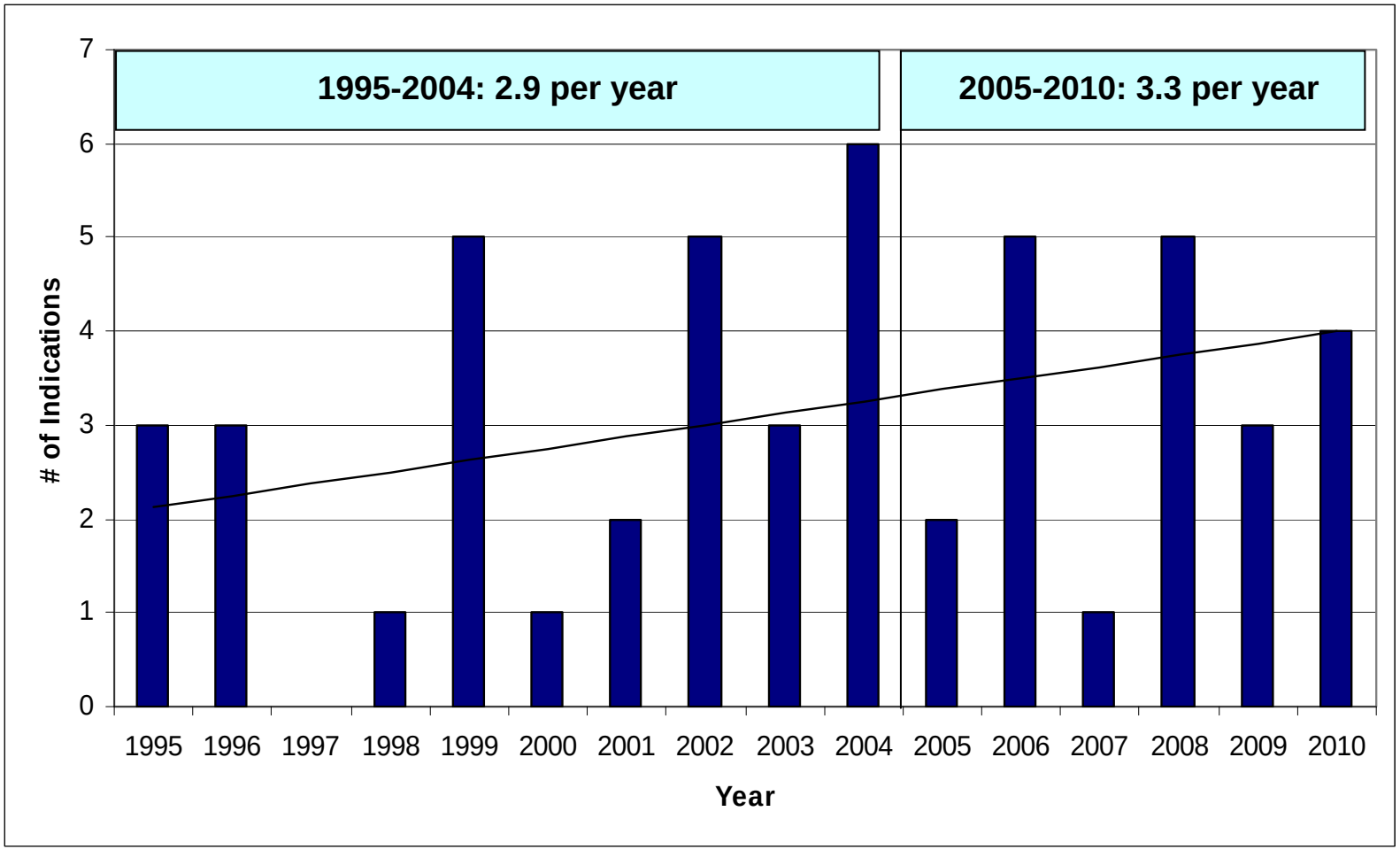
Trial Design – Initial AA

- Trial design for initial accelerated approval (AA)
  - 20/49 were randomized comparative
  - 29/49 were single arm
- Surrogate endpoints used:
  - Response Rate and Duration = 36
  - Time to Event = 10 (PFS, DFS and TTP)
  - Other = 3
    - measures of cardiomyopathy, creatinine clearance and colonic polyp incidence

