# Fact Check: Comparing time to market in the United States and other countries

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## Key Takeaways

- Proposals to link Medicare payments to prices of drugs in other countries are often met with the critique that they would jeopardize US patients' access to drugs, which is generally described as faster and more comprehensive than in other countries.
- Studies generally suggest that:
    - Pharmaceutical companies frequently file for approval with the FDA before regulatory agencies of other countries.
    - FDA reviews more rapidly than regulatory agencies of other countries.
    - Pharmaceutical companies strategically delay launch in countries that use external reference pricing or have less marketing potential.
- The literature fails to consider:
    - The effect of facilitated review pathways in the US vs. other countries.
    - The amount of time between marketing approval and the manufacturer initiating the payer negotiation process.
    - The degree of availability to patients following payer coverage decisions for a drug.
- A more robust explanation of delayed launch of new drugs is that pharmaceutical companies prioritize drug launches in the countries that offer the greatest revenue and pricing potential. Adopting reference pricing based on other high-income countries, with an added markup, is unlikely to change the US's lead in drug pricing and revenue opportunity.

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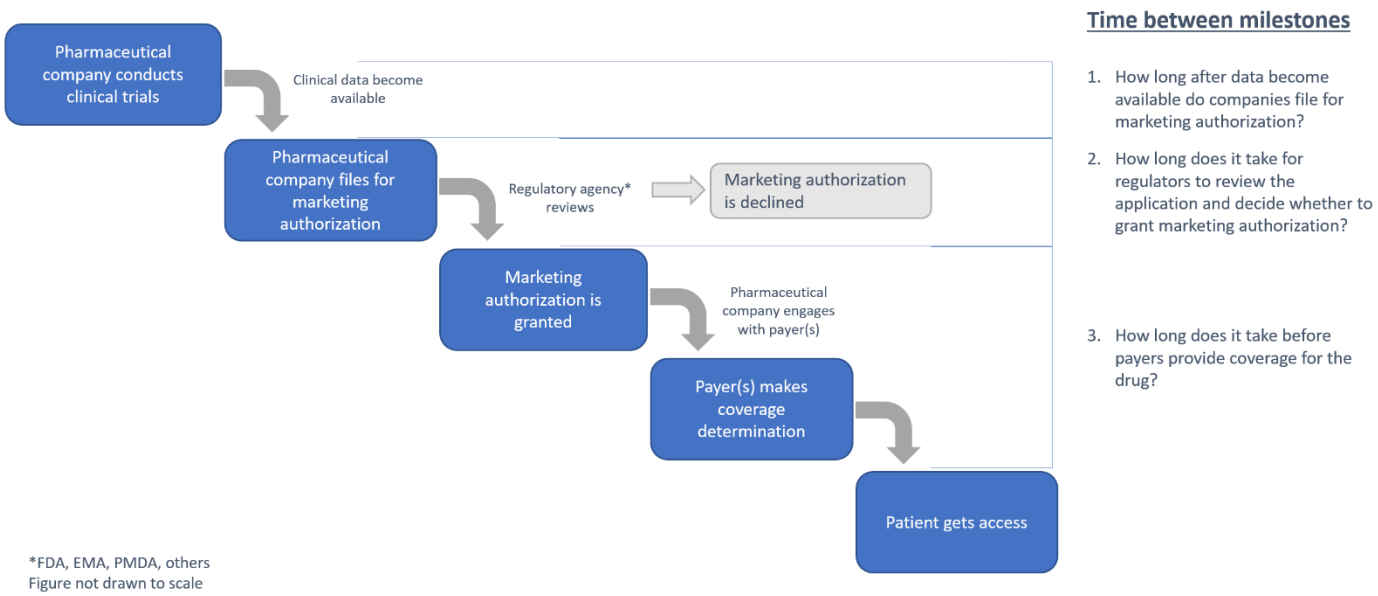
## Overview of the market access cascade

Two recent federal proposals seek to index Medicare payments for drugs against prices in other high-income countries. Both the International Price Index (IPI) proposed by CMS and a bill introduced in the House of Representatives this year aim to set payment rate ceilings based on average prices across other countries plus a markup. (CMS, Congress) The pharmaceutical lobby has argued that such changes in reimbursement would delay access for US patients. This hypothetical concern appears to rely on an assumption that it is the reimbursement levels in the US that drive manufacturers to prioritize filing for marketing authorization in the US ahead of other countries.

