Comparative Effectiveness Research 1

Generating comparative evidence on new drugs and devices before approval

Huseyin Naci, PhD
Maximilian Salcher-Konrad, MSc
Professor Aaron S. Kesselheim, MD
Beate Wieseler, Dr. rer. nat.
Professor Lise Rochaix, PhD
Professor Rita F. Redberg, MD
Georgia Salanti, PhD
Professor Emily Jackson, OBE
Professor Sarah Garner, PhD
Professor T. Scott Stroup, MD
Professor Andrea Cipriani, PhD

1. Department of Health Policy, London School of Economics and Political Science, London, UK
2. Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA
3. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany
4. Hospinnomics, Paris School of Economics, Paris, France
5. School of Medicine, University of California at San Francisco, San Francisco, CA, USA
6. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
7. Department of Law, London School of Economics and Political Science, London, UK
8. School of Health Sciences, University of Manchester, Manchester, UK
9. Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA
10. Department of Psychiatry, University of Oxford, Oxford, UK; Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

Correspondence to

Dr Huseyin Naci
Department of Health Policy
London School of Economics and Political Science
London WC2A 2AE
UK
Email: h.naci@lse.ac.uk
Summary

Fewer than half of new drugs have data on their comparative benefits and harms against existing treatment options at the time of regulatory approval in Europe and the US. Even when active-comparator trials exist, they may not produce meaningful data to inform decisions in clinical practice and health policy. Recently, the uncertainty associated with the paucity of well-designed active-comparator trials has been compounded by legal and regulatory changes in Europe and the US that have created a complex mix of expedited programs aimed at facilitating faster access to new drugs. Comparative evidence generation is even sparser for medical devices. Some have argued that the current process for regulatory approval needs to generate more evidence that is useful for patients, clinicians, and payers in health care systems. We propose a set of 5 key principles relevant to the European Medicines Agency (EMA), European medical device regulatory agencies, and the US Food and Drug Administration (FDA), as well as payers, that we believe will provide the necessary incentives for pharmaceutical and device companies to generate comparative data on drugs and devices and assure timely availability of evidence that is useful for decision making. First, labeling should routinely inform patients and clinicians whether comparative data exist on new products. Second, regulators should be more selective in their use of programs that facilitate drug and device approvals on the basis of incomplete benefit and harm data. Third, regulators should encourage the conduct of randomised trials with active comparators. Fourth, regulators should use prospectively-designed network meta-analyses based on existing and future randomised trials. Fifth, payers should use their policy levers and negotiating power to incentivise the generation of comparative evidence on new and existing drugs and devices, for example, by explicitly considering proven added benefit in pricing and payment decisions.
A record-breaking number of new drugs and devices have entered the market in recent years. In 2018, the US Food and Drug Administration (FDA) granted approval to 59 drugs and 106 devices (compared to an average of 28 drug approvals per year during the preceding decade), and the European Medicines Agency (EMA) approved 42 new drugs. In addition to new drugs for established therapeutic areas with large numbers of existing treatment options (e.g., antidepressants for depression, statins for coronary heart disease, and HbA1c-lowering therapies for diabetes), the research and development pipelines of pharmaceutical and device companies have in recent decades delivered new therapies for rare diseases. For example, several new agents are now available for the treatment of multiple myeloma, chronic myeloid leukemia, Gaucher disease, and pulmonary arterial hypertension.

This is good news for patients, since some of these novel therapies have turned out to be beneficial. For example, drugs like imatinib for chronic myeloid leukemia and sofosbuvir for hepatitis C have transformed clinical outcomes, improving and extending the lives of patients suffering from these serious and life-threatening conditions. However, other new drugs like the HbA1c-lowering rosiglitazone have turned out to have differing benefit/risk profiles than expected in certain populations and subsequently been removed from some markets. Also, there have been several important safety crises related to high-risk medical devices, resulting in their market withdrawal, such as pelvic mesh and metal contraceptive implants.

The market entry of larger numbers of new drugs and devices may also paradoxically complicate treatment decisions if there are little or no data on the comparative benefits and harms of new versus existing alternatives. “What is the treatment of choice for my patient with condition X?” is a key question for clinical practice. Without data on comparative benefits and harms, it may be difficult for patients and clinicians to identify the appropriate therapy.