Trial Design: Post-Marketing

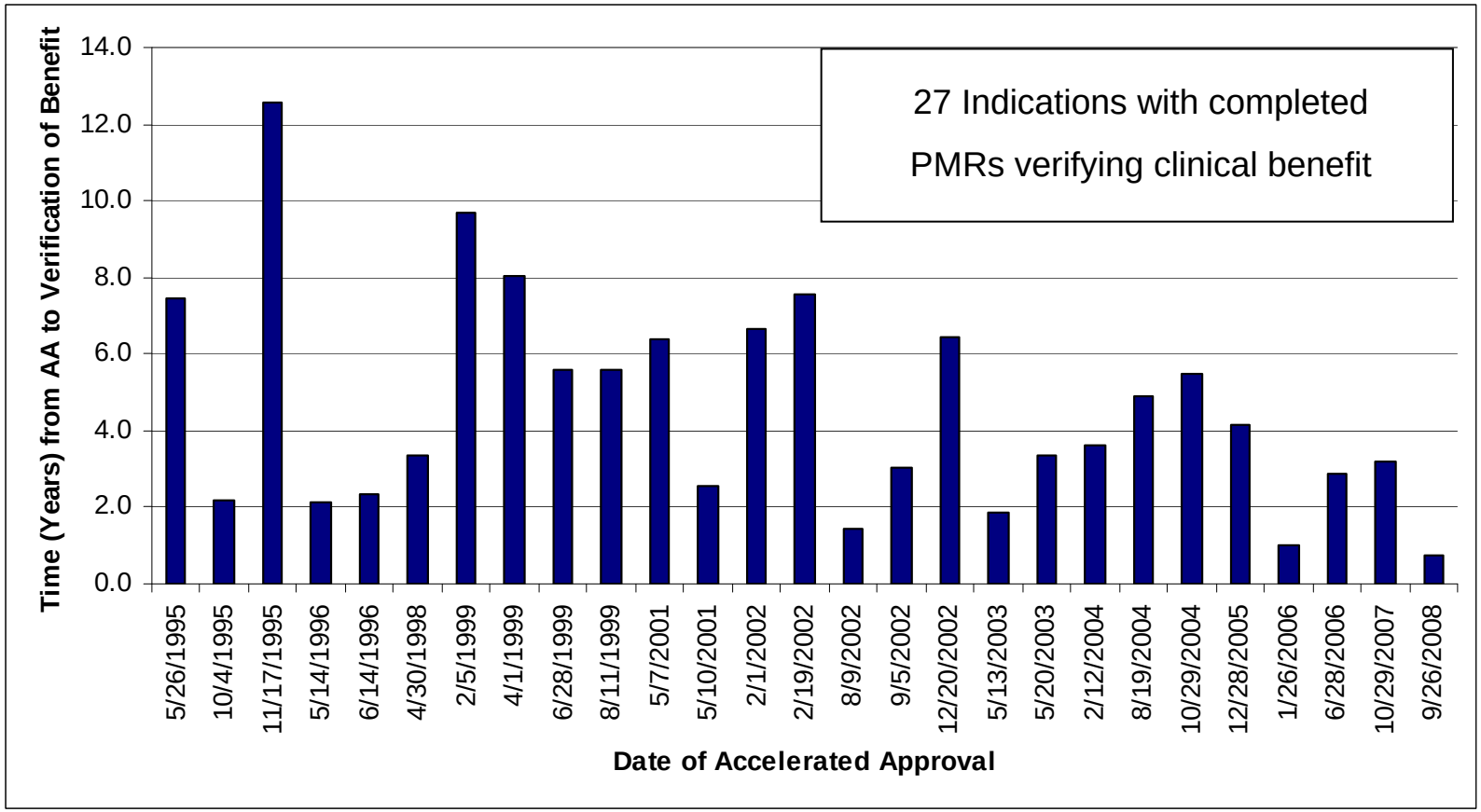
- Post-marketing trial design leading to verification of clinical benefit
  - Nearly all trials were randomized (24/27)
  - Endpoints for confirmatory trials
    - Survival 10/27
    - PFS or TTP 7/27
    - RR 6/27
      - Kaposi's Sarcoma, Cutaneous T Cell Lymphoma, Lymphomatous Meningitis, Ph+CML (3)
    - DFS 3/27
    - Cardiac safety 1/27

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	In process of Voluntary Withdrawal	11.0
5/17/2000	**Gemtuzumab**	**2nd line AML in patients >60**	**Voluntarily Withdrawn 6/21/2010**	**10.1**
5/5/2003	**Gefitinib**	**3rd line NSCLC**	**Restricted Distribution 6/17/2005 ***	**2.1**
2/22/2008	**Bevacizumab**	**1st line metastatic HER-2 neg Breast Ca**	**Withdrawal proceedings underway**	**2.9**

