Title: The dynamics of United States drug approvals are persistent and polycyclic: Insights into economic cycles and national policy

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Abstract: It is challenging to elucidate the extrinsic effects of social, economic, policy and/or other influences on the time evolution of US drug approvals. Here, a novel approach – termed the Chronological Hurst Exponent (CHE) – is proposed, which hypothesizes that changes in intrinsic long-range memory latent within the dynamics of time series data may be temporally associated with such influences. Using the monthly number FDA’s Center for Drug Evaluation and Research (CDER) approvals from 1939 to 2019 as the data source, it is demonstrated that US drug approvals are found to have a distinct S-shaped (trichotomized) long-range CHE structure: an 8-year (1939-1947) Stagnated (random; H=0.5), a 27-year (1947-1974) Emergent (time-varying persistent; 0.9>H>0.5), and the 45-year (1974-2019) Saturated (persistent; H~1). Further, dominant periodicities (resolved via wavelet analyses) are identified in the Saturated Period at 17, 8 and 4 years; thus, US drug approvals have been following a Juglar/Kuznet mid-term cycle with Kitchin-like bursts. As discussed herein, this work suggests that (1) macro-factors (such as policy and/or economic) during the Emergent Period have led to persistent growth in US drug approvals enjoyed since 1974, (2) the CHE may be a valued method to explore influences on time series data, and (3) adds further evidence that innovation-related economic cycles exist (as viewed via the proxy metric of US drug approvals).

Keywords: FDA, drug development, persistency, time series, economic cycle, Schumpeter
Introduction

Drug discovery and development (DDD) requires economic investment to maneuver a single medicine from discovery science to market approval for a given condition or disease. The investments cover the costs associated with acquiring both the hardware (e.g., laboratory materials and space) and software [explicit (e.g., patents) and tacit (e.g., know-how) know-how] as well as executing the various DDD activities [1]. Ultimately, should an investigational candidate survive the attrition process and obtain marketing authorization (also known as marketing approval) by a health authority, a sponsor (or manufacturer) then enjoys economic rents secured from supplying the approval medicine. On the demand side, the patient receives a trusted medicine associated with a market innovation based on a new chemical and biologic entity, a cost advantage (generic), or a more efficient delivery of drug product [2].

Since the early 20th century to the present, in terms of drug development, the social, economic, and political environments have evolved dramatically. For example, the growth in the amount of governmental investment in research and development (R&D) [3], the number of R&D firms [4, 5], the volume of intellectual property (e.g., patents, trademarks, as well as peer-reviewed publications) [5, 6], the number of R&D policy initiatives (see Table 1 and discussion below), and the rise of the R&D cluster [7] have seemingly grown synchronistically and exponentially. For example, in the US and across industries, Daizadeh [8,9] showed a statistical significant intercorrelation between R&D investment, the number of patent and trademark applications, peer-reviewed and media publications, and stock price of major indices in the US. However, from the author’s perspective, much more work is needed to better understand the historical dynamics of these variables (among others) (and across jurisdictions) that may continue and/or further expedite successful drug development (as well as cross R&D industries as well).
Importantly, the DDD industry is a regulated industry, requiring an objective, independent, and external agency (collectively known as a health authority (HA)) to attest to a medicine’s quality, safety, and efficacy profile and to formally authorize a drug for marketing purposes in a given jurisdiction. Focusing on US activities, similarly, from a policy perspective, there have been a concomitant evolution of the number and variety of initiatives focused on providing oversight to the DDD process. As briefly presented in Table 1, mirroring the modernization in science and technology, the FDA policy environment has evolved considerably from placing under regulation specific drugs (e.g., insulin and penicillin) and describing the basic tenets of the safety sciences in the early 20th century to building a robust infrastructure pushing the frontiers of regulatory science into the 21st century.

Economic cycles, a wavelength between crests of development maxima over stagnation minima, are an active area of inquiry, not without controversy [10]. Juglar defined this periodicity over three phases: prosperity, crisis, and subsequent liquidation, and suggested an “approximate length of the cycle with crisis/liquidation taking 1-2 years, followed by a 6-7 year phase of prosperity [11; pp. 7],” with drivers to prosperity to crisis transition due to exuberance and thus over-speculation (ibid). Kitchin derived ‘minor’ and ‘major’ inventory cycles with wavelengths of 3.5 years (40 month) and “aggregates usually of two, and less seldom of three, minor cycles,” respectively [12; pp. 10]. Subsequent to the introduction of these short and intermediate cycles, Kondratieff introduced the concept of the long-wave 50-60 year cycles [13]. Concomitantly, Kuznetz extrapolated 15-25 year cycles derived from data from “fluctuations in rates of population growth and immigrating but, also with investment delays in building, construction, transport infrastructure, etc...[14; pp. 2].” These perceived economic cycles were extrapolated by the original authors from a broad assortment of macro-economic data from US and Europe including climate, monetary, fiscal, consumption, among others.