Regardless of country, every pharmaceutical company is faced with the same "market access cascade", a series of steps that results in a drug becoming available to patients. The first step is to apply for marketing authorization. This is required in order to offer the drug in a country, and timing is dependent on how long after obtaining data from clinical trials a pharmaceutical company decides to submit its application to that country's relevant regulatory agency (e.g., FDA, EMA, PMDA, others). The review process occurs between this date of submission and the agency announcing its recommendation to grant or deny marketing authorization. For drugs that receive marketing authorization, companies then must engage with a country's payer or payers to negotiate coverage and reimbursement criteria. (See Figure 1)

We reviewed studies that evaluate the speed and scope of new drugs becoming available in the US compared to other countries, focusing on time from data availability to application for marketing authorization, duration of review for marketing authorization, and time from marketing authorization to payer coverage determination.

**Figure 1. The market access cascade**




## 1. How long after data become available do companies file for marketing authorization?

Although it is unclear how much time passes after manufacturers have a final analysis of data from their clinical trials to submission at regulatory agencies, the date of filing for marketing authorization varies by country. Manufacturers commonly file for marketing authorization at the FDA before submitting to the EMA and others. Out of the 23 oncology drugs approved by the FDA in the year 2014 and 2015, 65% were submitted for review to the FDA first and 11 were granted accelerated approval status (European Medicines Agency, U.S. Food and Drug Administration). Most often, applications were filed at the EMA less than 3 months later. One study examining drug launches between 1998-2008 suggests that firms strategically delay launch in countries with lower price potential (Varol).

## 2. How long does it take regulators to review a company's application and make a marketing authorization determination?

Regardless of the filing date relative to other countries, marketing authorization is granted more quickly in the US, largely due to the speedy review conventions of the FDA. (Samuel, Roberts). In a comparison of 134 new drugs approved by the FDA, EMA and the Scottish Medicines Consortium (SMC) between 2007 and 2016,

more than 66% were approved first by the FDA (Zeukeng). The dominance in first approval by the FDA is related to its relatively faster review process (Downing, Roberts, Gail, Rodier, Howie, Rawson, Algahtani, Dorr, Samuel). In a study of review times for new therapeutic agents of chemical or biologic origin approved between 2012 and 2016, the median time from filing to approval by the FDA was 304 days, whereas median time to approval for the EMA and Health Canada were modestly longer at 371 days and 364 days, respectively (Rawson). For cancer therapeutics, median regulatory review time was 6 and 12 months by the FDA and EMA, respectively (Roberts); time to approval for oncology drugs is faster at the FDA than at the EMA or HC and the FDA approved more oncology drugs, as well (Samuel, Hartmann).

Upon receiving market authorization, a drug can immediately be offered for sale in the United States, but this is not universally true in other countries. The EMA provides a recommendation for market authorization, and then a separate body, either the European Commission or country-level agencies, must adopt that recommendation to allow market authorization of the drug product (Roberts, Downing, European Commission). The time between the EMA recommendation and the European Commission's adoption of that opinion allowing for market authorization should be no more than 67 days, although this is not always the case. Nevertheless, even among comparisons that factor out the review time of the initial EMA decision and total review time of the FDA, the FDA is still faster (Downing, Rawson).

## 3. How long does it take payers to make coverage determinations about a drug?

Regardless of procedural timeframes and differences, receiving marketing authorization does not mean drugs immediately become available to patients, in the US or elsewhere. Time is needed for negotiations between pharmaceutical companies and payers in each country, and the ultimate coverage determination may include access restrictions that limit how often the drug is used. In the US for example, by one year of FDA approval, a median of 61% of Medicare Part D plans included novel therapeutic agents in their formulary, often with access restrictions such as prior authorization and step edits. (Shaw) Coverage determination is variable across and within other countries as well. One study found that the time between marketing approval and launch of a new drug was related to how quickly after marketing authorization the manufacturer filed for review with a country's payer, the presence of a local representative of the country, and having evidence available to describe unmet need and the drug's value. (Ferrario) A study focusing on approval of oncology products in Italy estimated an average delay of 151 days between EMA opinion and action by the manufacturer to submit a dossier for coverage and reimbursement determination by AIFA (Italian Medicines Agency). (Russo)

