The Origin of First-in-Class Drugs: Innovation Versus Clinical Benefit

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First-in-class (FIC) designation became a hallmark of innovation, however, even at the marketing authorization stage, little is known about the clinical benefits these products deliver. We identified the provenance of the FIC drugs that entered the French market from 2008 to 2018 and matched these medicines to the clinical benefit grading by Haute Autorité de Santé (HAS) and Prescrire. Analyses were performed using descriptive statistics to present our findings by drug origin and therapeutic area and to establish the degree of concordance between HAS and Prescrire. Of the 135 FIC drugs identified, 71.1% ($n=96$) originated from the industry, 16.3% ($n=22$) from academia, and 12.6% ($n=17$) from joint partnerships. Three therapeutic areas accounted for most FIC medications: antineoplastic (25.9%, $N=35$), anti-infective (14.1%, $N=19$), and metabolic (11.1%, $N=15$) agents. HAS and Prescrire agreed on 60.74% of clinical benefit gradings. According to HAS, only 5% of all FIC drugs had substantial added benefit, and only 3%, according to Prescrire. HAS and Prescrire graded 45.9% and 68.2%, respectively, of FIC drugs as no clinical benefit and 48.9% and 28.9%, respectively, as some clinical benefit. FIC-designated drugs are primarily of industry (> 70%) rather than academic origin. We found that 55% of FIC medicines that entered the French market over the 10-year period deliver no additional clinical benefit. Whereas FIC medicines may represent important scientific advancements in drug development, in > 50% of cases, the new mode of action does not translate into additional clinical benefits for patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ First-in-class (FIC) medicines represent important scientific advancements in drug development and have become a representation of pharmaceutical innovation. Most drugs entering the market provide no or low-added clinical benefit.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Who discovers the US Food and Drug Administration (FDA)-designated first-in-class drugs, and what clinical benefit do they deliver?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ FIC drugs originate primarily in the industry (> 70%) rather than in academia. Over 55% of the FIC medicines deliver no additional clinical benefit to patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our findings have implications for drug selection in formularies, clinical pharmacology inputs in practice guideline development, and can also facilitate priority-setting policies for Health Technology Assessment agencies.

Governments, the pharmaceutical sector, healthcare systems, and patients all stand to benefit from clinically superior and cost-effective therapies.[1] Since the 1970s, critical advancements in scientific and technological efforts, such as combinatorial chemistry, DNA sequencing, high-throughput screening, the biotechnology industry, and new drug targets, have been significant contributors to drug research and development.[2] Despite these advances, health outcomes have not been proportionally improved.[2,3] Although some newly approved medications have revolutionized patient outcomes, many "innovative" drugs fail to deliver significant improvement while demanding higher prices. As a result, healthcare payers and stakeholders have begun to resist increasing prices, instead emphasizing the added therapeutic benefit provided.[4]

Few recently approved drugs are truly innovative. Lexchin, in 2016, reported in his study that only 16% of first-in-class drugs ($n=292$) that entered the Canadian market between 1997 and 2012 were found to be therapeutically innovative.[5] Ward *et al.* (2014) explored new drugs added to the British National Formulary (BNF) from 2001 to 2012.[1] The study found that over a quarter of the 290 new drugs were highly innovative, just under a fifth were moderately innovative, and over half were slightly innovative.[1] Prescrire, the French non-profit educational organization

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that evaluates the therapeutic value of innovative drugs marketed in France since 1981, found that more than half of the 984 new drugs or new indications authorized between 2000 and 2009 did not offer anything novel.[6] Other studies that have defined and assessed the innovation of new drugs using diverse methods have concluded that just a small number of new medicines are "highly innovative."[7–13] Overall, from 2004, there was a positive trend toward slightly innovative drugs, with anticancer drugs and medications for skin disease most likely to be ranked as highly innovative.[1]

In the United States, the US Food and Drug Administration (FDA) awards the "first-in-class" (FIC) designation to products that "use a novel and unique mechanism of action to treat a medical condition," indicating that it is inventive, cutting-edge, and with the potential to create unparalleled patient results.[14] Back in 2014, the McKinsey & Company analysis has shown that FIC players, on average, achieve a greater-than-fair market share.[15] Importantly, they also receive a longer market exclusivity period than additions to the class.[16] Lanthier *et al*. discusses that pharmacy benefit management firms which process prescription drug claims are less likely to pay for high-priced addition to class drugs. This may have led drug manufacturers to focus on FIC medicines.[17] The definitions and labeling of pharmaceutical innovation differ between countries, raising concerns for healthcare payers who seek to maximize value in pharmaceutical purchases. Morgan *et al*. state that neither mode of action novelty nor effectiveness alone is enough to qualify a medicine as a pharmaceutical innovation.[9] A drug can be considered a pharmaceutical innovation only if it meets otherwise unmet or inadequately met healthcare needs.[9]

