



An Empirical Analysis of Innovation in the Pharmaceutical Industry by Drug Class: Implications for Regulatory Policy

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Abstract

The pace of innovation, the creative engine of the pharmaceutical industry, has been variably described as stagnant, stable, or accelerating depending on the metric used for assessment or the quality of evidence. If the predominant perception holds that the speed of innovation is sluggish, pressure for changes in the regulatory environment intensify. To explore further, a systematic evaluation of the course of innovation in this industry was performed by applying a formula derived from economic market share theory to estimate the innovative contribution of each new molecular entity approved since 1938. The total and average innovation score per year is described based on the therapeutic class, mechanism, and drug target. These data are compared to the number and percent of first-in-class drugs per year. The average annual score based on therapeutic class novelty has been declining; however, the therapeutic class total innovation score has been stable since the mid-1970s with occasional significant peaks of activity. While the average score based on mechanism or target experienced a decline beginning in the 1950's and '60's, it has begun to rise since the early 1990's. Notably, the total innovation score has steadily increased since the 1970's. These variations closely parallel the number of first-in-class drugs approved on an annual basis. While the reasons underlying these activities are likely complex, there is a temporal association between regulatory efforts to expedite drug development and approval may and these positive trends.

Introduction

The most commonly accepted definition of innovation is derived from the Organization of Economic Cooperation and Development's Oslo Manual Guidelines for Collecting and Interpreting Innovation Data (OECD, 2005). The fundamental concept in product innovation is that a new product is produced.

An innovation is the implementation of a new or significantly improved product (good or service), or process, a new marketing method, or a new organisational method in business practices, workplace organisation or external relations.

The minimum requirement for an innovation is that the product, process, marketing method or organisational method must be new (or significantly improved) to the firm.

The state of innovation in the pharmaceutical industry in recent scientific and economic papers, as well as the popular news, varies greatly with descriptions range from completely stagnant to rising. Several analyses have concluded that while R&D expenditures have skyrocketed, innovation has slowed to an all-time low despite major scientific advances (Cuatrecasas, 2006; Kola, 2008). Drews (1998) noted that the top 50 pharmaceutical companies were only producing 0.5 to 0.8 New Chemical or Molecular Entities (NCE or NME) per year which is too small to sustain necessary growth of the industry. These reports point to time to discover lead candidates, attrition in development, changes within management, and rising costs to explain the decline, and claim that these must be fixed through major management overhauls and changes in development processes to decrease attrition, especially at late stages (Cuatrecasas, 2006; Drews, 1998; Kola, 2008).

Others report that innovation is stable or even increasing to an all-time high. Lanthier et al. states that according to the most common measure of pharmaceutical innovation, the number of NME approvals per year, innovation has been sluggish yet steady for the last 20-30 years, outside of a peak of approvals in 1996 and 1997. Furthermore, the number of first-in-class approvals has been stable in the 21st century and the approvals activity in 1996 and 1997 mostly occurred in less innovative addition-to-class drugs (Lanthier, Miller, Nardinelli, &

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Woodcock, 2013). When innovation is measured by the number of priority reviews, a more optimistic picture is painted as these are steadily climbing to all-time highs despite fluctuations in number of NCE approvals per year (Schmid & Smith, 2005).

The outlook on innovation is highly dependent on the measure of innovation used. Throughout the literature, there appear to be four main categories of measurement that have been used, assessment of therapeutic value, economic markers, patents, and new drug approvals. Each of these has limitations in its utility to characterize innovation (A S Kesselheim, Wang, & Avorn, 2013). Therapeutic value may take years or decades to understand and economic indices are confounded by the underlying marketing support. Patents may not be considered supportive once tested in court. While new drug approvals seem to fit the definition best, a method is needed to assign higher innovation scores to more original inventions, such as first-in-class NMEs, that recognizes which product came first, an economic concept known as the order of market entry (Gurumurthy Kalyanaram & Glen L. Urban, 1992).