In this Series on Comparative Effectiveness Research, we describe and highlight some fundamental principles related to developing comparative data on drugs and devices, particularly if multiple options exist to treat the same condition. Our primary focus is on the FDA and EMA, which serve as gatekeepers to the largest pharmaceutical markets worldwide that collectively account for over 60% of total sales. In the US, FDA is also responsible for medical device regulation; in the EU, notified bodies designated by national authorities are responsible for conformity assessments of devices (Table 1). FDA and EMA are tasked with the goals of granting expeditious access to promising new treatments while also requiring adequate data before approval to protect patients from ineffective and potentially harmful products. Regulatory agencies’ evidence standards for approval shape the quantity and quality of clinical studies generated on new drugs (and also devices in the US).
In this first paper of the Series, we examine the availability of comparative effectiveness data, and outline how the current regulatory approaches to approving new medicines and devices address the evidence needs of patients, clinicians, and other decision makers in health systems. Recent policy changes aimed at speeding up the development, review, and approval of new products have complicated health system-wide efforts to generate comparative data on drugs and devices before and after approval. We therefore propose strategies to improve the future availability of comparative data at the time of market entry. The second paper of the Series focuses on the generation of comparative evidence in the post-marketing period for drugs and devices but also interventions for which often there is no commercial developer and no dedicated regulatory system, e.g., surgical interventions. The third paper analyses the ethical tensions in comparative effectiveness research.

**Availability of comparative evidence on new drugs and devices**

Comparative evidence on newly-approved drugs is limited for a number of reasons. One primary reason is that pharmaceutical manufacturers do not routinely collect such data in the studies leading to drug approval. In both the US and Europe, the regulatory agencies’ statutory mandate is to evaluate a drug’s benefit-risk balance and intended effects, not its comparative benefits and harms against existing alternatives. Placebo controls in randomised clinical trials (RCTs) can establish ‘assay sensitivity,’ or the ability to distinguish between an effective and ineffective treatment. Of course, for some truly innovative drugs, active comparators may not exist at the time of approval.

According to earlier estimates (covering regulatory approval decisions through 2010), fewer than half of drugs approved in the US and Europe had one or more RCTs with an active comparator at the time of approval. To obtain recent estimates in Europe (covering regulatory approval decisions after the EMA’s recommendation for active-comparator trials), we reviewed the characteristics of clinical studies that served as the basis for EMA drug approvals from 2015 through 2018 (Figure 1). During this period, the annual proportion of new drugs that had at least one RCT with an active comparator at the time of approval ranged from approximately a quarter to one half.

Lack of an active comparator can lead to uncertainty regarding the relative benefits and harms of treatments at the time of market approval (Panel 1). Although these questions could be answered in the post-marketing period, they are not often fully addressed, as we discuss in Paper 2 of this Series.
Another reason for lack of comparative data is that choosing an active comparator can be difficult. For example, several products may be suitable candidates due to differences in their clinical benefit, safety, or cost profiles. One review found that active comparators used in pivotal trials leading to regulatory approval do not always represent the best available treatment. Also, manufacturers can compare their new treatments to sub-optimal comparators (e.g. lower doses than recommended or ineffective treatments) rather than the best available option.

Comparative evidence generation is even sparser for medical devices. The majority of high-risk devices are approved for use without any clinical data rigorous studies (Table 1). In the US, even the most stringent regulatory pathway for high-risk devices tends to involve a single clinical study that is typically non-randomised and with no control group. Approximately 90% of high-risk devices were approved by the FDA on the basis of a single pivotal trial. Less than half of studies supporting the FDA approval of high-risk cardiovascular devices between 2000 and 2011 included active comparators. Currently, corresponding figures for European device approvals are not available due to lack of transparency. However, new European medical device regulations, which will come into effect in 2020 will make information on approval decisions publicly available.

Expedited programs

Over the past few decades, legislatures and regulators have established several expedited development, review, and approval programs for drugs (see Panel 2 for an overview of programs in the US and Europe). An expedited program also exists for high-risk medical devices in the US, but not in Europe. Although expedited programs differ in their scope and focus, which range from putting deadlines on regulatory review times to approving products on the basis of earlier-stage data than what is typically required, their shared objective is to provide faster access to new products.