Memory characteristics (also termed persistency) in the dynamics of typical econometrics captured over time are intimately connected with cycles and thus also to the underlying processes [15]. Technically,
however, these same characteristics such as long-range memory processes are challenging to analyze and interpret due to (in part) self-similarity and typical non-stationary properties (as they confound spurious from true signals) [16]. The Hurst constant and wavelet analyses are statistical time series tools that may be calculated in such a way as to avoid these challenges [17]. While there are other ways to define a Hurst constant, a measurement of memory, it is classically defined as $H \sim \ln(R / S)_t / \ln(t)$, where $R$ and $S$ is the rescaled range and standard deviation, respectively, and $t$ is a time window. An $H=0.5$, an $H<0.5$, and an $H>0.5$ indicates a random walk, an anti-persistent, and a persistent (trend reinforcing) time series, respectively [18]. Wavelet analyses is a well-established group of time-series methods that leverages the expansion and contraction of wave functions to resolve time series properties [19].

In this work, and to the author’s knowledge, this is the first investigation of the existence and evolution of persistency, and the existence of approval cycles (akin to economic cycles) within US drug approvals, which is treated as a macro-economic variable and a proxy metric for FDA policy. This work is exploratory and empirical in nature. As presented in the Materials and Methods section below, the data source is a time series of monthly values of US drug Approvals from Jan. 1939 through Dec. 2019 from the Centers of Drug Evaluation and Research (CDER) branch of the Food and Drug Administration (FDA), which “regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs.” While this is not the only institution that regulates the DDD process within the FDA, it is one that provides a publicly, reliable and valuable source of longitudinal metrics regarding the DDD process from the dawn of the review process (1939) to the present time. The methods are standard with the exception of the Chronological Hurst Exponent to explore the persistency latent in the time series. All datasets and R Project code are provided in the Electronic Supplementary Materials section for the sake of transparency and replicability as well as to encourage future researchers in investigate a potentially

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1 [https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder](https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder)
very interesting and informative aspect of drug development. This work then discusses the key results of both the descriptive and inferential statistics followed by a discussion on how the statistical work positively supports the hypotheses mentioned above (viz., persistency and economic cycles are latent within US drug approvals), and the ramifications of this work including potential linkages to sociological, economic, and policy features experienced over the nearly 100 years of data.

**Materials and Methodologies**

The following summarizes the data sources and the statistical approaches used. This work is applied by nature and thus differing the mathematical formulae and technical discussion to original sources, as cited. All data and the R Project code for the statistical analysis are provided in the Electronic Supplementary Materials section supporting this article for transparency and reproducibility, as well as for purposes of future work.

*Data Sources and Data Preparation*

The data was obtained from the FDA repository accessed at [https://www.accessdata.fda.gov/scripts/cder/daf/](https://www.accessdata.fda.gov/scripts/cder/daf/) on July 16 and July 17, 2020. The data was culled from a monthly report and described as follows:

“All Approvals and Tentative Approvals by Month.

Reports include only BLAs/NDAs/ANDAs\(^2\) or supplements to those applications approved by the Center for Drug Evaluation and Research (CDER) and tentative NDA/ANDA approvals in CDER. The reports do not include applications or supplements approved by the Center for Biologics Evaluation and Research (CBER).

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\(^2\) BLAs/NDAs/ANDAs: Biologics License Application, New Drug Application, Abbreviated New Drug Application
Approvals of New Drug Applications (NDAs), Biologics License Applications (BLAs), and Abbreviated New Drug Applications (ANDAs), and supplements to those applications; and tentative approvals of ANDAs and NDAs.”

Upon entry into the data-repository via the website, the number of approvals from Jan. 1939 to Dec. 2019 was then determined by month. The values were placed in Excel and then exported as a comma delimited comma-separated values (CSV) file for input into the data analysis routine.

