Coping with the Consequences of Accelerated Approval

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Objectives

To discuss:

- The significance of the shifting landscape and the dilemmas of the FDA accelerated approval process
- The current landscape of accelerated approval processes in the US and globally
- Global responses to the accelerated approval of products
- US payer options for managing coverage decisions given accelerated drug approvals

Coping with the Consequences of Accelerated Approval

Global Experience

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Outline of Presentation

- What are the objectives of accelerated approval programs?
- Have these objectives been met?
- What have been the consequences for payers?
- What actions can global payers take?

Objectives of Accelerated Access Programs

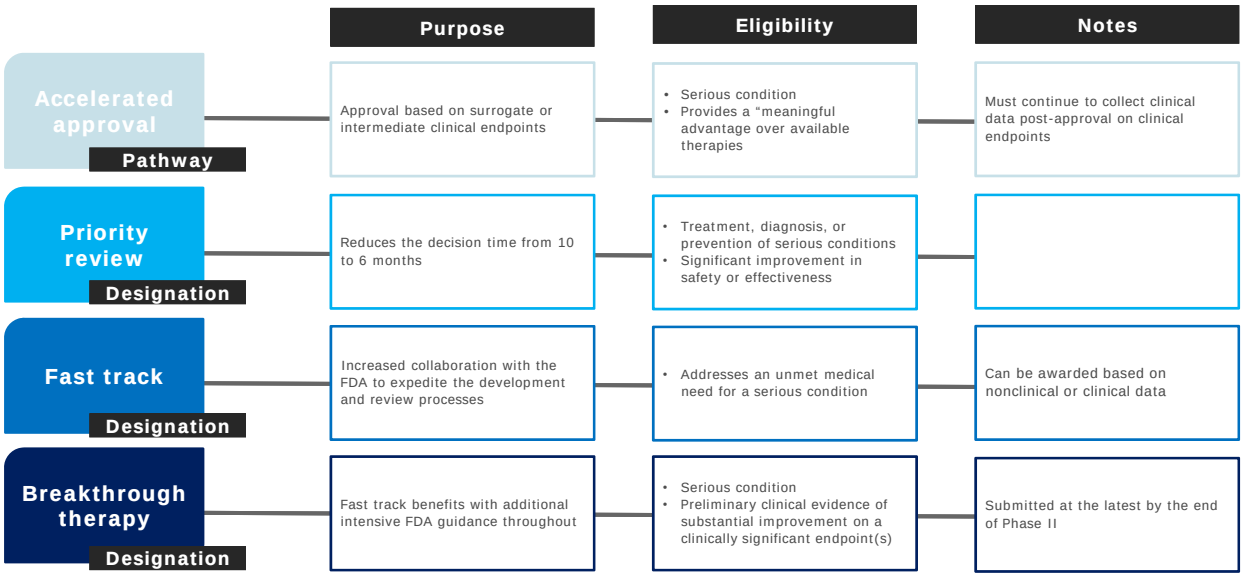
Faster introduction of promising medicines

- lifecycle management from clinical development to market adoption
- iterative development (eg approval on more limited data, conditional approval)

Greater involvement of patients

- involvement of patients in research discussions
- development of patient-reported outcomes and exploration of patients' preferences

FDA Approval Programmes for Innovative Drugs



Achievement of Objectives: Faster Access

- Enthusiastic response by pharmaceutical industry
- Fast-track licensing
- Reliance on surrogate endpoints
- Increased uncertainty for payers
- Final outcomes (eg improved overall survival) not always achieved

Breakthrough Therapy Designation: Early Experience in the US

- Many requests and extensive use in first 2.5 years (January 2013 to June 2015):
  - 308 total requests for Breakthrough designation
  - 90 requests granted,169 requests denied
  - 23 full FDA approvals
- Faster FDA review of new drug applications.
  - The median time for approval for drugs that have received the designation is 5.6 months.
  - For priority NDAs, the median approval time in 2014 was 6.5 months.
- Full impact on drug development timeline not yet clear, though some approved drugs for cancer, hepatitis C had much shorter timelines and cost from initial human testing to approval