Additional clinical benefit is measured by a few organizations using various scales and for different purposes. For example, there are specific scales in oncology developed by the European Society for Medical Oncology (ESMO)[18] and the American Society of Clinical Oncology (ASCO),[18] and there are agency-based processes in Canada,[19] the United States,[20] and Germany.[21] In France, two organizations, the Haute Autorité de Santé (HAS) and Prescrire assess the clinical benefit of drugs. HAS is an autonomous non-governmental organization established by the French government in August 2004. HAS assesses medicines mainly in terms of how the medicine compares to existing treatments, and drugs are classified into five benefit categories: major, important, moderate, minor, and not present. Prescrire is a not-for-profit continuing educational organization committed to better patient care. Established in 1981, Prescrire has supplied healthcare professionals and, indirectly, patients with simple, detailed, and accurate information about pharmaceutical drugs and other therapeutic and diagnostic treatments. Like HAS, Prescrire evaluates how a drug compares to currently available therapies and then classifies it into seven categories: bravo, a real advance, offers an advantage, possibly helpful, nothing new, unacceptable, and judgment reserved.

In this study, we examine FIC drugs that entered the French market between 2008 and 2018 and evaluate their clinical advantages and origins (academic vs. industry). Furthermore, we assess these FIC medicines' clinical benefit by therapeutic category and determine the degree of concordance between the HAS and Prescrire's clinical benefit grading scales.

METHODS

Data sources

The dataset (the list of medicines) for this study was made available by Prescrire. These data are in the public domain in Prescrire publications. Publicly available reports from the FDA[22] were reviewed to identify medicines that received the FIC designation between 2008 and 2018. These medicines were matched to the products evaluated for clinical benefit by Prescrire. Two researchers conducted this exercise independently and compared their outputs to check each other's work. A third researcher re-evaluated the list for accuracy and coherence. We extracted data on added clinical benefit for each medicine in our study sample from the provided Prescrire dataset. The HAS data (ASMR - Amélioration du service médical rendu) grading on clinical benefits were collected from a publicly available online database.

Identification of drug origins

To verify a product's provenance, at least two independent sources had to confirm the same origin without cross-referencing each other. The main source of information used was the Pharmaceutical Substances database: Syntheses, Patents, and Applications of the most relevant active pharmaceutical ingredients, version 4.8. Additionally, we searched the AdisInsight database, previously published material on the origins of pharmaceuticals, and the Pharmaceutical Manufacturing Encyclopaedia.[23] Last, we also screened Google and Google Scholar to find papers, book chapters, and corporate or institutional websites with drug origin information. Two independent researchers identified the origins of drugs and then cross-checked their results. To address any disagreements, a third researcher performed further searches and rechecks.

The origin of drugs was categorized as follows: (1) industry (which includes both pharmaceutical and biotech companies as well as collaborations between industry and biotech), and (2) academia (which includes drugs invented in academia or through industry/academia or biotech/academia collaborations). See our data set in the zenodo.org public repository for details.

Therapeutic categories

Broad therapeutic categories for the classification of medicines were sourced from Drugs.com, an independent medication information website. Medicines in our sample size were classified into 15 therapeutic categories: (1) anti-infective, (2) antineoplastic, (3) biologicals, (4) cardiovascular agents, (5) central nervous system agents, (6) coagulation modifiers, (7) gastrointestinal agents, (8) genitourinary tract agents, (9) hormones, (10) immunologic agents, (11) metabolic agents, (12) miscellaneous agents, (13) psychotherapeutic agents, (14) topical agents, and (15) respiratory agents. Therapeutic categories were assigned to the list of FIC medicines selected for analysis by two researchers with pharmacology training. A third researcher resolved discrepancies.

Clinical benefit

We created a unified matched scale of drug clinical benefit assigned by Prescrire and HAS (**Table 1**) to enable comparison. **Table 1** lists the original grading scales used by both Prescrire and HAS. For each drug, we identified the indication with the highest grade assigned by HAS and the corresponding grade assigned by Prescrire for the same indication. The new scale (also listed in **Table 1**) consisted of three grades: (1) substantial added benefit, (2) some added benefit, and (3) no added benefit. Because judgment reserved is a category assigned by Prescrire but not by HAS, we integrated this grading into the no clinical benefit category for comparative purposes (**Table 1**).