One rationale for introducing such programs is to meet patient demand for potentially effective therapies for life-threatening diseases for which there is no existing treatment. Studies have confirmed that drugs that qualify for expedited programs have shorter development times and receive regulatory approval faster. Between 2012 and 2016, the duration of clinical development was almost one year shorter for drugs in the FDA’s expedited programs than for drugs that were not.

In the US, more than three-quarters of new drugs are now approved through such programs (Figure 2). While some products that benefit from such programs offer added therapeutic benefit over existing alternatives (for example, lumacaftor for cystic fibrosis), others
For example, cancer drugs that received the FDA’s breakthrough therapy designation between 2012 and 2017 did not outperform other cancer drugs approved during the same period on trial endpoints. In addition, drugs that entered the market via expedited programs have been more likely to be the subject of drug safety communications after approval, new boxed warnings, and even market withdrawals.

Although not all expedited programs lower the evidence standards for regulatory approval (Panel 2), reviews show that eligible drugs enter the market on the basis of studies with smaller sample sizes and shorter follow-up durations that are less likely to be randomised and blinded. Expedited programs have also further reduced the prospect of evidence on the comparative benefits and harms of new and existing drugs and devices. Clinical studies that support expedited versus regular approvals are also more likely to lack comparator treatments.

For example, “single-group” studies, which test an experimental treatment on its own (without a concurrent control group), are commonly used for evaluating drugs targeting rare conditions and those that are the subject of expedited development or review. The rate of successful “single-group” study submissions to regulatory agencies more than doubled over the past decade.

Between 1995 and 2017, the proportion of FDA approvals with “single-group” studies increased only for drugs in expedited programs, and not for those that did not benefit from such programs.

Also, studies supporting the approvals of drugs in expedited programs are more likely to collect data on surrogate measures of benefit – biomarkers, laboratory values, or other physical measures – rather than patient-oriented clinically-relevant outcomes, such as improved functioning or longer survival. While surrogate measures reduce the duration, size, and cost of clinical studies, thereby facilitating faster patient access to promising new treatments, they further magnify the uncertainty associated with the lack of active comparators (see Panel 1). Use of surrogates is only helpful if the treatments are ultimately proven to be effective. Some surrogate measures such as systolic blood pressure in cardiovascular disease and viral load in HIV/AIDS may correlate with long-term clinical outcomes. However, many surrogate measures used in regulatory approvals are not validated predictors of clinical outcomes. At the time of approval, it remains unknown whether short-term findings will materialise into long-term improvements in morbidity or mortality.

A fragmented evidence base for decision making in health systems

When new drugs and devices lack active comparators at the time of approval, it has several important implications for stakeholders in health systems, including health technology...
Several European health technology assessment organisations like the National Institute for Health and Care Excellence (NICE) in England, Haute Autorité de Santé (HAS) in France, and the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany explicitly require comparative data for their assessments.53,54 Assessments conducted by these organisations serve as the basis of subsequent pricing and payment decisions. Private and public insurers in the US could also benefit from such evidence for their pricing and formulary coverage negotiations with pharmaceutical and device manufacturers.55

The evidence generated at the time of regulatory approval has spillover effects on data availability for health technology assessment organisations and payers.56 The time interval between approval and payment decisions is short and declining (similar to regulators, health technology assessment organisations are under pressure to expedite their reviews);57 therefore, regulatory agencies, health technology assessment organisations, and payers often assess near-identical clinical data, albeit to address different objectives. In the absence of comparative data at the time of drug and device approval, many health technology assessment organisations and payers resort to using data with varying levels of limitations and uncertainty.58

Current evidence standards may give patients and clinicians false reason for optimism that new treatments are beneficial and safe.59,60 Clinicians and patients often overestimate the quality and quantity of evidence supporting new treatments.61–64 Media reporting on new drugs may contribute to patients’ overly optimistic expectations about drug benefits.55 For example, news reports on cancer drugs rarely discuss treatment failure and adverse events.65 Complicating matters further is the regulatory agencies’ increasing use of terms like “breakthrough therapies” in the US and “priority medicines” in Europe to refer to products in expedited programs.67 In a randomised survey study among US adults, labeling a drug as a “breakthrough” altered people’s planned behaviour and increased their positive perceptions in the drug’s effectiveness.68