The total dataset comprised 181,157 total approvals from Jan. 1939 until Dec 2019 (for a total of 972 monthly observations).

Statistical Analysis

As mentioned above, as this is an applied paper, reference is made to the various theoretical formulae in the respective supportive citations. Many of the distribution-inquiring statistical tests selected are considered ‘standard’ in the sense that they are typically used in the context described and are readily available and interpretable. All methods presented below followed standard implementation; default parameters were used (as appropriate) throughout the analyses. While the R code [20] is presented in the Electronic Supplemental Materials section of this article, the steps to perform the analysis were as follows:

I. Load US Approvals as a time-series and perform descriptive statistics (including autocorrelation functions) [21; R package: ‘moments’].

In this step, the data is read as a time series into the R program, and descriptive statistics including moments and serial and partial correlation functions calculated.

II. Assess attributes of the time series, including:
o Normality [22; R package: ‘nortest’] using the Anderson-Darling and Cramer-von Mises normality tests

o Stationarity [23; R package: ‘aTSA’] using the Kwiatkowski-Phillips-Schmidt-Shin (KPSS) Unit Root Test for both the original and single difference

o Long-memory [24; R package: ‘LongMemoryTS’] using the Qu and local Whittle score tests

o Seasonality [25; R package: ‘seastests’] using the WO, QS, Friedman and Welch tests

o Nonlinearity [26; R package: ‘nonlinearTseries’] using the Teraesvirta’s and neural network tests, and Keenan, McLeod-Li, Tsay, and likelihood ratio tests.

III. Determine the Chronological Hurst Exponent (that is, evaluate if the Hurst exponent over time evolves):

For a given time-series, the Hurst constant [27; R package: ‘tsfeatures’] is a statistical indicator of the memory in a time-series process (or processes). In this calculation, the time-varying nature of the H constant was investigated using time windows from the first datapoint (Jan. 1939) to the end of the window length, with 1-month increments. The algorithm to calculate the Chronological Hurst Exponent is as follows:

```r
hurstApprovals=0; end<-length(time)
for (I in 1:end) { hurstApprovals[i]  <- hurst (time[1:(1+i*1)]) }
hurstApprovals<-ts(hurstApprovals,start=c(1939,1),end=c(2019,12),frequency=12)
```

IV. Determine the periodicities within the time series:

Wavelet analyses used to investigate the structure of the periodicities within the time series given its dynamics (particularly its non-stationarity; see step II). Two wavelet methods were utilized: one with a smoothing (Loess) approach [28; R package: ‘WaveletComp’] and one [29-31; R Package: ‘dplR’] without. The average period versus the average power for each method was then calculated to elucidate the
main periodicities. The dominant frequency was then re-checked with spectral analysis [32-33; R Package: ‘forecast’].

Results

Descriptive statistics: Elementary properties of the chromodynamics of US drug approvals

The time series of US drug approvals follows an interesting flow given the dramatic rise starting in the 1970s to 2000 then after a drastic fall with a subsequent re-rise (Figure 1).

< Insert Figure 1 here. Figure 1: Time evolution of total US CDER Approvals >

The US drug approvals time series distribution is non-normal, platykurtic and positively skewed, with an average of 186 approvals (191 standard deviation) (Table 2 and 3). Importantly, the time series is non-stationary, non-seasonal, and non-linear, with intrinsic persistent memory (Table 2 and figure 2), which is removed with single differencing (that is, the time series has an order of integration (number of differences to attain stationarity) of 1, I(1)). I(1) processes are rather well-represented across a spectrum of different disciplines and a broad assortment of the economic variables including US drug approvals [34].

< Insert Table 2 here: Table 2: Descriptive statistics of US approvals (rounded to tenths; units in months) >

< Insert table 3 here: Table 3: Summary of tests investigating normality, stationarity, seasonality, long-memory, and non-linearity>

< Insert Figure 2 here: Figure 2: Serial and partial correlation functions: lag is presented in months >

Chronological Hurst Exponent: Existence of economic cycles and latent persistency
Using the Chronological Hurst Exponent approach to investigate the long-term memory processes of the time-series shows, interestingly, a unique trichotomized structure (Figure 3). Three periods are clearly shown: Period 1: prior to June 1947, a period of stagnation with $H \sim 0.5$; Period 2: June 1947 to May 1974, a period of time-varying nature (also herein called emergent), where the H constant fluctuates rises under a degree of fluctuation; and, Period 3: May 1974 to Dec 2019, a period of saturation in which the $H \sim 1$.