Analysis

A descriptive statistics analysis was performed in STATA to calculate proportions expressed as percentages and frequencies of FIC medicines graded for clinical benefit by Prescrire and HAS in the following

Table 1 Clinical benefit scales

HAS[a]	Prescrire[b]	Matched scale
Major	Bravo	Substantial added benefit
Important	A real advance	
Moderate	Offers an advantage	Some added benefit
Minor	Possibly helpful	
Non-existent Not acceptable	Nothing new	No added benefit
	Not acceptable judgment reserved	

[a]Haute Autorité de Santé (HAS) is an autonomous non-governmental organization established by the French government, and one of its responsibilities is to evaluate the benefits of drugs entering the French market. [b]Prescrire is a not-for-profit organization established in 1981 dedicated to providing unbiased information on therapeutic and diagnostic treatments and evaluates how a drug compares to currently available therapies.

categories: the origin of drugs, therapeutic category, and clinical benefit. Once the results were converted to the matched scale, we calculated the number of drugs on which HAS and Prescrire agreed in terms of clinical benefit to establish the degree of concordance using the Cohen's Kappa test. This test quantifies the level of agreement between two grading systems, considering the possibility of agreement due to chance alone (kappa = 0) and the highest level of agreement (kappa = 1). Because Prescrire provided the original data set, longitudinal analysis (clinical benefit and drug origin) was performed using Prescrire clinical benefit grading years; HAS grading for the same indication might not have been awarded in the same year but was usually within ±2 years of Prescrire grading.

RESULTS

A total of 135 FIC drugs were identified in the Prescrire data set. There were 71.1% that originated from industry, 16.3% from academia, and 12.6% from collaborations.

Figure 1 illustrates that Prescrire graded more FIC drugs as having no added benefit (68.2%, $N = 92$) than HAS (45.9%, $N = 62$). HAS graded more drugs as having some added benefit (48.9%, $N = 66$) compared with Prescrire (28.9%, $N = 39$). Both Prescrire (3%, $N = 4$) and HAS (5.2%, $N = 7$) awarded substantial added benefit to very few FIC products. When looking at medicines' provenance, between Prescrire and HAS, 49% of the FIC drugs originating from academia and 42% of those originating in industry were designated as having some or substantial clinical benefit.

The comparison between the Prescrire and HAS grading systems' agreement was evaluated using kappa statistics. If both agencies were to make their gradings randomly, the anticipated agreement between them, as determined by the kappa test, would be 45.57% concerning the classifications of medicines. However, the test revealed that the actual agreement reached 60.74%. This allows us to reject the null hypothesis ($P < 0.05$) that the agencies are arriving at their gradings randomly, showing fair agreement (kappa statistic is 0.28).

The top three therapeutic areas for the analyzed FIC medicines were antineoplastic drugs (25.9%, $N = 35$), anti-infective drugs (14.1%, $N = 19$), and metabolic agents (11.1%, $N = 15$). **Figure 2** (Prescribe) and **2B** (HAS) present clinical benefit grading data by therapeutic categories. For example, Prescrire graded 65.7% ($n = 23$) of the antineoplastic agents, 42.1% ($n = 8$) of the anti-infectives, and 86.7% ($n = 13$) of the metabolic agents as providing no added benefit. In contrast, HAS graded 28.6% ($n = 10$) of antineoplastics, 31.6% ($n = 6$) of anti-infectives, and 46.7% ($n = 7$) of metabolic agents as providing no added benefit. There were 28.6% ($n = 10$) of antineoplastics, 52.6% ($n = 10$) of anti-infectives, and 6.7% ($n = 1$) of metabolic agents that were graded as adding some benefit by Prescrire. Whereas HAS graded 65.7% ($n = 23$) of the antineoplastics, 68.4% ($n = 13$ of the anti-infectives, and 40% ($n = 6$) of the metabolic agents as adding some benefits. There were 5.7% ($n = 2$) of antineoplastics, 5.3% ($n = 1$) of anti-infectives, and 6.7% ($n = 1$ of metabolic agents that were graded as adding substantial benefits by Prescrire. There were 5.7% ($n = 2$) of antineoplastic agents, 0% ($n = 0$) of anti-infective agents, and 13.3% ($n = 2$) of metabolic agents that were graded by HAS as adding substantial benefits. Overall, we find some differences across therapeutic areas and depending on the grading system. Notably, both organizations agreed that very few medicines had substantial added benefit.