In this study, innovation is scored based on the order of market entry by classes of therapeutic area, mechanism, and drug target. While there is no formula that establishes the relationship between innovation and the order of market entry, the pace of innovation was analyzed based on a formula found in the field of economic market share theory equating value, in terms of market share, and the order of market entry. The creation of this formula is described in the Methods section and a critique in the Discussion. Using this formula, a score was assigned to every NME approved since 1938. Total and average innovation scores per year were calculated to gain a comprehensive view of the trends in innovation in the pharmaceutical industry since the passing of the Federal Food, Drug, and Cosmetic Act in 1938. The trends in these scores are compared to the number of first in class approvals, using the three classes, to corroborate its utility. The study is concluded by a discussion of the trends observed in the findings from the application of this formula, particularly with respect to the overall level of innovation as well as that observed in different therapeutic and molecular classes. The trends

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are further compared to the chronology of significant regulatory milestones to provide the basis of a discussion of the effect of regulation on pharmaceutical innovation.

Methods

Data Collection

A data set of 1485 NMEs was extracted from Drugs@FDA (<https://www.accessdata.fda.gov/scripts/cder/daf/>; last accessed 3/14/19) and included the application number, brand name, established name, approval year, approval date, approval type, and NDA class of every approval by the FDA from 1938 to the last access date of the dataset. Class 1 NDAs, NMEs or drugs that do not contain an active moiety previously approved, were extracted for the analyses (“Office of Pharmaceutical Quality: NDA Classification Codes,” 2015).

Coding

Variables for categories of Established Pharmacologic Classes (EPC), Medical Reference Terminology (MED-RT), and Target were collected from online sources. EPCs and MED-RTs were collected from <https://mor.nlm.nih.gov/RxClass/>, if they were available. The EPC is a pharmacologic class that is associated with a drug’s approved indication used by the FDA (Office of the Commissioner, 2019). The MED-RT is a code assigned by the Veterans Administration that takes into account multiple pharmacological classifications including mechanism, physical effect, EPC, and the relationships between them (Veterans Affairs, 2018). The Targets for each drug were collected from the DrugBank database (<https://www.drugbank.ca>) (Wishart et al., 2018). For variables that were not available, codes were assigned based on the codes of other drug within the same class, for the same indication, and /or with the same mechanism of action making it a reasonable assumption that the code would be the same if one had been assigned by the designated authority. Finally, in the instance that no compound existed with the same therapeutic class, pharmacological class, and/or target, a unique code was assigned of the same form as the variable of interest.

Scoring of Innovation by Variable Class

A formula quantifying product innovation was not apparent in the literature. The closest relationship described in the literature was for the relationship of market share to the order of entry (Kalyanaram, Robinson, & Urban, 1995). The author reasoned that these should be inversely related, and their empiric data suggested that the market share was proportional (k) to the square root of the order of market entry within a product class.

$$\text{Equation 1: } \textit{Market Share} = \frac{k}{\sqrt{\textit{Order of Market Entry}}}$$

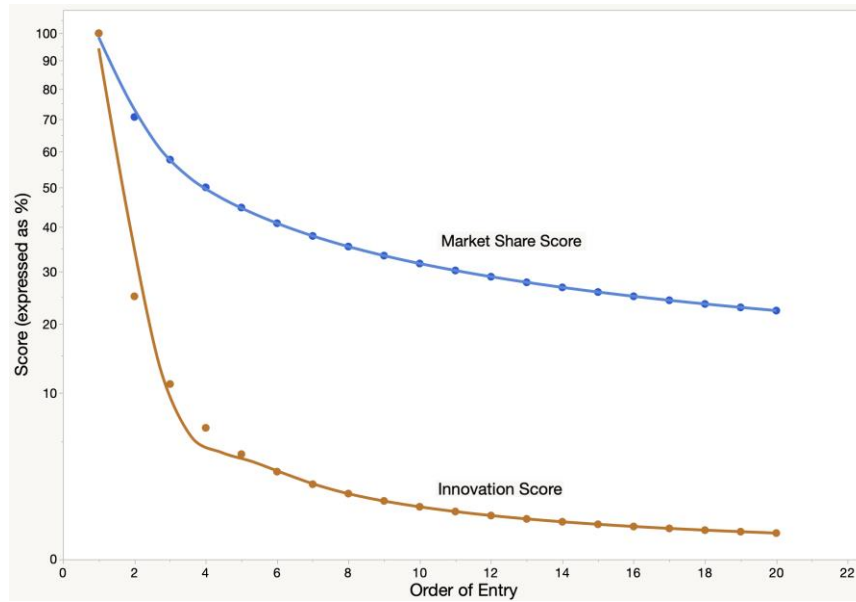
This is a slowly declining function because it becomes increasingly difficult for new entrants to offer incremental benefit to consumers as the market becomes saturated. The innovativeness of an NME likely follows a similar trend dropping at a faster rate, so Equation 1 was altered to show a steeper exponential decrease for follow-on products, such as:

$$\text{Equation 2: } \textit{Innovation Score} = \frac{k}{(\textit{Order of Market Entry})^2}$$

The proportionality constant k was set to 100 so the first in class would start as 100, making the scoring analogous to a decreasing series of percentages. A plot comparing the two scores is depicted below (Figure 1). Further thoughts on this formula are provided in the Discussion section *Limitations of the Study*.

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Figure 1 A Graph depicting the rate of Decline in Product Market Share and Innovation by Order of Market Entry



Analysis:

Graphic analyses of trends in innovation from 1938 to present were performed by plotting the total and average annual innovation scores by EPC, MED-RT, and Target class. The numbers and percent of first-in-class approvals were also plotted for comparison to the innovation score data. Graphs of the innovation data were visually explored for trends related to significant regulatory milestones (see Discussion section *Regulatory Impact*).

Table 1 A Text Box of Significant Regulatory Milestones

- **1938:** The United States Federal Food, Drug, and Cosmetic Act (Federal FD&C) gave authority to the FDA.
- **1962:** Kefauver-Harris Drug Amendments to the Federal FD&C Act requiring proof of effectiveness were passed.
- **1983:** The Orphan Drug Act was passed providing incentives for the development of drugs for rare diseases including extended market exclusivity.
- **1984:** The Drug Price Competition and Patent Term Restoration Act which expanded the drugs that qualify for ANDAs encouraging generic drug development was put into place.
- **1992:** The Prescription Drug User Fee Act mandated drug companies to pay user fees and in exchange the FDA committed to meet review timelines and established Priority Review. The Prescription Drug Amendments of 1992 were also passed which established Accelerated Approval.
- **1997:** The Food and Drug Modernization Act reauthorized user fees, supported accelerated approval, gave 6-months extra marketing exclusivity for carrying out studies in children, and established Fast Track Designation.
- **2012:** The Food and Drug Administration Safety and Innovation Act reauthorized and expanded user fees and put Break Through Designation into effect.