Concordantly, the wavelet periodogram during Period 3 demonstrates that the time series contains periodicities. Several relatively long-, medium-, and short-range periodicities are observed during this period: 16-18 years (with a maximum (black ridge) occurring at 17 years), ~4-8 years, and on the monthly, yearly, or biyearly periodicities presenting intermittently, respectively (Figure 4). The predominate periodicity is identified to be 17, 8 and 4 years from spectral analysis (Figure 5).

Discussion and Conclusion

Using time series analysis, this work finds two conceptually novel aspects of US drug approvals: the existence and evolution of persistency, and the existence of approval cycles (akin to economic cycles).

**Persistency**

Formally, persistency may be defined as the “rate at which its autocorrelation function decays to zero,” or “the extent to which events today have an effect on the whole future history of a stochastic
Persistency and cyclicity in US drug approvals

process\(^3\).” Translating to the context of our concern, it generally means that the value of US drug approvals at a given month is closely related to its value at the prior month. The Chronological Hurst Exponent proposed herein is a simple algorithm that reiteratively calculates the Hurst exponent (a measure of persistency) over an incrementally increased time period. With each iteration, an additional data point (here the next monthly observation of US approvals) is taken into account until the exponent of the full data set is calculated. The Chronological Hurst Exponent proposed in this work elucidated a S-shaped structure reflecting a trichotomized picture of the time evolution of persistency latent within US drug approvals:

- **Period 1:** An 8-year (1939-1947) stagnation period in which the Hurst exponent remained at or around 0.5. An Hurst exponent at these values suggest no persistency whatsoever.
- **Period 2:** A 27-year (1947-1974) time-varying (emergent) period in which the Hurst exponent gradually evolved from 0.5 to 0.9. This range in the Hurst exponent suggests a growing persistency within the time series data.
- **Period 3:** A 45-year (1974-2019) saturation period in which the Hurst exponent remained at or around 1. A saturated Hurst exponent implies that the time series has become (for lack of a better term) inelastic; that is, any further changes in the degree and/or number of exogenous variables do not affect the persistency course of the time series (as it is already maximized).

**Cyclicity**

Interpreting US drug approvals as an economic variable – a singular outcome of several complex macro-(national), meso-(cluster), and micro-(firm)-inputs such as national policy and R&D spend (government, firm), potential of future rents (individual buyer, payor), science and technology innovation (tacit (staff

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\(^3\) Caporale, Guglielmo Maria and Pittis, Nikitas, Persistence in Macroeconomic Time Series: Is it a Model Invariant Property?. Revista de Economia del Rosario, Vol. 4, No. 2, pp. 117-142, 2001, Available at SSRN: https://ssrn.com/abstract=928506
dexterity) and explicit (e.g., patents) know-how), and resource availability (e.g., chemicals, vials) – the existence of business cycles were investigated. Several tiered periodicities (17 years, 4-8 years, and intermittent monthly/yearly) were identified within Periods 2 and 3 of the CHE.

**Persistence and Cyclicity Interpreted**

During Period 2 (27-years (1947-1974)), it is observed that 1947 was the first year in which there were one or more approvals during much of the year and had the largest number on an annual basis since the start of the collection cycle in Jan 1939. After 1947, a general rise in the number of approvals per month and per annum is observed. It is also a period of commensurate changes to the policy and social landscape pertaining to DDD, as well as continued investment into R&D. These changes were seemingly due to end of World War II (1939-1945), the beginning of the so-called ‘Golden Age of Capitalism,’ and the associated economic progress [35] with a relatively small number of economic disasters (see Figure 3 in [36] henceforth. Since the 1938 Food, Drug and Cosmetic act, no significant advances in policy occurred until the 1962 Drug Amendments (see Table 1), while there were significant milestone activities in terms of congressional review (the Kefauver Hearings dealt with pricing and market control [37]. One could therefore speculate that it may not have been FDA activities that drove the changes in the persistency measurement, but overall increased economic activity.