Mark McClellan, OHE Lecture, London July 2015:

Source: EvaluatePharma, FDA – Center for Drug Evaluation and Research

Surrogate Endpoints: Are they Reliable? (1)

- Surrogate endpoints in oncology include: tumour reduction and progression free survival (PFS)
- They are intended to be predictive of the primary clinical outcome, i.e., overall survival (OS)
- The European Network of Health Technology Assessment (EUnetHTA) considers surrogate endpoints to be important and admissible in Relative Effectiveness Assessment (REA), as long as they have been validated
- PFS can also independently be accepted as a relevant outcome due to its impact on patient experience (e.g. lesser symptoms and better QoL).

Surrogate Endpoints: Are they Reliable? (2)

- Systematic review to assess the suitability of progression-free survival (PFS) and time-to-progression (TTP) using three validation frameworks
- Considered evidence in colorectal, lung, breast and ovarian cancer, plus renal cell carcinoma and glioblastoma multiforme
- According to IQWiG's validation framework, only PFS achieved evidence of surrogacy in metastatic colorectal and ovarian cancer treated with cytotoxic agents

Source: Ciani et al Int. J. Tech. Assess. in Health Care 2014

FDA Breakthrough Medicines: Have they Caused Breakthrough Headaches For HTA Agencies?

- Breakthrough medicines approved by the FDA up to 31 December 2014 were identified
- The appraisals by 6 payers/HTA agencies were analyzed in order to assess:
  - the proportion of all breakthrough medicines assessed by October 2015
  - the proportion of medicines deemed acceptable for reimbursement
  - the time taken to reach an outcome

Wonder M, Dunlop S, Chin G, Biggs J, Sullivan S, Drummond M. Value in Health 2015: 14: A550

Comparison of Payer/HTA Agencies *Wonder et al, 2015*

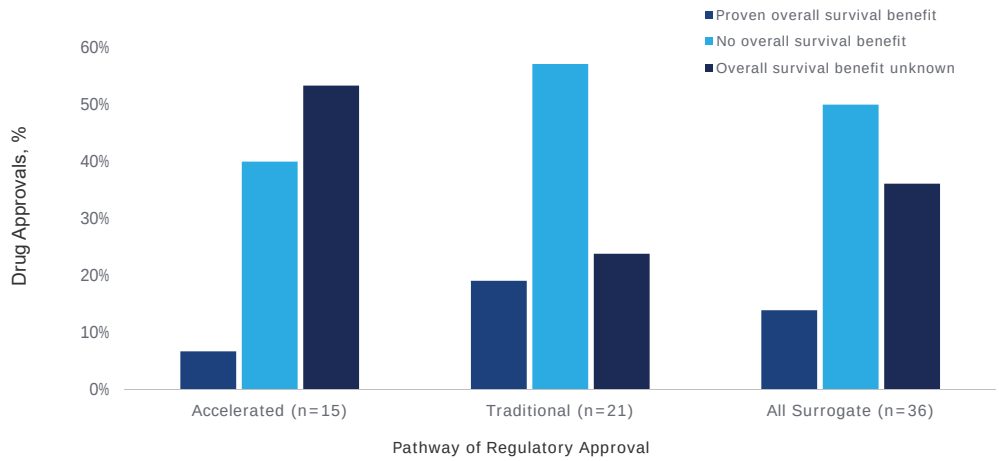
Metric	US (Premera Blue Cross)	England (NICE)	France (HAS)	Germany (IQWiG/G-BA))	Canada (CADTH)	Australia (PBAC)
Number of medicine/patient population pairings registered by local regulatory agency	17	14	14	14	16	11
Number of medicine/patient population pairings with a payer/HTA agency outcome*	17	6	11	12	10	10
Number of medicine/patient population pairings deemed acceptable for reimbursement / coverage by payer/HTA agency	16	6	11	9	8	7
Period (date of local registration to date of payer/HTA agency outcome) (mean; days)	63	244	291	160	134	49
Medicines not yet supported by payer/HTA agency	Idelalisib (non-preferred on standard incentive formulary)	Nil	Nil	Ceritinib, idelalisib, pirfenidone	Ofatumumab acetate, pirfenidone	Idelalisib, ibrutinib (CLL), nintedanib esylate