Results

Trends in Innovation by Category Scores

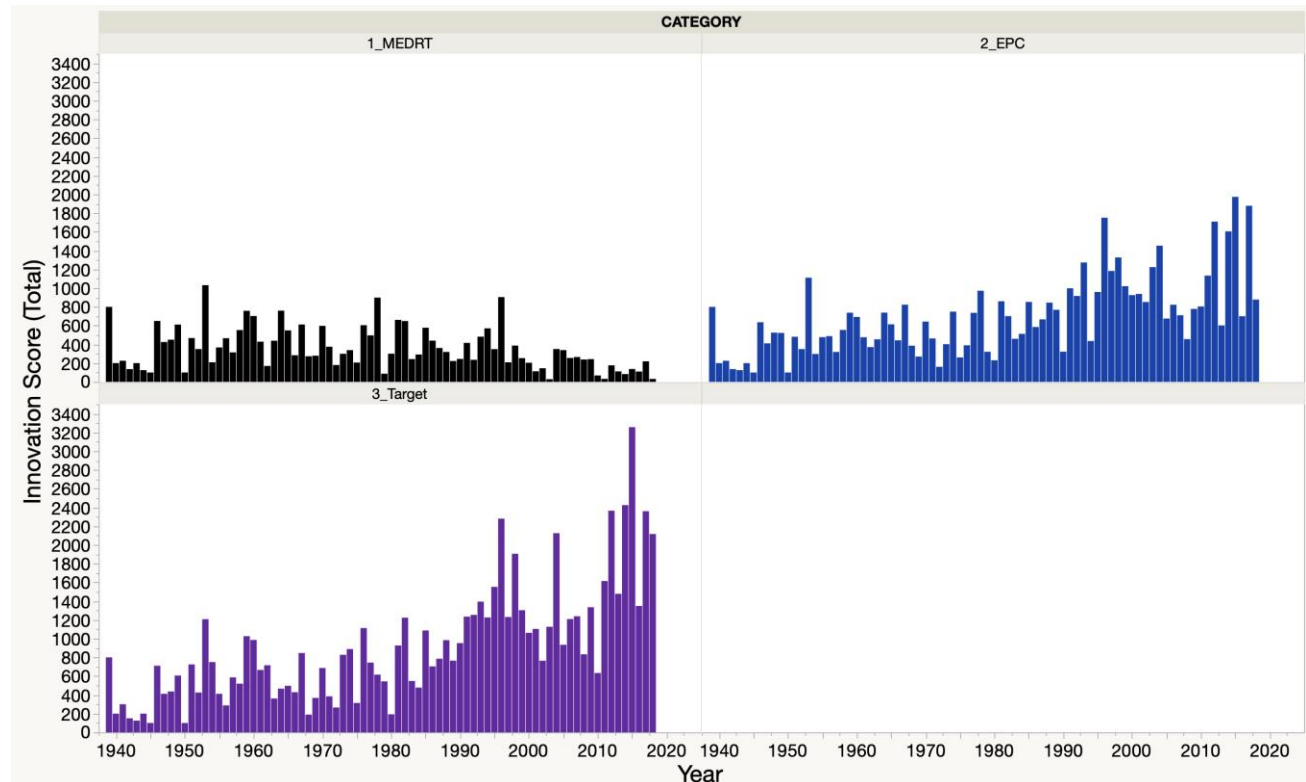
Sum of the Annual Innovation Scores

When evaluated by the therapeutic class, as represented by the MED-RT, the Sum of the Annual Innovation Scores (SAIS) have had a median score of 2.8 and a mean (95% confidence intervals; **95% CI**) of 19 (17, 21) corresponding to an innovation level centered at the therapeutic class level of a sixth in class but skewed to an average correlating to about a second in class from numerous first-in-class approvals. The trend appears constant from the 1940s through the early 1990's. This score seems to level off at a level similar to the prior pattern but with less spikes of activity in the period from the late 1990s to the present. When organized by the pharmacologic class (EPC), the Sum of the Annual Innovation Scores have

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had a small peak in the 1950's with a dip from the 1960's to 1980 with occasional spikes in scoring. From this point, the scores have increased with a peak in the mid '90's and a dip in the late 2000s that has increased to the present date. When organized by Target, the Sum of the Annual Innovation Scores have had a similar trend but with a median score ($SAIS_{Target} = 25$) more than twice that of the EPC ($SAIS_{EPC} = 11$).