The appearance of Period 3 (45-years (1974-2019)) suggests a uniform pressure onto the time series. Two general reasons present themselves to foment such a sustained persistent alteration in the fabric of US drug approvals: some sort of substantive and everlasting change (1) to accounting practices regarding US drug approvals (that is, how the source data was initially contrived and/or collected); or (2) in the scientific, social, economic, and/or legislative landscape. The former is unlikely to cause a persistent shift. To illustrate, FDA data sources state a change in department ownership in and around
that time, as well as issues regarding changes from fiscal to calendar year practices.\textsuperscript{4} It is unlikely that either of these reasons would have changed the time series in such a permanent manner. The latter reason, while likely, however, is ill-defined, but does allow for hypothesis generation.

One hypothesis that could be tested is that of a significant change in the FDA regulatory landscape may have caused the formation of a cycle (see Table 1). From an FDA perspective, the 1960s and 1970s were a transformative vicennial [38]. In 1962, the Kefauver-Harris amendments to the original Food, Drug and Cosmetics Act (FD&C) of 1938 introduced (inter alia) broad requirements on drug efficacy (including key concepts of ‘substantial evidence’ and ‘adequate and well-controlled studies’), drug quality (via good manufacturing practices), ethical guidelines (patient informed consent), and physician-researcher supervision of the clinical trials. Subsequently, in the late 1960’s and into the early 1970s, led to a re-review of prior to 1962 drugs to retrospectively investigate the evidentiary standard based on the amendments, leading to revocation of “over 1000 ineffective drugs and drug combinations from the marketplace (page 13 of \textit{ibid}).” The concepts such as those introduced in the amendments (partly listed above) have been refined and reinforced through ongoing congressional action. While it is much more difficult to ascertain the origin of the other periodicities, ongoing actions, such as Prescription Drug User Fee Act initiated and its subsequent amendments commencing in 1992, or the introduction of new technologies may have directly contributed to intermittent periodicities, leading to significant increases in the promulgation of guidelines that may have furthered approvals [34, 39].

Thinking outside of the drug development process and continuing considering the periodogram (Figure 5) and thinking of the original time-series (Figure 2), the complex periodicity profile may have been motivated by socio-economic factors. Substantive economic pulses that may have affected the overall approval flow may include: Black Monday Market Crash (October 19, 1987), the Dot-Com bubble burst

\textsuperscript{4} Data record information from \url{https://www.fda.gov/about-fda/histories-product-regulation/summary-nda-approvals-receipts-1938-present} (extracted on July 30, 2020).
(Q3, 2002), and the subprime mortgage crisis (September 17, 2008), among others. Visually, the Dot-Com bubble burst seemed to coincide with a downsizing of amplitude. However, it is difficult to ascertain if the other triggers may have affected the time series.

Interestingly, if one considered the US drug approvals strictly as an economic variable, and assuming the theory of Schumpeter’s economic cycles, the identified periodicities seem to coincide with certain macro-economic periodicities, with exception as no canonical long-term (> 40 years) periodicities were identified in this analysis (see Table 3). The periodicities began at different times with different durations (Figure 4). The dominant periodicity of 17, 8 and 4 years has reoccurred during the longest (45 years), medium (20 years), and short-term (intermittent) durations, respectively (Figure 5). Thus, it seems that US drug approvals follow a Juglar/Kuznets mid-term cycle with Kitchin bursts. Only time will tell if a longer-term cycle (Kondratieff) emerges, irrespective of any downside pressures (such as multi-decade bear cycles). A key difference between the identified approval cycles as compared with economic cycles may be the degree of importance of the regulatory context. While a potentially coarse interpretation, without the legal requirement for market approval there would not have been a US drug approvals time series, whereas for variables such as gross domestic product typically used to consider economic cycles this is not the case (as the legal regimes do not define (as much as support) the existence of these more traditional economic variables).

< Insert table 3 here. Table 3: Mapping of broad canonical economic cycles with that of periodicities associated with US Approvals >

Further Thoughts in Light of Limitations of Current Study

There are extensions and limitations to any statistical analyses, especially when dealing with social-economic variables. Examples of future investigation may include:

Hypothesis:
• One could argue that the number of US drug applications may have been a more insightful variable, as applications may be either withdrawn (by the Sponsor) or rejected (by the FDA). Unfortunately, the author could not find this dataset.

• The number of initial US drug applications or approvals for new molecular and/or biologic entities may provide additional insight into the economics of the innovative process. In this article, the total number of US drug approvals including generics and line extensions (e.g., new indications or dosage forms) were considered, as reflected “market innovation.” That is, a sponsor would not have considered seeking an approval without a market driver of some sort.