Analysis of 5 Years of FDA Approvals Based on Surrogate Endpoints

- 36 drugs were analysed, 19 of which were approved based on rate of response (RR), 17 based on progression-free or disease free survival (PFS or DFS)
- Based on a median follow-up of 4.4 years, only 5 drugs had demonstrated improvement in overall survival in randomized clinical trials
- 18 had failed to show any improvement and 13 had no results
- Crossover was allowed in 11 of 36, but there no significant difference in eventual overall survival between those with and without crossover
- The authors argue that the FDA should determine a timeline for drugs approved on the basis of a surrogate endpoint to prove their effectiveness

Kim C, Prasad V. JAMA Intern Med. Online: October 19, 2015. doi:10.1001/jamainternmed.2015.5868

Post-approval Survival Profiles of Cancer Drugs Stratified by FDA Approval Pathway



All marketing approvals between January 1, 2008 and December 31, 2012

Achievement of Objectives: Involvement of Patients

- ISPOR SIG survey of patient engagement in research
- Statements on the relevance of outcomes in oncology by ASCO and NICE (patient involvement?)

ISPOR Patient Centred Special Interest Group Survey (1)

- Targeted literature review to identify existing theoretical frameworks and patient engagement in research
- Identified three frameworks
- Found that engagement was reported most often in the early stages of research (agenda setting, study design, recruitment)
- Argue that current practice is primarily a one-way communication (consultation) and there is a lack of bi-directional engagement

Harrington et al Value and Outcomes Spotlight, Sept/Oct 2016

ISPOR Patient Centred Special Interest Group Survey (2)

- Survey of ISPOR membership
- N=39; 84% of respondents were aware of some form of patient engagement activities within their organization
- Results confirmed the results of the literature review, in that most engagement was one-way communication from the patient in research organized by the researcher
- Involved patients or the patient community in:
  - discussions with approval or review agencies (41%)
  - study design (39%)
  - research methods or clinical trials (7%)

American Society for Clinical Oncology (ASCO) Clinically Meaningful Endpoints

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

			Primary End Point		Secondary End Point	
Cancer Type	Patient Population	Current Baseline Median OS (months)	Improvement Over Current OS That Would Be Clinically Meaningful (months)	Target HRs	**Improvement in 1-Year Survival Rate(%)***	**Improvement in PFS (months)**
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 to 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxeleligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 to 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 to 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 to 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 to 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard secondor third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 to 35	3 to 5

Reproduced from:

Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, et al. American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes. Journal of Clinical Oncology. 2014.

NICE'S Supplementary Guidance for 'End of Life' Therapies (2009)

If the therapy:

- is for a small patient population with life expectancy of less than 24 months;
- where the therapy adds three months or more to life expectancy.

Then:

- the QALYs gained should assume full quality of life in the added months;
- in addition the Committee can consider that the QALYs gained should be weighted sufficiently high for the therapy to be approved, given NICE's current threshold.

What Actions Can Global Payers Take?

- Insist on more debate about relevant outcomes and the role of surrogates
- Develop a more organized approach to the gathering and analysis of 'real world' data

Relevant Outcomes on the Role of Surrogates

- Need to understand more about patients' trade-offs between survival, risk and quality of life
- Need to reach agreement on which surrogates are valid as predictors of long term outcomes, in which tumour types
- Need to agree on whether some surrogates can be considered an outcome in their own right

Organized Approach to the Gathering and Analysis of 'Real World' Outcomes

Need agreement on:

- methodology (eg are observational data reliable?)
- financing of studies
- linking the results of studies to coverage and pricing decisions
- the overall process for requesting and managing studies

Will 'Real World' Observational Data Generate Reliable Evidence of Effectiveness?