## Discussion

Criticisms of reference pricing proposals that link time to market with pricing potential fail to consider several other factors that explain market access variations across countries. Lower evidence standards and options for accelerating review may explain at least some part of manufacturer decisions to file for approval first in the US (Downing, Algahtani). Out of six agencies, the FDA offers the greatest number of expedited review pathways. In 2018, 75% of new active substances approved by the FDA benefited from a facilitated regulatory pathway (FRP), whereas 28% benefited from an FRP at the EMA (Rodier). Between 2014 to 2017, the percentage of drugs approved after being assigned a breakthrough designation by the FDA went up from 22% to 37% (Darrow). Lower levels of evidence required by these pathways may also play a role in the higher approval rate in the US compared with other countries. (Hartmann) In effect, several factors combine to make filing with the FDA a lower risk and higher reward proposition when compared with regulatory agencies in other countries.

The assumption that drugs become available to patients immediately upon marketing authorization in the US is also misplaced. As in other countries, coverage and reimbursement decisions take time. Because US payers are decentralized and make such decisions independently, it may take longer to achieve the more widespread levels of access that other countries are able to establish with centralized federal or regional decisions.

Regardless of these caveats, it is possible that the richness of reimbursement is the primary reason companies file first in the US, although confirming this would require studies that include drugs filed in countries other than and not including the US, and also examine drugs that were declined in the US and elsewhere. An alternative theory is that external reference pricing leads to launch delays in countries with lower willingness-to-pay relative to others. Studies suggest that there are some incentives for pharmaceutical manufacturers to strategically delay launches in countries that rely on external reference prices as a main method in negotiation, while prioritizing countries in their market baskets that achieve relatively higher prices. (Maini) However, this logic does not extend naturally to the US and other developed countries. In many instances, reliance on external reference pricing (particularly when coupled with discounting) appears to be associated with lower levels of economic development. (Kanavos) Research has shown that, other things being equal, manufacturers are incentivized to sequence launch in rank order of price potential. (Houy) Drug prices in the US are highest among developed countries, effectively setting the upper bound for reference prices elsewhere. In current proposals, the US would draw from a market basket of other highly developed countries that also lead the global market in reimbursement rates and add a markup, maintaining the US lead in incentives for launch.

## References


Algahtani S, Seoane-Vazquez E, Rodriguez-Monquio R, Equale T (2015) Priority review drugs approved by the FDA and the EMA: time for international regulatory harmonization of pharmaceuticals? Pharmacoepidemiol Drug Saf 24(7): 709-715

CMS (Centers for Medicare & Medicaid Services). Proposed Rule: Medicare Program; International Pricing Index model for Medicare Part B Drugs. Available at: https://www.federalregister.gov/documents/2018/10/30/2018-23688/medicare-program-international-pricing-index-model-for-medicare-part-b-drugs. Accessed 10/10/2019.

116th Congress, 1st Session. H.R.3 – Lower Drug Costs Now Act of 2019. Available at: https://www.congress.gov/bill/116th-congress/house-bill/3/text?q=%7B%22search%22%3A%5B%22H.R.+3%22%5D%7D&r=1&s=3. Accessed 10/102019.

European Commission. "Authorisation Procedures - The Centralised Procedure." *Public Health - European Commission*, 2 May 2019, ec.europa.eu/health/authorisation-procedures-centralised_en.

Darrow, Jonathan J., et al. "The FDA Breakthrough-Drug Designation - Four Years of Experience | NEJM." New England Journal of Medicine, Apr. 2018, www.nejm.org/doi/full/10.1056/NEJMhpr1713338.

Dörr, P., Wadworth, A., Wang, T., McAuslane, N., & Liberti, L. (2016). An Analysis of Regulatory Timing and Outcomes for New Drug Applications Submitted to Swissmedic: Comparison With the US Food and Drug Administration and the European Medicines Agency. Therapeutic Innovation & Regulatory Science, 50(6), 734–742.