Data:

• Data integrity and completeness: This study relies on a single source dataset from the FDA. While the author feels comfortable with the data source, there is uncertainty in how the data is collected, maintained, and presented given the duration of data collection and limited-to-no ability to cross-reference.

• Data transformation: The data was transformed from irregular to a regular time-structure. That is, FDA drug approvals occurred as a function of day; these data were then aggregated into monthly values to facilitate the statistical analyses. Thus, some information may have been lost in terms of structure, as there are limited statistical routines able to manage such data.

Statistical analysis:

• R Project: While the presence of the R Project has been invaluable to the author, and the author checked all calculations (including utilizing more than one method to ensure veracity of results), there could still be a ‘bug’ in the routines utilized.
• Methods: Statistical methods are ever evolving, becoming more generalizable (model agnostic).

Nonetheless, the author evaluated many approaches to ensure appropriateness of the analyses used based on the (distribution) characteristics of the data.

In the author’s opinion, these data are an important artifact of R&D expenditures related to the DDD industry and therefore have interesting utility. Future investigations may consider these data and analyses to support research questions such as those related to forecasting and long-memory effects of non-stationary and non-linear data. It will be interesting to revisit these analyses on a yearly basis given the recent COVID-19 crises and resultant economic challenges, with a hope that the US drug approvals remain persistent with respect to these significant triggers.

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Disclosures

The author is an employee of Takeda Pharmaceuticals; however, this work was completed independently of his employment. The views expressed in this article may not represent those of Takeda Pharmaceuticals. As an Associate Editor for Therapeutic Innovation and Regulatory Science, the author was not involved in the review or decision process for this article. See Electronic Supplementary Materials for all data and methods to replicate (or extend) the results presented herein.
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https://doi.org/10.1016/j.dendro.2008.01.002).

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Table 1: Brief Milestones in FDA Drug Regulation [Daizadeh, 2020].

| Year | US Drug Regulation |
|------|-------------------|
| 1938 | Act and Requirements for Premarket Drug Safety and New Labeling |
| 1941 | The Insulin Amendment |
| 1945 | The Penicillin Amendment |
| 1951 | Durham-Humphrey Amendment |
| 1962 | Kefauver-Harris Drug Amendments |
| 1977 | Introduction of the Bioresearch Monitoring Program |
| 1981 | Revision of the regulations for human subject protections |
| 1982 | Tamper-resistant Packaging Regulations issued |
| 1983 | Orphan Drug Act |
| 1984 | Drug Price Competition and Patent Term Restoration Act (Hatch–Waxman Act) |
| 1987 | Investigational drug regulations |
| 1988 | FDA Act of 1988 and Prescription Drug Marketing Act |
| 1989 | Guidelines on significant use in elderly people |
| 1991 | Accelerated review of drugs for life-threatening diseases; Common Rule adopted across agencies |
| 1992 | Generic Drug Enforcement Act; co-establishes International Conference on Harmonization (ICH); Prescription Drug User Fee Act (PDUFA I) |
| 1993 | MedWatch launched; revising women of childbearing potential in early phase drug studies policies and assessments of genders-specific medication responses |
| 1994 | Uruguay Round Agreements Act |
| 1995 | Cigarettes as ‘drug delivery devices’ |
| 1997 | FDA Modernization Act (FDAMA); reauthorization of PDUFA II |
| 1998 | Adverse Event Reporting System (AERS); Demographic Rule; Pediatric Rule |
| 1999 | ClinicalTrials.gov; guidances for electronic submissions; drug facts; Prescription Drug Broadcasting Advertising Final Guidance; Managing the Risks from Medical Product use: Risk Management Framework published |
| 2000 | Data Quality Act |
| 2002 | Best Pharmaceuticals for Children Act; Public Health Security and Bioterrorism Preparedness |

5 [https://www.fda.gov/about-fda/virtual-exhibits-fda-history/brief-history-center-drug-evaluation-and-research](https://www.fda.gov/about-fda/virtual-exhibits-fda-history/brief-history-center-drug-evaluation-and-research)
and Response Act of 2002; Current good manufacturing practice (cGMP) initiative; PDUFA III; outcomes of pregnancies registries guidance

2003
Medicare Prescription Drug Improvement and Modernization Act; Pediatric Research Equity Act

2004
Project BioShield Act of 2004; Anabolic Steroid Control Act of 2004; “Innovation or Stagnation?—Challenge and Opportunity on the Critical Path to New Medical Products” published; bar code introduced