**Importance of generating comparative evidence before market entry**

Comparative data on new drugs and devices usually does not emerge after regulatory approval. When drugs and devices are originally approved for particular indications without randomised, active-comparator trials, such data are unlikely to emerge in the post-marketing period.69 Even when post-marketing studies are required by the FDA and EMA, they can remain incomplete years after approval.70–74 Just about half of drugs with FDA accelerated approvals from 2009 and 2013 fulfilled their post-marketing requirements after at least three years on the market.75 Fewer than 15% of initiated post-market studies for high-risk medical devices in the US were completed five years after approval.25 Even when post-marketing studies are completed,
the design characteristics of studies conducted after approval closely resemble those of pre-
approval studies (e.g., use of surrogate measures, lack of comparators). For example, 42% of
post-marketing studies requested by the EMA for conditional approvals from 2006 to 2016 were
non-randomised, and 73% were not blinded.

**Figure 3** illustrates the persistent lack of comparative data after market entry in selected
therapeutic areas. In rheumatoid arthritis, for example, the evidence base for biologic agents is
comprised predominantly of placebo-controlled trials. Despite significant research investment in
this area over the past 30 years, culminating in 200 placebo-controlled trials and over 100 meta-
analyses, rich randomised, comparative evidence on different available biologic agents for this
condition is still lacking.

**Prioritising the generation of comparative data before approval**

The evidence requirements for market authorisation of new treatments have important
implications for the research conducted on new drugs and devices. Routine regulatory approval
of drugs and devices on the basis of placebo-controlled or “single-group” studies may
disincentivise manufacturers from investing in more clinically useful active-comparator trials.
Manufacturers may also interpret regulatory flexibility in data requirements in certain areas as a
shorter and cheaper route to market and shift their research priorities accordingly. Evidence
from clinical trials in cancer suggests that manufacturers’ recent research investments have been
shifted away from long-term projects.

Continuing the recent trajectory of approving most new drugs and devices on the basis
of limited and weak data may further fragment the evidence base with adverse health and
economic consequences. Ineffective treatments may remain on the market for long periods of
time, at substantial cost, exposing patients to treatments without reliable evidence of benefit.
From an economic perspective, if health systems pay for expensive products when cheaper
alternatives may work just as well, fewer resources are available for services and treatments
proven to be cost-effective.

We therefore recommend five strategies, which we believe will promote and facilitate the
generation of comparative data (**Table 2**).

1. Greater transparency on comparative data availability

   Product labelling (also known as the package insert in the US and the summary of
product characteristics in Europe) is the primary regulatory tool for communicating information
about newly-approved drugs to clinicians and patients. In the US and Europe, product labelling
guides clinicians and patients on safe and effective use of new therapies.
Currently, product labelling does not include statements about what is or is not known about the relative benefits and harms of new and existing drugs. For devices, the recently published European guidance on the Summary of Safety and Clinical Performance, which will accompany high-risk medical device approvals, will require manufacturers to summarise “possible diagnostic or therapeutic alternatives.” No such explicit requirement exists for high-risk devices approved by the FDA.

Without this information, patients and clinicians remain largely unaware that most new treatments are not tested against other alternatives. According to a national survey in the US, almost three-quarters of clinicians believed that FDA approval is based on at least comparable effectiveness of a new product to other approved alternatives. Several RCTs confirmed that improving the content of product labeling can result in a better understanding of available data on benefits and harms, thereby improving decision making and subsequent treatment choices.

We recommend that product labelling report in non-technical language whether head-to-head studies have been conducted at the time of approval (e.g., “this drug/device has not been tested against other drugs/devices indicated for the same condition”).

2. More selective use of expedited programs

Flexibility in regulatory standards enabled by expedited programs is warranted in cases when there is significant unmet need. Although some of the most transformative drugs benefited from these programs, qualification for expedited programs has expanded in recent years. In the US, an increasing share of products have benefited from multiple expedited programs simultaneously. The FDA recently introduced an expedited program also for medical devices; no such program exists in Europe.

There are questions about when in the preclinical testing process drug manufacturers may qualify for such programs. According to senior FDA officials, consideration of the accelerated approval pathway during the first decade of the program often arose only when the manufacturers submitted their applications to the FDA, not before. Although the conditional marketing authorisation pathway in Europe has been less frequently used than similar programs in the US, recent reviews showed that the EMA used this pathway to grant approval in some cases despite no such formal request from the manufacturers.