** Access limited to patients already obtaining benefit from gefitinib.*

Withdrawal Procedures

CFR 21 314.53 and 601.43

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

Bevacizumab indication on the market for a relatively short amount of time

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5/17/2000	Gemtuzumab	2nd line AML in patients >60	Voluntarily Withdrawn 6/21/2010	10.1
5/5/2003	Gefitinib	3rd line NSCLC	Restricted Distribution 6/17/2005	2.1
2/22/2008	**Bevacizumab**	**1st line metastatic HER-2 neg Breast Ca**	**Withdrawal proceedings underway**	**2.9**

-**Post marketing trials for bevacizumab in metastatic breast cancer, AVADO and RIBBON-1, were <u>ongoing at time of accelerated approval</u>**

-**This may, in part, explain the relatively short period of time on market**

Marketing potentially ineffective therapies: The risk of the AA process

- The proportion of indications failing to confirm a benefit (10.2%) has slightly increased since 2005 (7.1%).
  - The delay from accelerated approval to restriction or withdrawal of the five indications is 2.1, 2.9, 10.0, 10.1 and 11.0 years
- Decreasing the time on the market for potentially ineffective therapies is critical
  - Due Diligence
  - Early integration of accelerated approval planning

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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

Conclusions

- **Accelerated approval tradeoff: earlier marketing of drugs but increased uncertainty**
  - 5/49 (10.2%) failed to confirm a benefit or failed to complete confirmatory trial accrual
- **Due diligence** and **early integration** of post-marketing trial design into a comprehensive drug development plan remains critically important to attenuating exposure to potentially ineffective drugs

"Given that there seems to be a sense of urgency in completing the trial upon which accelerated approval is granted, is it fair to assume that we would have the same sense of urgency for the confirmation of benefit? In the first case we are in danger of keeping dying patients away from potentially effective therapies, however there is an equal danger that we are exposing patients to the toxicity of therapy without certainty of benefit. In both cases it is incumbent upon those in drug development to decrease these time periods…"

– Thomas Fleming, 2003 ODAC on Accelerated Approval

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Sponsors presentations selected based on:

- Granted AA prior to 2009
- Outstanding post-marketing requirements
- Not under active FDA Review

AA Date	Drug	Abbreviated AA Indication	Years on Market as of 12/31/2010
2/12/2004	Cetuximab	With irinotecan in EGFR+ mCRC refractory to irinotecan-based chemotherapy	6.9
12/22/2004	Tositumumab-I131	Refractory CD20+ low grade FL or transformed NHL not treated with Rituximab	6.0
12/28/2004	Clofarabine	Pediatric relapsed/refractory ALL after 2 prior regimens	6.0
10/28/2005	Nelarabine	Relapsed/refractory T cell ALL and T cell lymphoblastic lymphoma after 2 prior regimens	5.2
9/27/2006	Panitumumab	EGFR+ mCRC following flouropyrimidine, oxaliplatin and irinotecan containing chemo	4.3
12/19/2008	Imatinib	Adjuvant treatment of adult CD117+ GIST	2.0

Sponsor Presentations

For Ongoing Confirmatory Studies:

1. Has accrual been satisfactory?
2. If not, what strategies would you suggest to address this?

For Planned Trials:

1. Have changing circumstances impeded the conduct of such trials ?
2. If so, describe them and indicate what alternative designs should be contemplated