Figure 2 Sum of the Annual Innovation Scores by Drug Class

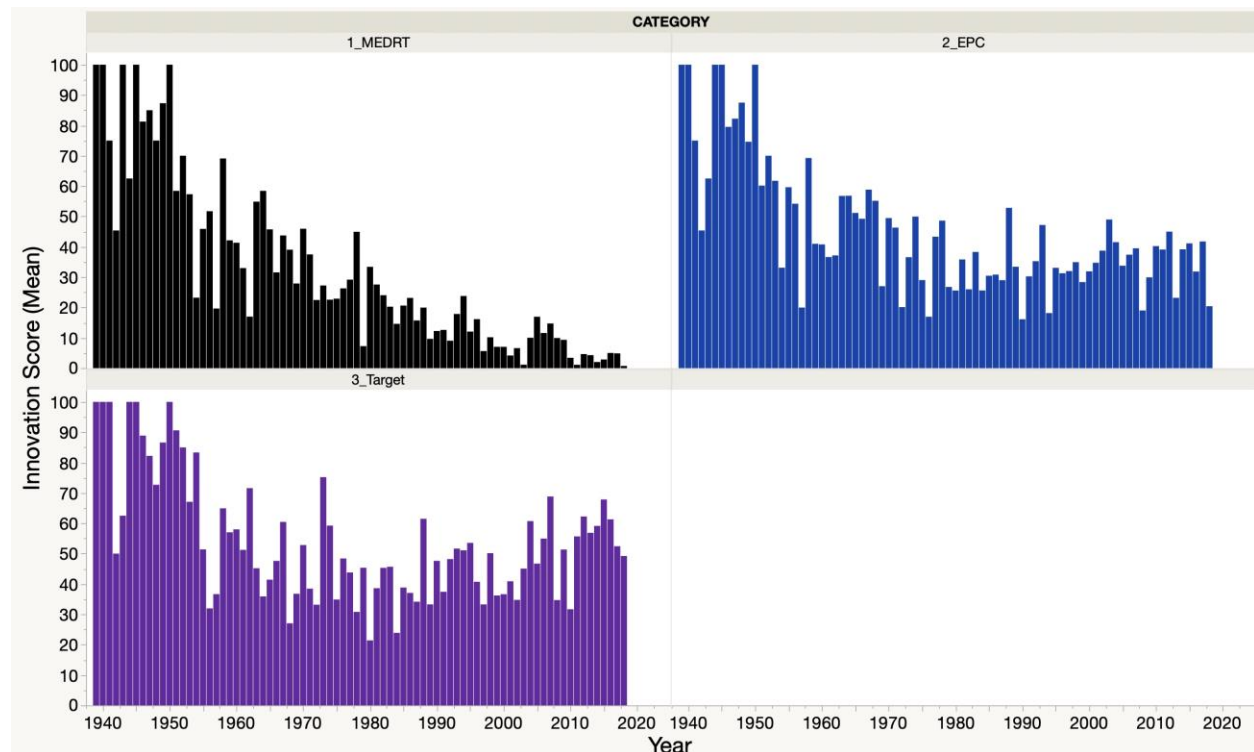


Mean Annual Innovation Scores

When evaluated by the therapeutic class as represented by MED-RT, the median of the Mean Annual Innovation Scores (MAIS) is 23 corresponding to an innovation level of approximately a second in class drug. The scores have consistently trended down since the late 1940's with occasional small spikes and have been at their lowest since the mid-2000's. When organized by pharmacological class (EPC), the scores decreased from the late 1960's until the late 1970's when they leveled off and have been increasing since the 2000s leveling off at a higher level than the previous decades. The median MAIS score by EPC is significantly higher than by

Therapeutic class ($MAIS_{EPC}=39.3$) and the median Target score is more than twice as high ($MAIS_{Target}=50.6$). The Target scores trended down from the early 1960's to the 1980's when they leveled off before a spike in the early to mid-1990's and then has been trending up until present. In recent years, the $MAIS_{Target}$ scores have hit their highest points since a brief two-year spike in the early 1970's with a score of 68.8 in 2007, 67.8 in 2015, and 62.2 in 2012.