We recommend that expedited programs be reserved for a clearly demarcated, prospectively defined set of circumstances in both Europe and the US. Regulators in both settings should work collaboratively with patient groups and the industry to develop new
guidelines to determine the eligibility of drugs for inclusion in such programs. In addition to factors such as availability of alternative treatment options, disease severity, and prevalence, manufacturers should be required to present well-designed and credible evidence-generation plans to ensure timely completion of additional studies in the post-marketing period. These post-marketing studies should be underway with clear milestones at the time of approval as a condition for inclusion in expedited programs.

When expedited programs are used, regulators should publicly report the qualifying reasons. Regulators should also strengthen their oversight of post-marketing evidence commitments and requirements. Although both the FDA and EMA have statutory authority to enforce timely completion of post-marketing studies, including imposing civil monetary penalties (FDA) and rescinding approval (FDA for accelerated approval drugs and EMA for conditional marketing authorisation drugs), they tend not to invoke such power, citing resource constraints.

3. More routine use of active comparator RCTs

RCTs have been the mainstay of phased drug development since the 1960s. Over the past half century, the vast majority of therapeutic agents have been approved on the basis of RCTs, albeit predominantly with placebo controls. RCTs are also essential to determining the effectiveness of moderate- and high-risk devices. In recent years, however, the role of RCTs in drug and device development has been increasingly contested due to their high complexity and cost. Other common criticisms of RCTs include the poor generalisability of their findings due to inclusion of selective participant populations that do not adequately represent populations in actual clinical practice. Also, RCTs are rarely large enough to detect reliably uncommon harms.

A particular source of controversy related to RCTs is whether they are applicable to rare disease treatments. While RCTs might be more challenging to conduct in rare disease settings, evidence from FDA approvals in the US confirms their feasibility. In one study, incidence of disease was not associated with the likelihood that evidence from a RCT was available at the time of approval. In addition, over a third of trials in very rare diseases with a prevalence of <1 per million were randomised. Over half of “single-group” studies in a recent review of cancer drug approvals had sufficiently large sample sizes to include control groups.

RCTs with active comparators should be more routinely used for drug and device approval. Strategies aimed at improving trial efficiency may help offset the additional costs of including active comparator arms in RCTs. Trial efficiency could be improved by simplifying participant recruitment and data collection through clinical registries. RCTs embedded in
registries have recently been touted as “the next disruptive technology in clinical research.” Regulators should routinely investigate the availability, validity, and completeness of outcome data in existing clinical registries to facilitate embedding active-comparator trials. Moreover, manufacturers can substantially reduce trial complexity by imposing fewer restrictions on participant selection, thereby also improving the external validity of outcomes.

4. Prospectively designed network meta-analyses

Network meta-analysis is a statistical method to assess the relative benefits and harms of multiple treatments that are not compared directly. Currently, network meta-analyses are often based on a retrospective collection of RCTs conducted by different researchers at different times including different patient populations. Such analyses may be at risk of bias due to the relative availability of documents that describe trial conduct and analysis, potential reporting biases, and differences in the characteristics of patient populations or standards of care (some of which may be unknown or unmeasured). These limitations may jeopardise the validity of network meta-analyses and their usefulness for decision making. Of the 71 network meta-analyses submitted to IQWiG from 2011 to 2016, only 11 (15%) were deemed valid.

We recommend prospectively designing network meta-analyses to address these limitations and produce comparative evidence on new treatments at the time of market entry. A prospectively designed network meta-analysis would rely on a pre-determined set of RCTs with broadly similar design features (patient population characteristics, follow-up durations, core outcome sets) so that their findings can be synthesised upon completion. Prospectively designed network meta-analyses would generate comparative data earlier and more efficiently than alternative methods. Regulatory agencies would be uniquely positioned to conduct such analyses, as individual participant data that can be made available to regulators would improve the validity of network meta-analyses. As there is no centralised regulatory agency for medical devices in Europe, greater collaboration among national competent authorities would be needed when performing network meta-analyses of medical devices.