Accelerated Approval (AA) Overview of HIV Drug Approvals

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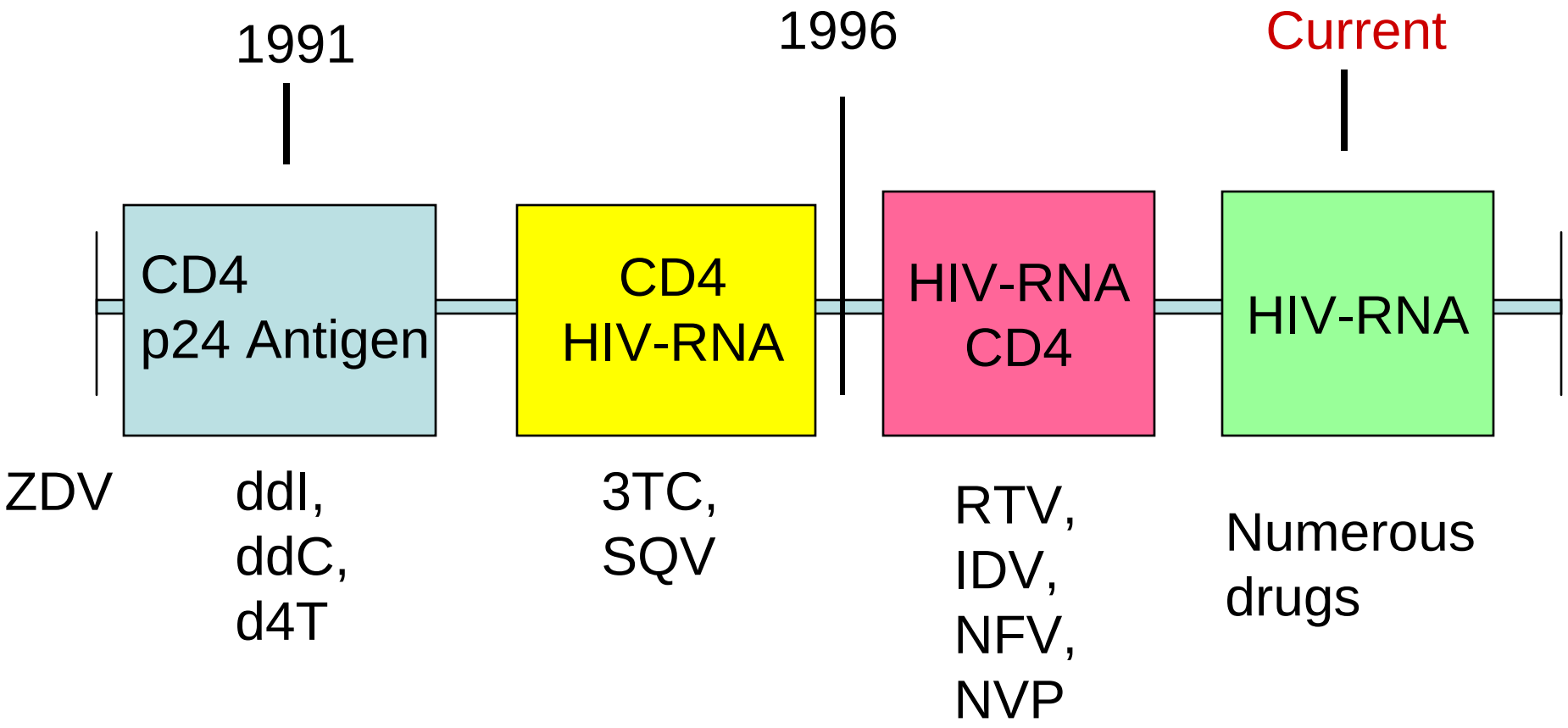
Outline

- Antiretroviral Accelerated Approval History
- Validation Process of Viral Load
- Accelerated Approvals: Times to Regular Approval
- Conclusions

Accelerated Approval History

- Regulations for accelerated approval codified in 1992 in response to AIDS epidemic
- Didanosine was the first drug approved using this type of process in 1991
- Hivid technically the first drug approved under AA regs
- HIV Drug Approval History has two distinct periods.
  - Period 1: 1987-1996
  - Period 2: 1997-present

Evolution of Surrogate Endpoints



Antiretroviral Approval History

- After Accelerated Approval, the applicant must: "Verify and describe the drug's clinical benefit…where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit."
- Prior to 1997, Clinical Endpoint studies required after accelerated approval
  - Endpoint = CDC criteria for an AIDS defining Event (20) and death
- After 1997, HIV-RNA considered validated endpoint

Clinical Endpoints

- Originally a case definition used for epidemiologic purposes
- Approximately 20 different conditions
- Infections, syndromes (wasting), malignancies
- Infections: viral, fungal, bacterial, parasitic, mycobacterial
- Occur at different levels of immune function, but in clinical trials weighted equally
- Studies counted only first occurrence for most infections

Difficulties with Conducting Clinical Endpoint Studies after 1996

- Real-time viral load monitoring became standard of care in 1996.
- Physicians and Study Participants unwilling to stay on randomized treatment after viral rebound and wait for clinical progression or even CD4 cell decline.
- Because HAART (Highly Active Antiretroviral Treatment) greatly reduced the incidence of clinical events, Clinical Endpoint Studies would have required very large patient numbers and would likely be confounded by treatment switches based on viral load changes.