- Once a drug is recommended, precedent suggests it is difficult to stop its use
- Observational data cannot provide unbiased evidence of effectiveness
- Relying on observational data will not give manufacturers incentives to conduct RCTs
- The Cancer Drugs Fund (CDF) should be used to conduct timely, pragmatic clinical trials within routinely collected data sources

Grieve R et al British Medical Journal 2016; 354:i5090 doi: 10.1136/bmj.i5090

Revision of the Cancer Drugs Fund in the UK

- Originally a 'safety net' to fund drugs given negative recommendations by NICE
- In July 2016 became a 'managed access' fund
- NICE, or the NICE Appraisal Committee, can recommend that drugs be funded by the CDF while additional data are collected
- A formal *managed access agreement* is reached, specifying the data to be collected and period of the agreement

Some Examples

- As of September 2017, 5 drugs have been referred to the CDF
- TA 416 Osimertinib for locally advanced or metastatic epidermal growth factor mutation-positive non-small cell cancer* (ongoing clinical trials)
- TA 465 Olaratumab, in combination with doxorubicin for advanced soft tissue sarcoma* (ongoing clinical trial and observational data)
- TA 472 Obinutuzumab, in combination with bendamustine followed by obinutuzumab for adults with follicular lymphoma* (ongoing clinical trial and observational data)

** The full descriptions of the indications have further restrictions, based on previous therapy or ineligibility for other therapies*

Conclusions

- Faster access has largely been achieved, in that HTA bodies/payers have not refused to reimburse drugs that have received accelerated approval
- Some doubts exist concerning long-term outcomes for fast-tracked drugs
- Patient engagement in the research process has been mixed
- The future emphasis is likely to be on managed access agreements to formalize real world data collection

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US Experience

Elizabeth Sampsel, Pharm.D, MBA, BCPS
Vice President, Payer Strategy and Relations, Dymaxium

US Payer Challenge

- Complexity of coverage decisions for products with uncertain evidence of clinical benefits and significant costs
- Payer coverage varies based on line of business
- Medicaid and Medicare have more strict rules vs private insurance

N Engl J Med 2017; 376:2001-2004 DOI: 10.1056/NEJMp1700446

Payer Perspective

"It's a complex tradeoff. Accelerated approval processes are challenging for payers. **Products can launch with only minimal evidence. Intermediate endpoints may not tell the whole story.** "Breakthrough" products can make a big difference to patients, but it's not really a breakthrough if it doesn't actually deliver the proposed benefit.

Our P&T Committee will not consider adding a drug to formulary unless it meeting minimum evidence standards.

Or, as I sometimes say: **A 'breakthrough' is only a breakthrough if it *actually breaks through* something!"**

- John Watkins, PharmD, MPH, Formulary Manager, Premera Blue Cross

Payer Perspective

"When newer drugs are approved through the accelerated pathway it may be more difficult to assess whether they have a true clinical benefit because the solid evidence may not be there. It would be **hard to justify coverage for these drugs through the P&T process**. If they don't make it to regular approval, they could be taken off the market and the result is a huge waste of resources, which are already scarce. It would be better for us to **focus our effort on drugs that are backed by strong evidence instead of surrogate or intermediate endpoints."**

- Jessica Huang, PharmD, BCPS, Clinical Pharmacist, Partnership Health Plan of California

PBM Perspective

"PerformRx reviews and considers all new drugs and biological products approved by the FDA with a high level care and clinical scrutiny. We understand the important role accelerated approvals have in bringing breakthrough therapies into the hand of patients sooner, but in turn this presents unique challenges and potential risks to the members we serve. An accelerated process may allow for an approval based on surrogate or intermediate endpoints. **It is sometimes challenging to make a formulary recommendation since the clinical endpoint may not have been achieved.** Our diverse team of clinical professionals give extra care and consideration to these products, examining the best available data and keeping up to date on the latest available clinical evidence and post-marketing surveillance reporting. At PerformRx, we strive to bring a pharmaceutical formulary to our members which is diverse and comprehensive, with demonstrated quality and safety profiles."