Prospectively designing network meta-analyses would require regulatory scientific advice on the design of RCTs of products seeking the same (or similar) indications. As the validity of network meta-analyses depend on the quality of relevant RCTs, efforts are needed to improve the design features of RCTs used for regulatory decisions. Although intensive regulatory scientific advice is already an integral part of drug and device development in the US, and drug development in Europe, it is typically centred around the clinical studies of one product at a time. What is instead needed is a more holistic approach that considers each RCT as part of an
evolving research landscape in a therapeutic area. When giving advice to manufacturers about study designs, regulators should consider the RCTs of different products as components of future network meta-analyses. Regulators should encourage manufacturers to design trials that are similar enough to be synthesized but with a degree of variability that gives information about differences across populations and settings. Making regulatory scientific advice publicly available would support the design and conduct of sufficiently similar studies in a given therapeutic area. Such analyses can first be pilot-tested by multi-stakeholder initiatives involving regulators.

5. Considering comparative effectiveness evidence in pricing and payment decisions

Health technology assessment reviews conducted on the basis of available evidence have found that the majority of new product approvals offer no proven added therapeutic benefit compared to existing alternatives. Yet, there is currently no direct association between the manufacturer-set launch prices of new drugs and devices and the comparative benefits they offer. In some cases, manufacturers have even sought to charge more for their less-effective products.

When making pricing and payment decisions, payers in different countries consider a complex mix of factors beyond clinical data on benefits and harms, including the availability of alternative treatments, rarity of disease, cost-effectiveness, budget impact, and perceived novelty of the treatment. Such scientific and social value judgements serve as guiding principles in what are inherently complex, multi-faceted decisions. We recommend making comparative effectiveness evidence an explicit criterion in future pricing and payment decisions. Payers’ negotiating power could incentivise the generation of comparative evidence on new and existing drugs and devices. Such developments are already underway in Germany and France, and their experiences can be instructive for other countries.

What would pricing and payment arrangements look like if guided by explicit comparative effectiveness principles? Companies that demonstrate the superiority of their products against the current standard of care on the basis of meaningful outcomes in active-comparator RCTs should command higher prices or payment levels. Standards of care may differ across settings and change over time, which may complicate formally incorporating comparative effectiveness evidence into decision making. Conversely, drugs and devices that do not demonstrate added benefit should be priced and paid at a lower level than other treatments on offer. If only tentative evidence is available (from weak study designs or on the basis of surrogate measures), manufacturers should be required to give price concessions to payers until meaningful comparative data emerges from ongoing studies.
Conclusions

Comparative data on the benefits and harms of new and existing drugs that are essential to make evidence-based decisions in clinical practice and health policy are hard to come by. The broad use of expedited programs in both the US and Europe has compounded the already-substantial shortcomings of the available evidence on new drugs at the time of market entry, further complicating efforts to determine how new drugs fare against existing alternatives.

Comparative evidence generation is even sparser for medical devices. Policymakers and regulators can facilitate timely generation of comparative data on drugs and devices by promoting greater transparency, using expedited programs in a more clearly demarcated set of circumstances, encouraging the use of RCTs with active comparators, prospectively designing network meta-analyses, and linking the prices or payment levels of new products to their demonstrated comparative benefits and harms.
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Contributors

HN and AC conceived and designed the study. HN wrote the first draft of the manuscript. All other authors contributed to the writing of the final version of the manuscript, and agreed with the results and conclusions of this Article.

Declaration of interest

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References


74. Bloem LT, Mantel-Teeuwisse AK, Leufkens HGM, De Bruin ML, Klungel OH, Hoekman J. Postauthorization Changes to Specific Obligations of Conditionally Authorized...


O’Connor AB. Building comparative efficacy and tolerability into the FDA approval process. *JAMA.* 2010;303(10):979-980.


Table 1. Medical device regulation in the European Union and the United States.