Collaborative Approach

- 1996 Surrogate Marker Working Group
  - Industry, academia, and government
- Sponsors, FDA, NIH analyzed data to assess:
  - Correlations between viral load and clinical outcome
  - Correlations between short-term viral load suppression and durability of viral load response
- July 1997 Antiviral Advisory Committee
- Meta-analysis

Analyses: Summary of Findings

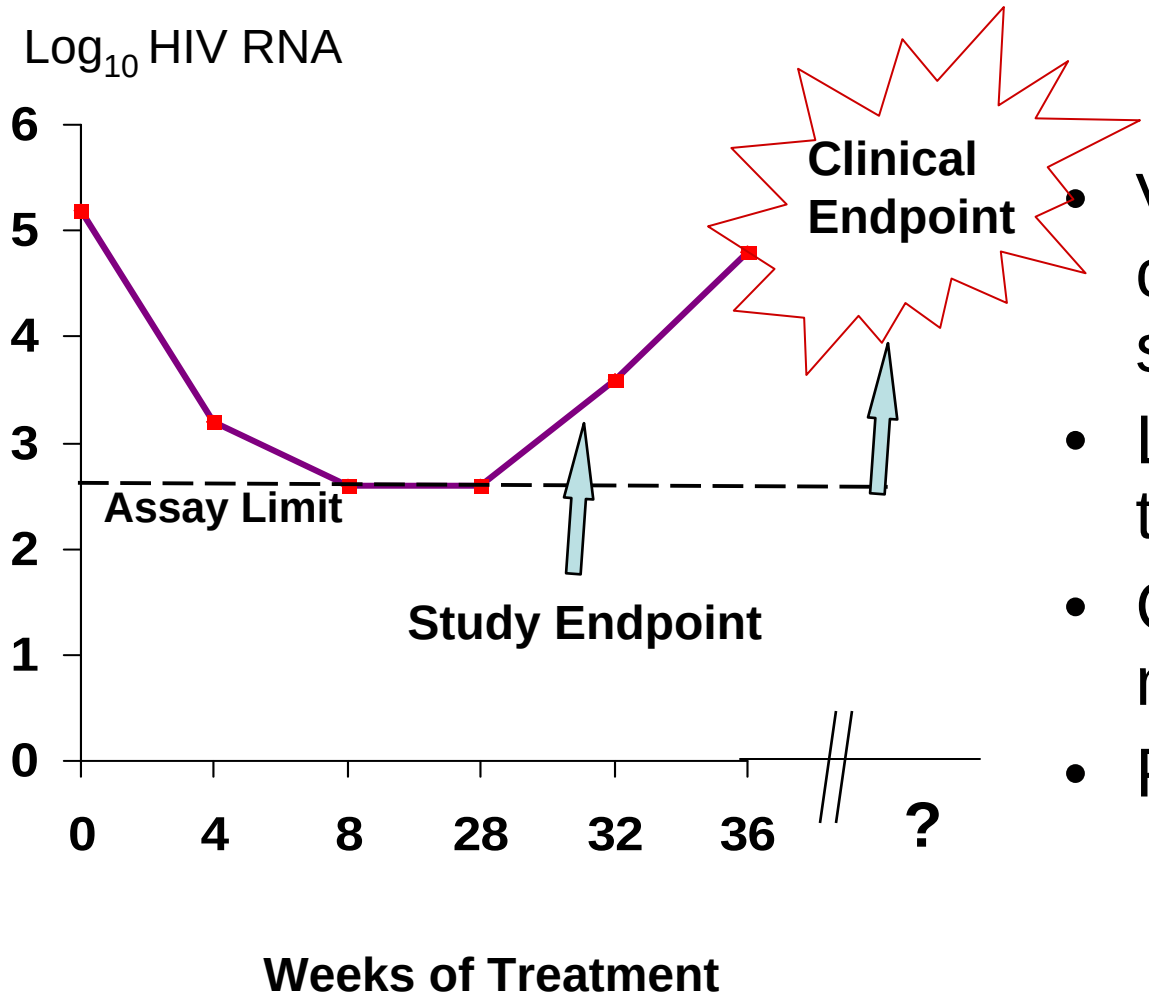
- HIV RNA decreases (> 0.5 log) are associated with lower risks of disease progression
- Greater Reductions associated with lower risks of progression
- More Sustained Reductions (> 8-12 weeks) in HIV RNA are associated with lower risks of disease progression
- Suppression of HIV-RNA below assay quantification is associated with longer duration of virologic suppression and less emergence of HIV resistance.
- Goal: “complete” and durable viral load suppression