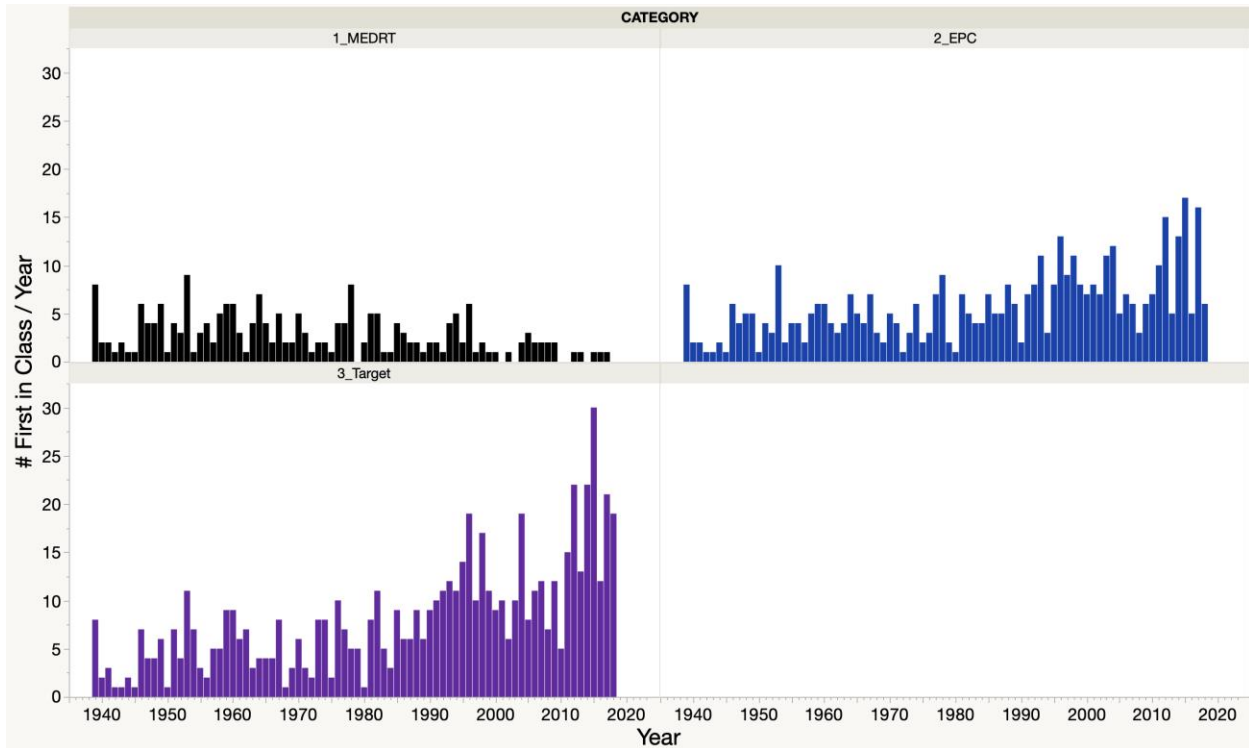
Figure 3 Mean of the Annual Innovation Scores by Drug Class



Number of Annual First-in-Class Approvals

The annual trend in the number of FIC molecules in each of the three categories is virtually identical to the pattern observed with the Sum of the Annual Innovation Score, albeit with slightly less occurrence of spikes superimposed on the general trends described above. The trend in FIC approvals by Target is very similar to that of EPC, but with a more dramatic increase in approvals from the early 1990's to present especially from 2011-present. In that time frame, every year has had double-digit approvals, with a record high of 30 in 2015.