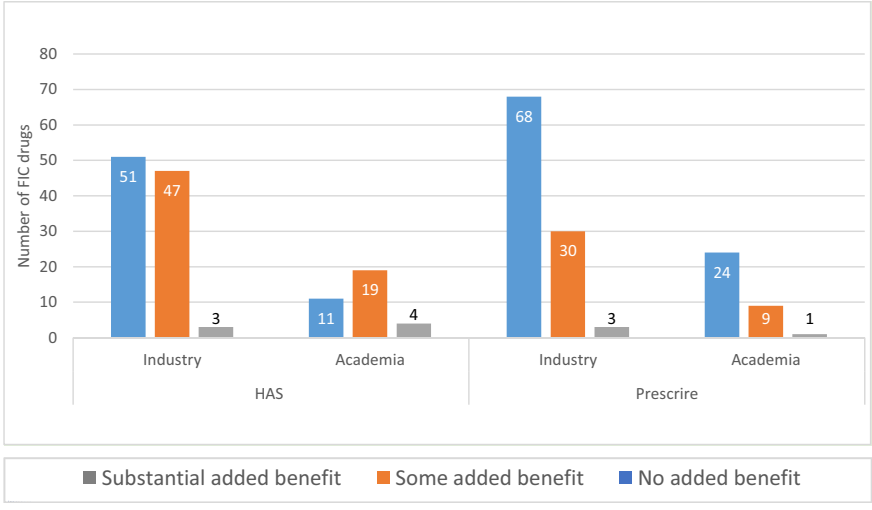

Figure 1 Clinical benefit of first-in-class drugs by origin and grading organization. FIC, first-in-class; HAS, Haute Autorité de Santé.

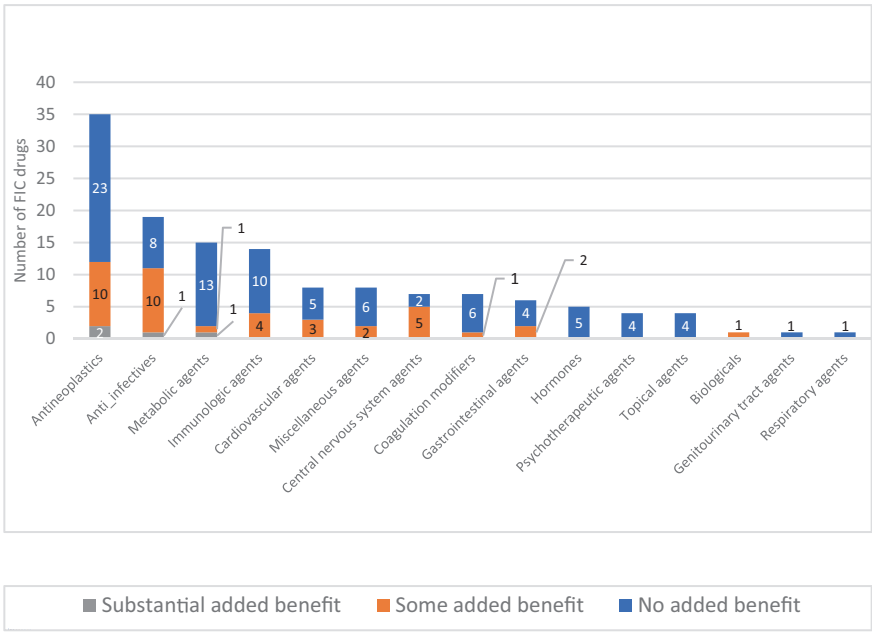

Figure 2 (**a**) FIC clinical benefit by therapeutic area (Prescrire grading) *N*=135. (**b**) FIC clinical benefit by therapeutic area (HAS grading) *N*=135. FIC, first-in-class; HAS, Haute Autorité de Santé.