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<th>European Union</th>
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| **Regulatory agency** | - There is no centralised agency responsible for regulating medical devices in Europe.  
- EMA’s regulatory role is primarily limited to medicinal products that include a medical device (combination products, medical devices with an ancillary medicinal substance, in-vitro diagnostics, and medical devices made of substances that are systematically absorbed).  
- For medical devices, private and for-profit “notified bodies” designated by national competent authorities are responsible for conducting conformity assessments.  
- A medical device can only be marketed in the European Union after receiving Conformité Européenne (CE) marking. |
| **European Union** | - FDA is responsible for regulating medical devices in the US.  
- A medical device can only be marketed in the US after receiving FDA approval. |
| **Risk categorisation** | - Class I: low-risk (e.g., wheelchairs)  
- Class IIa: moderate-risk (e.g., tracheotomy tubes)  
- Class IIb: moderate-risk (e.g., lung ventilators)  
- Class III: high-risk (e.g., heart valves)  
- Class I: low-risk (e.g., stethoscopes)  
- Class II: moderate-risk (e.g., non-invasive blood pressure monitors)  
- Class III: high-risk (e.g., implantable cardioverter-defibrillators) |
| **Evidence standards for approval** | - Generally, notified bodies require proof that a device works as intended (for moderate and high-risk devices).  
- Although clinical data are typically required for high-risk devices, design features of clinical studies are not specified.  
- Evidence standards are opaque and may vary across different notified bodies.  
- Moderate-risk devices and some high-risk devices can be “cleared” through the 510(k) pathway, which typically does not require clinical data.  
- High-risk devices are approved through the pre-market approval (PMA) pathway, which requires clinical trials evaluating the effectiveness and safety of devices. |
| **Availability of expedited programs** | - No  
- FDA’s Breakthrough devices program offers intensive interaction and priority review to expedite the development and review for “devices that provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions.” |

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Panel 1. Sources of uncertainty when generating comparative data on newly-approved drugs.

**Lack of active-comparator trials**
- Of the 448 clinical studies that supported the US FDA approval of 188 new drugs between 2005 and 2012, more than half had only placebo controls. In some therapeutic areas such as neurology and oncology, fewer than one fifth of clinical studies had active comparators.
- Esketamine was approved for treatment-resistant depression in 2019 by the FDA on the basis of placebo-controlled trials despite the availability of another approved drug for this indication.

**Weak study designs**
- Between 2012 and 2017, fewer than one fifth of studies supporting the FDA approval of drugs with both breakthrough therapy designation and accelerated approval status relied on surrogate measures and accelerated approval status were randomised and only about 9% were blinded.
- Of the 26 drugs with EMA conditional marketing authorisations until 2015, fewer than half had blinded studies.

**Features of study designs associated with expedited programs**

**Lack of appropriate active comparators**
- Brexpiprazole was approved for the treatment of schizophrenia in 2018 by the EMA on the basis of 4 RCTs, 3 of which were placebo-controlled. The only active-comparator RCT included quetiapine as the control treatment, which was judged to be an inappropriate choice according to the EMA who concluded that aripiprazole would have been a better option.

**Single-group studies**
- Almost two thirds of clinical studies in the FDA's accelerated approval pathway between 2009 and 2013 had no comparators.
- From 1992 to 2017, “single-group” studies provided the data for almost three quarters of the 93 accelerated approvals in cancer indications.
- Between 2012 and 2017, more than 80% of studies that supported the 18 drugs with a combination of both the breakthrough therapy designation and accelerated approval status had no comparators.
- Between 2006 and 2016, over half of EMA conditional marketing authorisations for cancer drugs were based on single-group studies.

**Non-inferiority designs**
- One of the pivotal studies supporting the 2018 EMA approval of the glucose-lowering drug erenumab tested its non-inferiority against glipizide.
- More recently, the FDA approved lenvatinib for the first-line treatment of unresectable hepatocellular cancer on the basis of a non-inferiority trial against sorafenib.

**Surrogate measures**
- Almost four fifths of studies supporting drugs in the FDA's breakthrough therapy designation relied on surrogate measures alone.