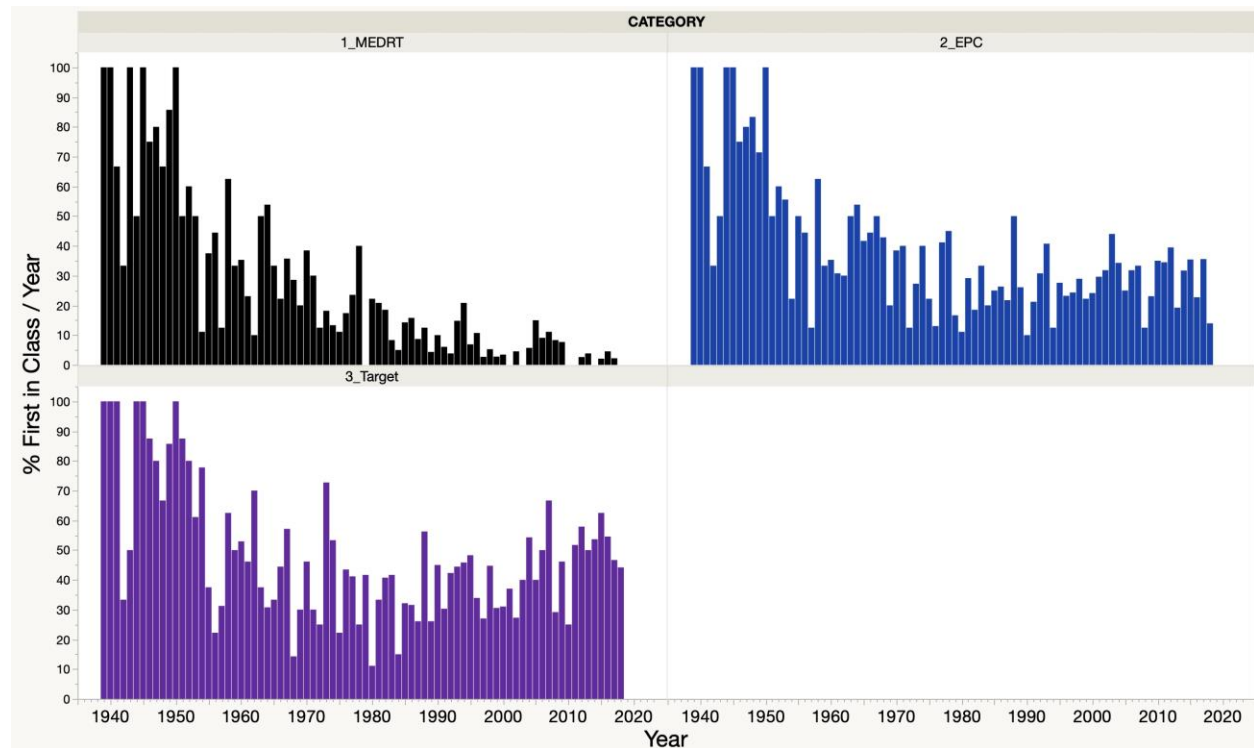
Figure 4 Number of Annual First-in-Class Approvals by Drug Class



Percent Annual First-in-Class Approvals:

Similarly, the median annual percentage of First-in-Class Approvals is quite similar to the pattern observed with the Mean of the Annual Innovation Scores. Since the 1980s, in the PAFC by EPC and Target has increased until present with notable spikes of activity from 1992-1995, 2003-2007, and 2011-present.

Figure 5 Percent Annual First-in-Class Approvals by Drug Class



Discussion

This research attempts to quantify innovative contribution of NMEs approved from 1938 to present, giving a chronologically comprehensive picture of innovation in the pharmaceutical industry. This was done by compiling a database of every NME over this period and their therapeutic class, pharmacological class, and target. A formula derived from economic market share was then applied to these variables to find the average and overall innovation scores that were graphically compared with the annual number and percent FIC approvals. In the recent past, the literature has claimed that innovation in the pharmaceutical industry is declining to all-time lows or is stagnant and that this may put the industry and patients at risk. They have made these claims based on rising R&D costs, attrition in development, annual NME approval rates, and a belief that the pharmaceutical industry has failed to keep pace with biomedical research (Cuatrecasas, 2006; Drews, 1998; Kola, 2008). Previous research has mostly relied on limited datasets of approvals from a single perspective. In contrast, my methods differentiate the level

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of innovativeness using market entry by multiple drug classifications. This may give a more complete picture of innovation in the pharmaceutical industry. Innovation in the pharmaceutical industry, using this methodology, is not only not declining, but is rising to levels not seen in decades.

The trends seen by innovation score highly parallels those seen with annual FIC approvals. The reductions apparent since the 1940's and a lag in the 1960's bear further consideration. The peaks seen in the 1940's and 1950's occur because the dataset starts with the year of the passage of the Food Drug and Cosmetic Act in 1938. These represent the first approvals so most all the early approvals would be considered first-in-class and the innovation scores correspondingly high. Events potentially surrounding the lag following the 1960's are described in the following section.

Regulatory Impact

A popular theme in the literature is that regulations negatively impact innovativeness in the pharmaceutical industry. In order to examine this further, the trends in innovation compared to the timing of important regulatory milestones since the passing of the Federal Food, Drug, and Cosmetic Act in 1938 (Text Box 1) were graphically analyzed. While these observations are not claimed to be causative, there are several interesting correlations between the innovation trends and the regulatory milestones.