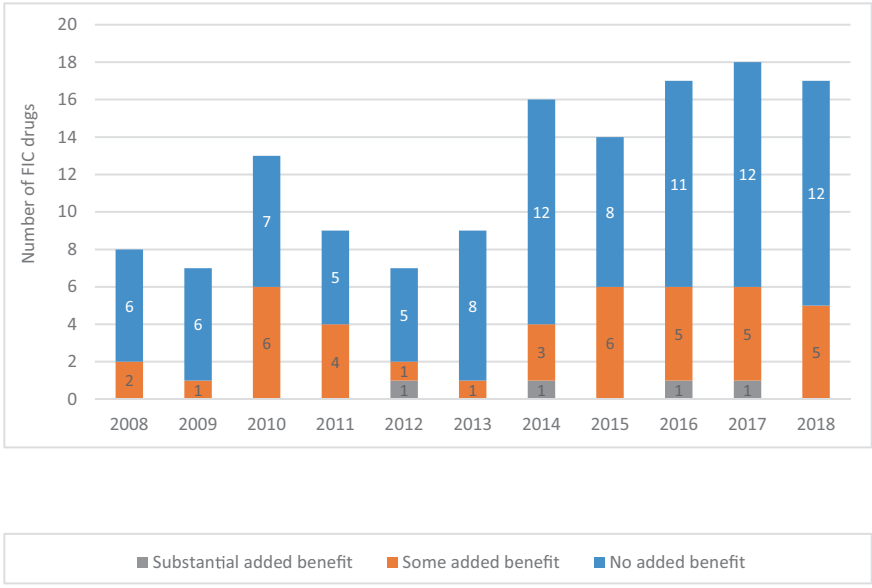

Figure 3 FIC drugs by year[a] and clinical benefit grading from Prescrire *N*=135. ([a]According to Prescrire assessment rather than award of first-in-class (FIC) status by the FDA.) FDA, US Food and Drug Administration; FIC, first-in-class; HAS, Haute Autorité de Santé.

Figure 3 shows a longitudinal analysis indicating a rise in FIC designations over time but no apparent trend toward variations in clinical benefit. Between 2008 and 2018, the most prevalent grade awarded by Prescrire was no added benefit, ranging from 53.9% (*N*=7) in 2010 to 88.9% (*N*=8) in 2013. The next most prevalent grade was some added benefit, with an average of 27.6% per year, ranging from 11.1% (*N*=1) in 2013 to 46.2% (*N*=6) in 2010. The least awarded grade was substantial added benefit, which was only present in 4 years: 2012 (14.29%, *N*=1), 2014 (6.25%, *N*=1), 2016 (5.88%, *N*=1), and 2017 (5.56%, *N*=1). Overall, the general trend we observe across our study period is that very few medicines demonstrated substantial added clinical benefit.

DISCUSSION

Pharmaceutical innovations must create value for society by generating improvements in patient health (net of treatment risks) that were previously unattainable. It is the uniqueness of such health improvements that should define pharmaceutical innovations.[9] Our analysis shows that only a few (5% and 3% as respectively graded by HAS and Prescrire) FIC drugs that entered the French

market between 2008 and 2018 offer substantial added clinical benefit. More than half of the medicines analyzed were graded as not offering any additional clinical benefit by both organizations. Our work supports earlier findings that few FIC medicines offer therapeutic innovation to patients.[5] For example, our list includes such medicines as bevacizumab (Avastin), lenalidomide (Revlimid), imatinib (Glivec), bortezomib (Velcade), ibrutinib (Imbruvica), olaparib (Lynparza), losartan (Cozaar) and many others which are or have been bringing billion-dollar annual revenues for many years. However, in recent years, there has been a shift from treatment for common conditions to treatment for rarer conditions.[24] The shift toward rare diseases and personalized medicines (particularly in oncology) is characterized with a steadily growing number of FIC designations awarded every year (since 2017) by the FDA.[25] This trend was demonstrated in our study as well for the 2008–2018 time period. The growth in FIC medicines entering the market is likely to continue thanks to multiple incentives. For example, at the FDA, majority of FIC medicines receive a priority review rating, meaning that the FDA deems these products to be potentially substantial advances relative to existing therapies.[17] The Orphan Drugs Act in the United States[26] and the Innovative Medicines Initiative (IMI)[24] in Europe, have also encouraged the shift toward development of new classes of medicines focusing on specific targets and populations.[26,27]

