

Accelerated Approval in 2008

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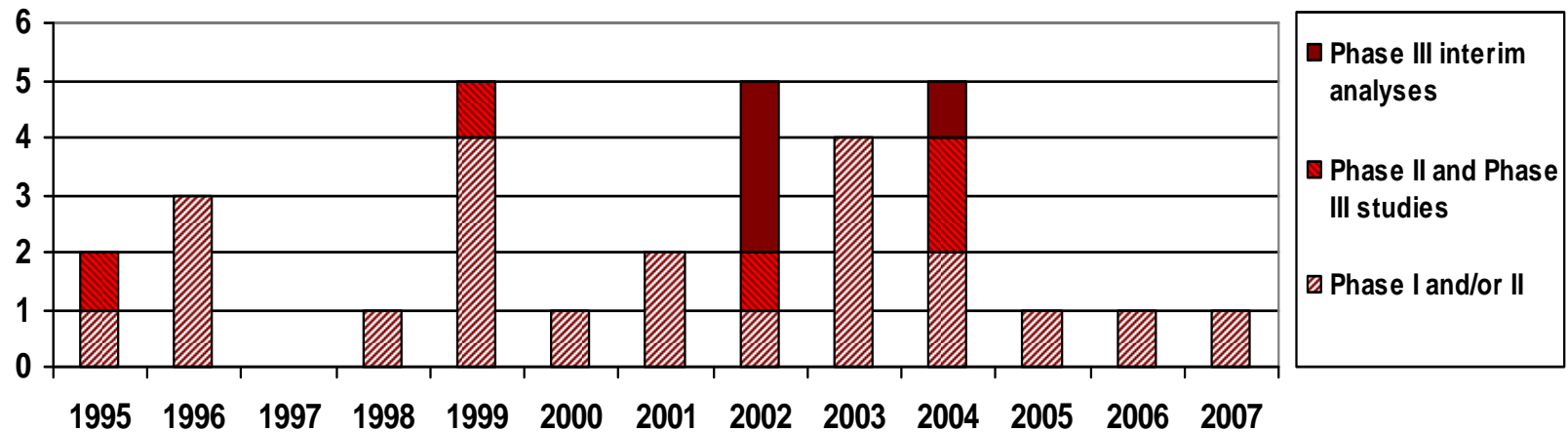
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Background on AA

- Established in 1992
- Approval based on surrogate outcome measures
 - Tumor response, lab response, etc.
- Complements other mechanisms:
 - Regular Approval
 - Fast Track, priority review
 - (Off-label prescribing)

13 years of Accelerated Approval

Indications Receiving Accelerated Approval (n=32)



Summary of AA for Cancer

- 27 drugs for 32 indications
 - 29 cancer treatment, 2 supportive care, 1 cancer prevention
 - 20 new molecular entities
- Clinical trials supporting AA
 - 83% of indications supported by Phase I or II
 - 30% of indications supported by Phase III
 - 18% of indications supported by interim analysis of Phase III