**Source:** Authors

**References:**


Panel 2. Overview of current expedited development and regulatory review programs for drugs and devices

- **FDA Priority review designation**: guarantees “shorter clock for review of marketing application (6 months compared with the 10-month standard review) for drugs that treat a serious condition and have the potential to provide a significant improvement in safety or effectiveness.” ¹

- **FDA Fast-track designation**: provides “actions to expedite development and review, including rolling review, for drugs intended to treat a serious condition or address unmet medical need.” ¹

- **FDA Accelerated approval pathway**: offers “approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit for drugs that treat a serious condition and provide a meaningful advantage over available therapies.” ¹

- **FDA Breakthrough therapy designation**: provides “intensive guidance on efficient drug development, organisational commitment, rolling review, and other actions to expedite review for drugs intended to treat a serious condition or have the potential to demonstrate substantial improvement on a clinically significant endpoint over available therapies.” ¹

- **EMA Approval under exceptional circumstances**: “granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical.” ²

- **EMA Conditional marketing authorisation**: “grants approval on the basis of less comprehensive data than normally required for drugs that address unmet medical needs of patients.” ³

- **EMA Accelerated assessment**: guarantees “rapid assessment (150 days vs 210) for medicines that are of major interest for public health, especially ones that are therapeutic innovations.” ⁴

- **EMA Priority medicines (PRIME) scheme**: offers “enhanced early dialogue with manufacturers to optimise development plans and accelerated assessment of medicines that target an unmet medical need.” ⁵

References:

2. https://www.fda.gov/media/108135/download
Figure 1. Proportion of EMA drug approvals from 2015 to 2018 with at least one randomised, active-comparator trial.

Source: Authors
Data extracted from publicly available European Public Assessment Reports of new active substances with first time approvals by the European Medicines Agency, 2015-2018.
Figure 2. Proportion of FDA drug approvals in at least one expedited program, 2009-2018.

Source: Authors  
Data extracted from the publicly available Drugs@FDA database of new molecular entity approvals by the FDA, 2009-2018.
**Figure 3.** Lack of comparative evidence in selected therapeutic areas. Each node represents a different active treatment and the lines connecting the nodes represent direct head-to-head comparisons between active treatments.

This network diagram shows the availability of randomised controlled trials directly comparing available treatments for rheumatoid arthritis.

Of 214 possible comparisons between 22 treatments, only 11 are available.

This network diagram shows the availability of randomised controlled trials directly comparing available percutaneous coronary interventional strategies for treatment of in-stent restenosis.

Of 28 possible comparisons between 8 treatment strategies, only 12 are available.

This network diagram shows the availability of randomised controlled trials directly comparing available treatments for multiple sclerosis.

Of 105 possible comparisons between 15 treatments, only 7 are available.
References:


### Table 2. Strategies aimed at incentivising pharmaceutical and device manufacturers to generate comparative data on drugs and devices.

<table>
<thead>
<tr>
<th>Overall strategies</th>
<th>Key recommendations</th>
<th>Target stakeholders</th>
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| (1) Greater transparency on comparative data availability at the time of market entry | • Product labels should routinely report whether head-to-head comparisons of new and existing treatment options are available at the time of market entry. | • Regulatory agencies (FDA and EMA)  
• Pharmaceutical manufacturers  
• Device manufacturers |
| (2) More selective use of expedited programs                                         | • Expedited programs should be reserved for a clearly demarcated set of circumstances.  
• New guidelines should be developed to determine the eligibility of drugs and devices for inclusion in expedited programs in the US and eligibility of drugs in Europe.  
• Reasons for eligibility should be routinely and openly reported.               | • Regulatory agencies (FDA and EMA)  
• Pharmaceutical manufacturers  
• Device manufacturers  
• European national competent authorities |
| (3) More routine use of randomised, active comparator trials                        | • New products should be evaluated in randomised controlled trials with active comparators.  
• Trial efficiency should be improved by loosening trial eligibility criteria and by appraising the suitability of registry-based trials. | • Regulators (FDA and EMA)  
• Pharmaceutical manufacturers  
• Device manufacturers  
• National governments |
| (4) Prospectively designed network meta-analyses                                     | • Network meta-analyses should be prospectively designed within each therapeutic area.  
• Pre-approval scientific advice should harmonise trial designs, populations, interventions, comparators, core outcome sets, and follow-up durations to ensure broad similarity across different trials. | • Regulators (FDA and EMA)  
• Pharmaceutical manufacturers  
• Device manufacturers  
• European national competent authorities |
| (5) Considering comparative effectiveness evidence in pricing and payment decisions   | • Comparative effectiveness data should be a central tenet of pricing and payment decisions.  
• Only products with demonstrated superiority should warrant higher prices compared to alternatives. | • Public payers in the US and Europe  
• Health technology assessment organisations |