Several factors, including marketing and policies, determine the product's market share over time, and this may vary among healthcare systems.[18,28] The Spring *et al*. 2023 study evaluated 29 drug classes with novel mechanisms introduced after 2010, totaling 104 drugs.[29] Their analysis found that FIC drugs tend to acquire a larger market share than second-and-best-in-class drugs.[29] The value share of second-and-best-in-class drugs is 38% of first-best-in-class products.[29] From a financial point of view, focusing on FIC drugs may be a way for big pharma as well as biotechs to boost their pipelines and steal market share from competitors investing in the same therapy area.[14] The extended market exclusivity period granted to FIC developers provides a strong financial signal and economic incentives. Schulze and Ringe (2013) demonstrate that current market structures reward being first more than being best and commercial success in the form of market power is higher for FIC drugs than additions to the class given the same level of clinical benefit.[30] Whether the market forces push the industry toward personalized medicines or rare conditions, a sustainable long-term strategy by the pharmaceutical sector should focus on developing the culture and skills necessary to ensure biomedical breakthrough innovations that address unmet medical needs rather than flooding the market with medicines that deliver no additional clinical benefit.[31]

Unfortunately, in today's market, clinical benefit is not the most important factor in determining a drug's success.[28] Although there are strong economic incentives for the industry to focus on the FIC drugs, there are few regulatory and legislative stimuli for developers to pursue clinical benefit in innovation. The European Clinical Trial Act of 2014 does not require the pharmaceutical industry to demonstrate that their new medicine represents a therapeutic breakthrough, thus squandering a chance to stimulate comparative assessments of new drugs with existing ones.[32] Critics argue that the FDA has lowered its evidence criteria by approving drugs with debatable efficacy, and its decisions in areas of urgent unmet medical need have received particular attention.[33,34] Frequently, manufacturers are granted marketing authorization with insufficient data on clinical benefit. Comparative trials are often absent, or may suffer from various methodological issues, making it difficult or impossible to establish clinical effectiveness.[35–38] These are a few reasons why we have many "me too" drugs on the market. These products, whereas not offering additional clinical benefit, may offer important alternative treatment options to patients; however, overproduction of so-called "me too" options diverts important resources from pursuing developments which can make clinically important differences to patients.

Assessing additional clinical benefit is not an easy task. It is a subjective process lacking standardization and ideally requiring a dynamic approach to judgment (as available evidence evolves). Besides different agencies[19–21] and organizations[18,39] assessing additional clinical benefit, as we described earlier, in a systematic review Kesselheim and colleagues identified many other approaches by various authors to establish therapeutic value of medicinal products.[13] We compared only two grading scales (HAS and Prescrire) and to enable such comparison, we created a simplified matched scale (**Table 1**), which led to the loss of granularity and thus potentially a greater divergence in clinical benefit grading between the organizations (see results of the kappa test which show a fair agreement). Further methodological work standardizing processes for measuring additional clinical benefit would be of interest as well as the development of legislature to require the establishment of additional clinical benefit to become a value judgment in price setting and uptake of the product in clinical practice.

We echo Prescrire's (2018) message[38] and advise healthcare providers to "play a central role in choosing drugs that demonstrate benefit and limiting patients' exposure to poorly assessed drugs, that provide no tangible therapeutic value, or are more dangerous than useful."

Limitations

Our search for the origins of medicines was systematized; however, identifying or confirming original sources was not always possible, and errors might therefore exist in our findings/judgments for some drugs. We provide our dataset (with all references to the original data on every product) zenodo.org public repository[40] with the hope that it can serve as a useful resource for future researchers and cross-validation of our work.

To match the clinical benefit grading between Prescrire and HAS, we developed a simplified matched scale that allowed us to conduct comparative analyses. However, simplifying the scale may have resulted in some loss of granularity relative to the original scales.

Medicines that Prescrire graded as "judgment reserved, pending, or unavailable" (17 of 135) were classified in our revised grading system as having no additional clinical benefit. If further evidence become available for these medicines over time, their grading might change. However, as our research shows, over 50%

of these medicines are likely to remain in the no additional benefit category. Thus, our assumption is unlikely to change our overall conclusions.

CONCLUSIONS

Our study found that FIC-designated drugs were primarily of industry rather than academic origin. Regardless of the origin or organization assessing clinical benefit of FIC medicines, over 55% of them deliver no additional clinical benefit to patients. Although FIC medicines may represent important scientific advancements in the drug development pathway, the rhetoric for attributing success in drug development should, first and foremost, focus on the ability to advance therapeutic benefit to patients and carers. Formularies and clinical guidelines need to prioritize medicines offering additional clinical benefits to patients.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

L.O., S.U.-H., and E.M. wrote the manuscript. L.O. and E.M. designed the research. L.O., F.A., P.P., and I.P. performed the research. B.P., F.A., P.P., and I.P. analyzed the data.