July 1997 AC Meeting: Conclusions

- HIV RNA is a suitable endpoint for:
  - Accelerated Approval (24 weeks)..AND..
  - Regular Approval (48 Weeks)
- Concordance with other markers (CD4)

Typical Accelerated Approval Study Design

- Randomized placebo controlled two-arm study in patients who have failed multiple drug regimens but may have one or two drugs left
- Arm 1: new regimen consisting of Optimized Therapy with approved drugs
- Arm 2: Optimized Therapy plus investigational drug
- If viral suppression does not occur or occurs and then rebounds, patient can exit trial and is considered a nonresponder (endpoint not lost)



- Virologic Endpoint captured before Rx switches
- Less confounding due to treatment switches
- Coincides with clinical management
- Participant Acceptance

Antiretroviral Approval History

Regular Approval supported by Clinical Endpoint

Drug Name	Approval Date	Surrogate	Time to Full Approval
Retrovir (zidovudine, AZT)	MAR 87	N/A	N/A
Videx (didanosine, ddI)	OCT 91	CD4, p24	11 mos
Hivid (zalcitabine, ddC)	JUN 92	CD4, p24	49 mos*
Zerit (stavudine, d4T)	JUN 94	CD4, p24	18 mos
Epivir (lamivudine, 3TC)	NOV 95	CD4, HIV-RNA	17 mos
Invirase (saquinavir)	DEC 95	CD4, HIV-RNA	10 mos
Norvir (ritonavir)	MAR 96	HIV-RNA, CD4	38 mos*
Crixivan (indinavir)	MAR 96	HIV-RNA, CD4	23 mos
Viramune (nevirapine)	JUN 96	HIV-RNA, CD4	69 mos

**accelerated and traditional approvals split across indications (naive/experienced)*

Antiretroviral Approval History

Drug Name	Approval Date	Surrogate	Time to Full Approval
Viracept (nelfinavir)	MAR 1997	HIV-RNA, CD4	38 mos
Rescriptor (delavirdine)	APR 1997	HIV-RNA, CD4	49 mos
Sustiva (efavirenz)	SEP 1998	HIV-RNA, CD4	17 mos
Ziagen (abacavir)	DEC 1998	HIV-RNA, CD4	64 mos
Agenerase (amprenavir)	APR 1999	HIV-RNA	25 mos
Kaletra (lopinavir/ritonavir)	SEP 2000	HIV-RNA	26 mos
Viread (tenofovir)	OCT 2001	HIV-RNA	53 mos
Fuzeon (enfuvirtide)	MAR 2003	HIV-RNA	19 mos
Reyataz (atazanavir)	JUN 2003	HIV-RNA	N/A
Emtriva (emtricitabine)	JUL 2003	HIV-RNA	N/A
Lexiva (fosamprenavir)	OCT 2003	HIV-RNA	N/A
Aptivus (tipranavir)	JUN 2005	HIV-RNA	28 mos
Prezista (darunavir)	JUN 2006	HIV-RNA	17 mos
Selzentry (maraviroc)	AUG 2007	HIV-RNA	15 mos
Isentress (raltegravir)	OCT 2007	HIV-RNA	15 mos
Intelence (etravirine)	JAN 2008	HIV-RNA	22 mos

Antiretroviral Drug History

- All HIV drugs receiving accelerated approval eventually received regular approval
- Longest time to regular approval was 69 months or 5 years until submission of NDA
- 3 drugs received regular approval at initial approval and one drug had a split approval at initial approval
- 13 drugs were approved on 24 weeks of viral load data confirmed by 48 weeks of viral load data
- Two trials used to support regular approval in almost all cases. Trial size typically 600 patients per trial.

AAs: Average Times Until Regular Approval

- Prior to validation of viral load: 29 mos.
- After validation of viral load: 30 mos.
- Last decade: 24 mos.
- Given 10 month review clock, sponsors submitted applications within 14-20 months post accelerated approval

Reasons for Longer Times Under AA

- Initiating one or more confirmatory trials post-approval
  - Viracept, Ziagen, Viread
- Drug had less activity than other drugs in the same class
  - Rescriptor
- Approval Indication Split (accelerated/regular) according to patient population. Took longer to confirm in one population.
  - Norvir, Hivid

Conclusions

- Accelerated Approval process worked quite well for antiretrovirals
- Drug development for HIV is very different than for oncology
- Primary reason: viral load is an excellent surrogate that correlates well with disease progression
- Early and late viral load changes are highly correlated
- Ability to enroll two trials which often supported both approvals (24 weeks for AA and 48 weeks for regular approval)