- Andrew Maiorini, PharmD, FAHM, VP, Clinical Programs, PerformRx

US Payer Options

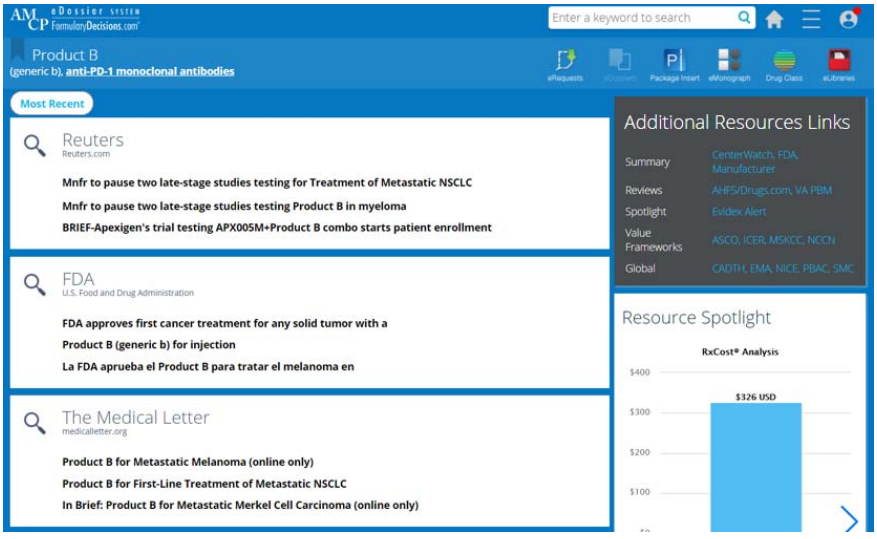
- Use the best evidence possible to determine coverage requirements
- Follow line of business regulations
- Consider outcomes-based contracts
- Review post-marketing surveillance as it is available to make coverage adjustments

Potential Improvements to Accelerated Pathway

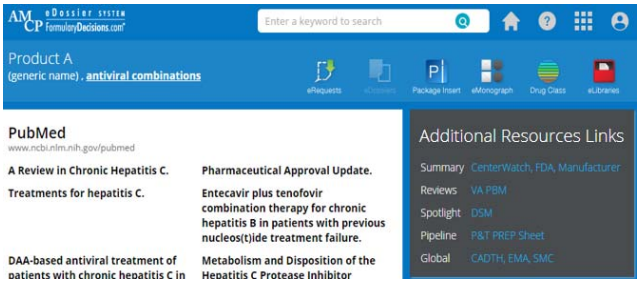
- Overall survival (OS) and quality of life (QoL) outcomes requirement for post-marketing studies
- Preapproved QoL measures published for specific drug classes
- Anticipated or clinically significant changes in OS and QoL measures defined a priori

Bauer SR, Redberg RF. Improving the Accelerated Pathway to Cancer Drug Approvals. JAMA Intern Med.2017;177(2):278.

Breakthrough Designation and Product Resources



P&T Prep Sheets




Product A® (generic name) P&T PREP Sheet

Product Overview

Current Treatment Landscape

- Starting point for breakthrough pipeline and new product evaluations
- Evidence aggregated from publicly available resources by Dymaxium P&T Analysts
- Feature considerations and insights with managed care pharmacist oversight

Conclusion

- US payers are challenged with using surrogate endpoints for coverage decisions, particularly with high cost drugs.
- A clear understanding of clinical and economic value will continue to be important in decision-making.
- Responses will vary by payer based on philosophy, regulatory requirements, and cost exposure.
- Resources are available to payers for breakthrough product reviews in the AMCP eDossier System.

Discussion & Questions

Thank you for participating!

For any questions, contact esampsel@dymaxium.com