ETHICAL APPROVAL

Not applicable.

TRANSPARENCY DECLARATION

The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted, and all discrepancies from the planned study have been explained.

DATA SHARING

The complete data set used in this research is available for download from the zenodo.org public repository.

1. Ward, D.J., Slade, A., Genus, T., Martino, O.I. & Stevens, A.J. How innovative are new drugs launched in the UK? A retrospective study of new drugs listed in the British National Formulary (BNF) 2001–2012. *BMJ open* **4**, e006235 (2014).
2. Scannell, J.W., Blanckley, A., Boldon, H. & Warrington, B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discov.* **11**, 191–200 (2012).
3. Daniel, G.W., Cazé, A., Romine, M.H., Audibert, C., Leff, J.S. & McClellan, M.B. Improving pharmaceutical innovation by building a more comprehensive database on drug development and use. *Health Aff. (Millwood).* **34**, 319–327 (2015).
4. Eichler, H.G., Enzmann, H. & Rasi, G. Added therapeutic benefit and drug licensing. *Nat. Rev. Drug Discov.* **18**, 651–652 (2019).
5. Lexchin, J. How safe and innovative are first-in-class drugs approved by Health Canada: a cohort study. L'innocuité et l'aspect innovant des nouvelles classes de médicaments approuvés par Santé Canada: Une étude de cohorte. Healthc. *Foreign Policy* **12**, 65–75 (2016).
6. Vitry, A.I., Shin, N.H. & Vitre, P. Assessment of the therapeutic value of new medicines marketed in Australia. *J. Pharmaceut. Policy Pract.* **6**, 2 (2013).
7. Motola, D., De Ponti, F., Rossi, P., Martini, N. & Montanaro, N. Therapeutic innovation in the European Union: analysis of the drugs approved by the EMEA between 1995 and 2003. *Br. J. Clin. Pharmacol.* **59**, 475–478 (2005).
8. Joppi, R., Bertele, V. & Garattini, S. Disappointing biotech. *BMJ* **331**, 895–897 (2005).
9. Morgan, S., Lopert, R. & Greyson, D. Toward a definition of pharmaceutical innovation. *Open Med.* **2**, e4–e7 (2008).
10. Ferner, R.E., Hughes, D.A. & Aronson, J.K. NICE and new: appraising innovation. *BMJ* **340**, b5493 (2010).
11. Kennedy, I. Appraising the value of innovation and other benefits. A short study for NICE. <https://www.nice.org.uk/Media/Default/About/what-we-do/Research-and-development/Kennedy-study-final-report.pdf> (2009) Accessed December 2022.
12. Aronson, J.K., Ferner, R.E. & Hughes, D.A. Defining rewardable innovation in drug therapy. *Nat. Rev. Drug Discov.* **11**, 253–254 (2012).
13. Kesselheim, A.S., Wang, B. & Avorn, J. Defining "innovativeness" in drug development: a systematic review. *Clin. Pharmacol. Therapeut.* **94**, 336–348 (2013).
14. Luscombe, E. Is being the first ever 'better'than being the best? *Expert Opin. Pharmacother.* **15**, i–ii (2014).
15. Cha, M. & Yu, F. Pharma's first-to-market advantage <https://www.mckinsey.com/~/media/McKinsey/Industries/Pharmaceuticals%20and%20Medical%20Products/Our%20Insights/Pharmas%20first%20to%20market%20advantage/Pharmas%20first%20to%20market%20advantage.pdf> (2014) Accessed June 1, 2023.
16. Wang, B., Liu, J. & Kesselheim, A.S. Variations in time of market exclusivity among top-selling prescription drugs in the United States. *JAMA Intern. Med.* **175**, 635–637 (2015).
17. Lanthier, M., Miller, K.L., Nardinelli, C. & Woodcock, J. An improved approach to measuring drug innovation finds steady rates of first-in-class pharmaceuticals, 1987-2011. *Health Aff. (Millwood).* **32**, 1433–1439 (2013).
18. Cherny, N.I. *et al*. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology magnitude of clinical benefit scale (ESMO-MCBS) [published correction appears in Ann Oncol. 2017 Nov 1;28(11):2901–2905]. *Ann. Oncol.* **26**, 1547–1573 (2015).
19. Patented Medicine Price Review Board. Compendium of guidelines, policies and procedures <https://www.pmprb-cepmb.gc.ca/view.asp?ccid=529#806> (2008) Accessed April 2023.
20. Institute for Clinical and Economic Review. 2020–2023 Value Assessment. January 2021. Updated February 2022 <https://icer.org/wp-content/uploads/2020/11/ICER_2020_2023_VAF_02032022.pdf> Accessed April 2023.
21. Gemeinsamer Bundesausschuss. The benefit assessment of medicinal products in accordance with the German Social Code, Book Five (SGB V), section 35a <https://www.g-ba.de/english/benefitassessment/> (2019) Accessed April 2023.
22. U.S. Food and Drug Administration Centre of drug evaluation and research. New Drug Therapy Approvals. 2008–2018 <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entit