Advantages and Disadvantages of AA

■ Benefits of AA

- Allow early release and limited marketing

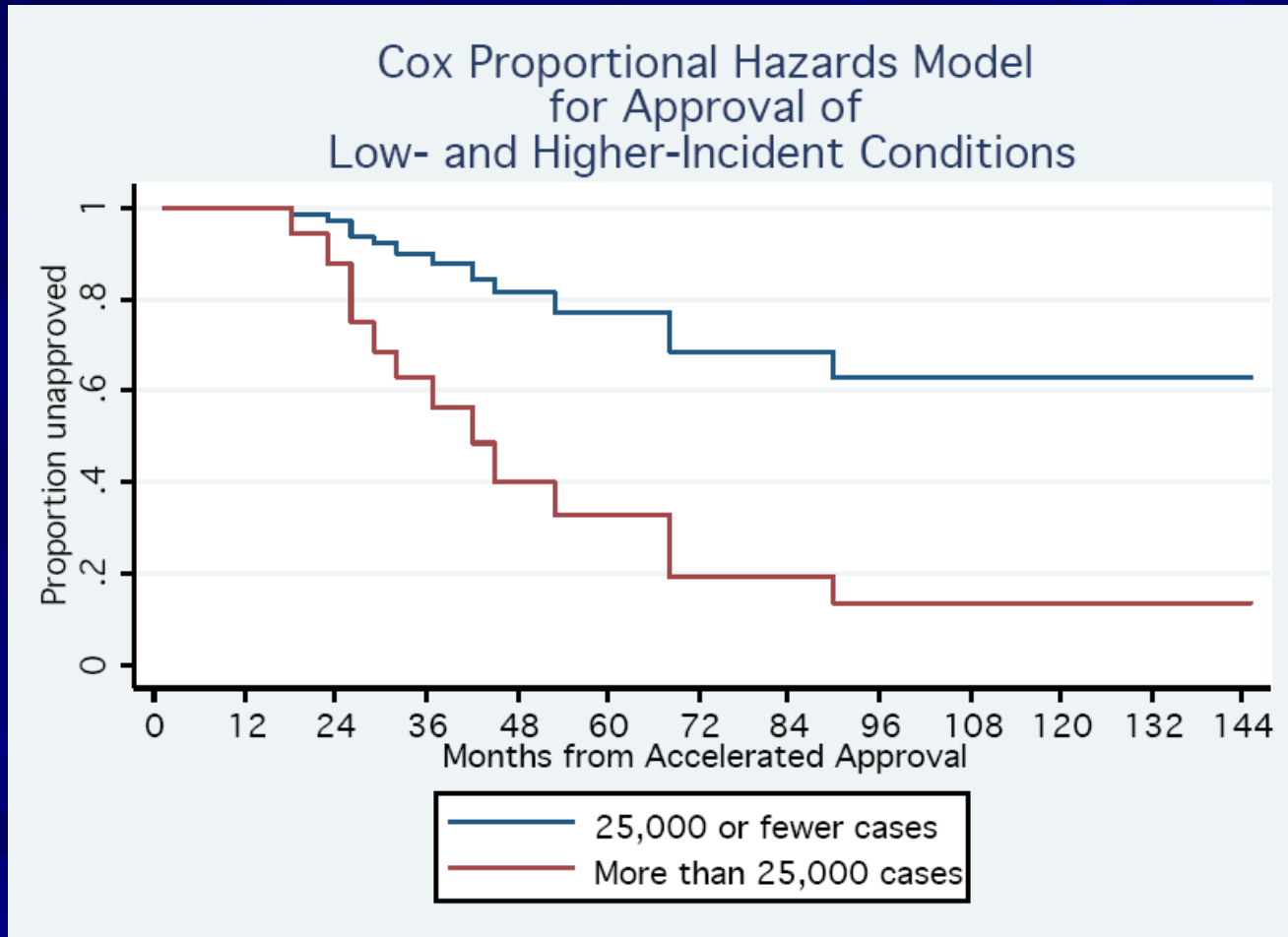
■ Downside

- Surrogate outcomes \neq survival or QOL
- Small number of patients in approval study
- Often based on Phase II trials compared to historical control
- Significant commitment to post-marketing Phase III trials
- Potential loss of approval

Post-marketing trials

- Nearly impossible to complete
 - Rational consumer does not want placebo
 - May violate clinical trial ethics
 - Trials are large and difficult to coordinate, particularly for rare indications
 - Follow-up study for nelarabine requires 1380 patients with 4 year follow-up. (1000 diagnosed annually)
- New technology faster than post-marketing studies
 - Liposomal doxorubicin, Amifostine

Completion of Follow-up studies



Conversion to Regular Approval

- Roughly 50% of AA indications have completed post-marketing studies
- Gefitinib use restricted after negative phase III trial
- Amifostine AA forfeited
 - Unable to complete follow-up trial

Recommendations to Increase Completion Rate

- ODAC meetings 2003 and 2005:
 - Add clinical trial sites in other countries
 - Follow-up after trial
 - Issues of coercion
 - Develop plans for completion of studies prior to submission of application
 - Use interim analysis of Phase III trials

Political Fallout

“It is outrageous that drug companies and the FDA have been dragging their feet when it comes to conducting required postmarketing studies... the American people have been left in the dark about their gamble when taking these drugs.”

Edward Markey (D-Mass)

Political Fallout

■ Subsequent legislation:

- Civil penalties for failure to conduct studies with due diligence
- Enhanced penalties for any harm that occurs to a consumer because postmarketing studies not completed in a timely manner.
- Provision for withdrawal of AA when postmarketing studies not completed.

Result of political pressure

- FDA has approved fewer AA applications:
 - Plan for Phase III completion required
 - Interim analysis of Phase III is preferred
- Corporations have acted rationally:
 - AA used sparingly
 - Second indications for small markets covered by off-label compendia listing
 - AA used for new molecular entities, or for expensive drugs with large potential markets

Additional FDA Changes

- Development time for new molecular entity including approval
 - 1995-1998
 - 4 AA – 2000 days
 - 11 Regular Approval 5300 days
 - 2002-2004
 - 7 NME with AA, 7 with RA, median development time of 2100 days regardless of approval pathway

Conclusions

- AA best suited for early distribution of new molecular entities, often irrelevant for second indications
- Time for standard or accelerated approval for NME has nearly equalized
- Post-marketing Phase III trials difficult to complete
- Consumers and manufacturers are acting rationally, resulting in decreased utilization of accelerated approval pathway

Potential Solution

- Instead of post-marketing Phase III study, allow use of Phase II studies to measure efficacy
- Include prospective drug safety monitoring as part of accelerated approval process