Downing NS, Aminawung J A, Shah ND, Braunstein JB, Krumholz HM, Ross JDS (2012) Regulatory review of novel therapeutics- comparison of three regulatory agencies. N Engl J Med 366(24): 2284-2293

European Medicines Agency. "Medicines." www.ema.europa.eu/en/medicines. Accessed July 23, 2019.

Ferrario A. Time to entry for new cancer medicines: From European Union–wide marketing authorization to patient access in Belgium, Estonia, Scotland, and Sweden. 2018; 21(7). 809-821.

Gail A. Van Norman, Drugs and Devices: Comparison of European and U.S. Approval Processes, JACC: Basic to Translational Science, Volume 1, Issue 5, 2016, 399-412.

Hartmann M, Mayer-Nicolai C, Pfaff O. Approval probabilities and regulatory review patterns for anticancer drugs in the European Union. Critical Reviews in Oncology/Hematology. 2013; 87(2). 112-121.

Houy N, Jelovac I. Drug Launch Timing and International Reference Pricing. Health Economics. 2015; 24(8): 978-989.

Howie, L. J., B.R. Hirsch, and A.P. Abernethy (2013) A comparison of FDA and EMA drug approval: implications for drug development and costs of care. Oncology (Williston Park), 27(12): 1195, 1198-1200, 1202.

Kanavos et al. The implementation of external reference pricing within and across country Borders. Available at: http://www.lse.ac.uk/business-and-consultancy/consulting/assets/documents/the-implementation-of-external-reference-pricing-within-and-across-country-borders.pdf. Accessed 10/7/2019.

Maini L, Pammolli F. Reference pricing as a deterrent to entry: evidence from the European pharmaceutical market. Available at: https://scholar.harvard.edu/files/lucamaini/files/reference_pricing_as_a_deterrent_to_entry.pdf. Accessed 10/7/2019.

Minette-Joëlle Zeukeng, Enrique Seoane-Vazquez and Pascal Bonnabry. A comparison of new drugs approved by the FDA, the EMA, and Swissmedic: an assessment of the international harmonization of drugs, European Journal of Clinical Pharmacology, 10.1007/s00228-018-2431-7, 74, 6, (811-818), (2018).

Nigel S.B. Rawson, Canadian, European and United States new drug approval times now relatively similar, Regulatory Toxicology and Pharmacology, Volume 96, 2018, 121-126.

Roberts SA, Allen JD, Sigal EV. Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the united states than in Europe. Health Aff (Millwood). 2011;7:1375-81.

Rodier C, Bujar M. McAuslane N, Liberti L. 2019. R&D Briefing 70: New drug approvals in six major authorities 2009-2018: Focus on Facilitated Regulatory Pathways and Orphan Status. Centre for Innovation in regulatory Science. London, UK.

Roy A. What Medicare Can Learn From Other Countries on Drug Pricing. The Foundation for Research on Equal Opportunity (FREOPP). 2019. https://freopp.org/what-medicare-can-learn-from-other-countries-on-drug-pricing-bf298d390bc5. Accessed September 12, 2019.

Russo P, Mennini FS, Siviero PD, Rasi G. Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers. Annals of Oncology. 2010; 21(10): 2081-2087.

Samuel, N., & S. Verma. "Cross-comparison of cancer drug approvals at three international regulatory agencies." Current Oncology [Online], 23.5 (2016): e454-e460. Web. June 21, 2019.

Shaw DL, Dhruva SS, Ross JS. Coverage of novel therapeutic agents by Medicare prescription drug plans following FDA approval. J Manag Care Spec Pharm. 2018;24(12):1230-1238.

U.S. Food and Drug Administration. "Drugs@FDA: FDA Approved Drug Products." *Accessdata.fda.gov*, www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 23, 2019.

Varol N, Costa-Font J, McGuire A. Explaining early adoption of new medicines: Regulation, innovation, and scale. CESIFO Working Paper No. 3459. May 2011.

Wilking N, Jönsson B. A pan-European comparison regarding patient access to cancer drugs. Stockholm: Karolinska Institutet in collaboration with Stockholm School of Economics, 2005.