In 1962, the Kefauver-Harris Amendments increased requirements for drug approvals in the United States, including establishing the requirement for two trials to prove effectiveness (Commissioner, 2018). According to our results, trends in innovation seemed to lag following the passing of this act and into the following decades. At about the mid-1980's, at the time of the Hatch-Waxman Act, that allowed for materials to be referenced for approvals through the 505(b)(2) pathway, the lag in innovation scores and FIC approvals seems to have relented. In 1990s, the Prescription Drug User Fee Act and the Drug Amendments of 1992 were passed which required that drug manufacturers pay user fees in exchange for the FDA commitment to

meet review timelines, established priority review, and established accelerated approval (Aaron S. Kesselheim, Wang, Franklin, & Darrow, 2015; US Food and Drug Administration, 2017). The Food And Drug Modernization Act (1997) further stimulated innovation by allowing approvals to be based on a single trial plus confirmatory evidence. When evaluated by this study's methodology, innovation scores increased following the passing of these Acts. In 2012, the Food and Drug Administration Safety and Innovation Act reauthorized and expanded user fees and established breakthrough designation (Office of the Commissioner, 2018). Again, innovation scores appear to have increased following the passing of this legislation. The remaining milestones listed in Text Box 1 were also evaluated, however; no significant trends were seen. Based on these observations, innovations slowed in the 1960s to ensure the efficacy and safety of drugs met a necessary standard. As needs for more expedited approvals arose, laws were passed that allowed innovation in the private sector to increase and even to stimulate this activity.

Limitations of the Study

Three principal limitations in this study were identified:

- There is no known formula to quantify innovation in the literature. The economic literature was evaluated and a modified formula used to calculate market share based on order of entry. While innovation most likely follows a similar trend, it was designed to drop at a much faster rate because it is not supported by outside efforts, such as marketing and sales.
- There are also some in the industry that believe that follow-on drugs are as innovative if not more so because they provide small improvements in safety and efficacy, therefore; producing best-in-class drugs that provide benefit to both patients and the pharmaceutical industry (Schmid, Smith, & Smith, 2002). While there is some merit to this argument, when evaluated by such narrow drug classes as EPC and Target as were used in our study, follow-on drugs are very likely to be similar in effectiveness and

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function. To improve or increase the innovation of these drugs, sufficient change would need to be made such that the new molecule would most likely be included in a different class, in terms of the mechanism or target.

- The MED-RT, EPC, and Target do not include all of the drugs in our database, especially those just recently approved. When this occurred, a code of similar compound known to be of the same class was used to create the new code. In the instance that no similar drug could be found, a nominal representation of the drug class was used.

Directions

In response to claims that innovation in the pharmaceutical industry is declining and due to the many serious life-threatening diseases without adequate treatments, multiple expedited paths and incentive programs have been created by congress and the FDA to solve these issues. These programs include fast-track, priority review, accelerated approval, break through designation, and the orphan drug program (Farrell, Goldberg, & Pazdur, 2017; Aaron S. Kesselheim et al., 2015). After examining the results of this study, innovation is occurring at a rapid pace and new incentivizing regulatory pathways are not necessarily needed. A greater focus should be made to ensure that clinical development is done in a more efficient manner. Finally, while this research suggests that innovation in the pharmaceutical industry is not declining and in many ways is increasing to all times highs, the commercial and pharmacoeconomic implications of this were beyond the scope of this project. Further research into the value of the innovation and how this corresponds with the rising costs in R&D is recommended. For example, it would be of interest to know whether the increase in innovation was equated with an increase in quality of life or the decrease in other healthcare expenditures. This additional research would give a useful perspective on the state of innovation in the healthcare industry.

Conclusion

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Many believe that innovation in the pharmaceutical industry has been declining or stagnant for years or even decades. While methods to reach this conclusion vary, the most common is a simple analysis of trends in NME approvals per year. Innovation in the pharmaceutical industry was quantified by applying an equation based on the order of entry by drug class. While there have been times of declining innovation in the industry, the last few decades have seen increases especially when evaluated by pharmacological and target class. Re-evaluation of innovation trends in the industry from these perspectives could have implications on future incentivizing regulations and policies.

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