ies-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2022>. Accessed January 2022.
23. Andrew, W. *Pharmaceutical Manufacturing Encyclopedia* 3rd edn. (William Andrew Pub, Norwich, N.Y., 2013) <https://www.perlego.com/book/1856646/pharmaceutical-manufacturing-encyclopedia-pdf>. Accessed August 30, 2022.
24. Collins, R. *Evolve or Die: The Urgent Need to Streamline RCTs* (Consilium Scientific, London, 2023) <https://www.youtube.com/watch?v=acdJwUcfXMU>.
25. Craven, J. FDA approved more first-in-class drugs, gave more accelerated approvals in 2021. *Regulatory News* <https://www.raps.org/News-and-Articles/News-Articles/2022/1/FDA-approved-more-first-in-class-drugs-more-with-a>. (2022) Accessed March 2022.
26. Herder, M. What is the purpose of the orphan drug act? *PLoS Med* **14**, e1002191 (2017).
27. Goldman, M. The innovative medicines initiative: a European response to the innovation challenge. *Clin. Pharmacol. Ther.* **91**, 418–425 (2012).
28. Vokinger, K.N. *et al*. Analysis of launch and postapproval cancer drug pricing, clinical benefit, and policy implications in the US and Europe. *JAMA Oncol.* **7**, e212026 (2021).
29. Spring, L., Demuren, K., Ringel, M. & Wu, J. First-in-class versus best-in-class: an update for new market dynamics. *Nat. Rev. Drug Discov.* **22**, 531–532 (2023).
30. Schulze, U. & Ringel, M. What matters most in commercial success: first-in-class or best-in-class? *Nat. Rev. Drug Discov.* **12**, 419–420 (2013).
31. Eder, J. & Herrling, P.L. Trends in modern drug discovery. *Handb. Exp. Pharmacol.* **232**, 3–22 (2016).
32. Prescrire International. New drugs and indications in 2014. Some advances this year, but many drugs are poorly evaluated, too expensive, or more dangerous than useful. *Prescrire Int.* **24**, 107–110 (2015).
33. Ward, A.S., Van Nuys, K. & Lakdawalla, D. *Impacts of First-in-Class Drug Approvals on Future in-Class Innovation. [White paper]* (USC Schaeffer Center for Health Policy & Economics, Los Angeles, USA, 2021 <https://healthpolicy.usc.edu/wp-content/uploads/2022/07/Impacts_of_First-in-Class_Drug_Approvals_on_Future_In-Class_Innovation.pdf>) Accessed January 2022.
34. Mitra-Majumdar, M. *et al*. Analysis of supportive evidence for US Food and Drug Administration approvals of novel drugs in 2020. *JAMA Netw. Open* **5**, e2212454 (2022).
35. Seruga, B., Templeton, A.J., Badillo, F.E.V., Ocana, A., Amir, E. & Tannock, I.F. Under-reporting of harm in clinical trials. *Lancet Oncol.* **17**, e209–e219 (2016).
36. Tannock, I.F. *et al*. Relevance of randomised controlled trials in oncology. *Lancet Oncol.* **17**, e560–e567 (2016).
37. Davis, C., Naci, H., Gurpinar, E., Poplavska, E., Pinto, A. & Aggarwal, A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009–13. *BMJ* **359**, j4530 (2017).
38. Prescrire International. Drugs in 2017: a brief review (2018) 110–111.
39. American Society of Clinical Oncology. Value in Cancer Care; ASCO Value Framework <https://old-prod.asco.org/news-initiatives/current-initiatives/cancer-care-initiatives/value-cancer-care>. (2016) Accessed April 2023.
40. The Origin and Clinical Benefit of First-in-Class Drugs that entered the French market between 2008 and 2018. Complete data set <https://zenodo.org/record/7823470#.ZDbwaezMIUs>.