2005
Drug Safety Board announced; risk management performance goal guidances

2006
Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products final rule

2007
PDUFA IV; FDA Amendments Act (FDAAA)

2008
Sentinel Initiative

2009
FDA Transparency Initiative

2010
FDA Transparency Results Accountability Credibility Knowledge Sharing (TRACK)

2012
PDUFA V; Launch of FDA Adverse Event Reporting System (FAERS); Food and Drug Administration Safety and Innovation Act (FDASIA); Generic Drug User Fee Amendment

2013
Drug Quality and Security Act; Mobile Medical Applications; Global Unique Device Identification Database (GUDID)

2016
21st Century Cures Act

2017
Current Good Manufacturing Practice (cGMP) Requirements for Combination Products; FDA Reauthorization Act (FDARA; PDUFA VI)

### Table 2: Descriptive statistics of US approvals (rounded to tenths; units in months)

| Minimum | 1st Quartile | Median | Mean | Standard Deviation | 3rd Quartile | Maximum | Kurtosis | Skew |
|---------|--------------|--------|------|--------------------|--------------|---------|----------|------|
| 0       | 5.0          | 164    | 186.4| 190.9              | 392.2        | 858     | 2.6      | 0.7  |

### Table 3: Summary of tests investigating normality, stationarity, seasonality, long-memory, and non-linearity

| Test Category | Test Name             | Test statistic     | Outcome against null hypothesis |
|---------------|-----------------------|--------------------|---------------------------------|
| Normality     | Anderson-Darling test | p-value < 2.2e^16   | Normal distribution rejected    |
|               | Cramer-von Mises test | p-value < 7.37e-10  |                                 |
### Stationarity

| Test                                      | Value                             | Result                  |
|-------------------------------------------|-----------------------------------|-------------------------|
| KPSS unit root test*                      | 0.01 (for no drift/no trend; for drift/no trend; for drift/trend) | Stationarity rejected   |

### Long memory

| Test                                      | Value                             | Result                  |
|-------------------------------------------|-----------------------------------|-------------------------|
| Qu test*                                  | 1.033545 versus 1.517             | Long memory accepted    |
| Multivariate local Whittle Score*         | 1.668473 versus 1.517             |                         |

### Seasonality

| Test                                      | p-value                           | Result                  |
|-------------------------------------------|-----------------------------------|-------------------------|
| Webel-Ollech test                         | 0.05                              | “The WO-test does not identify seasonality” |
| QS test, Friedman, Welch tests            | False — seasonality               |                         |

### Linearity

| Test                                      | p-value                           | Result                  |
|-------------------------------------------|-----------------------------------|-------------------------|
| Teraesvirta’s neural network test         | 0                                 | Linearity in "mean" rejected |
| White neural network test                 | 0                                 | Linearity in "mean" rejected |
| Keenan’s one-degree test                  | 3.889e^-5                         | The time series follows some AR process rejected |
| McLeod-Li test                            | 0                                 | The time series follows some ARIMA process rejected |
| Tsay’s test                               | 6.45e^-14                         | Time-series follows some AR process rejected |
| Likelihood ratio test for threshold non-linearity | 0.0004552571 | Time-series follows some TAR process rejected |

* Some tests require stationary data. As such, as the number of differences required for a stationary series from the original time-series was 1, the difference was used in the specific test demarcated.

### Table 3: Mapping of broad canonical economic cycles with that of periodicities associated with US Approvals

| Theory                             | Periodicity | US Approvals |
|------------------------------------|-------------|--------------|
| Kitchin Short-Term Cycle Cycle     | 3.5 years   | Months to biannual |
| Juglar Mid-Term Cycle              | 7-11 years  | 4-8 years    |
| Kuznets Medium-Term Cycle          | 15-25 years | 17 years     |
| Kondratieff Long-Term Cycle        | 40-60 years |              |
Figure 1: The number of monthly US CDER Approvals as a function of year from 1939 to 2019
Figure 2: Serial and partial correlation functions: lag is presented in months
Figure 3: The Chronological Hurst Exponent based on US Drug Approvals (Figure 1) from 1939 to 2019
Figure 4: Wavelet periodogram of US approvals: black lines are the wavelet power ridges and white contour lines to border the area of wavelet power significance of 99%
Figure 5: Wavelet period versus power with 95% significant levels in red
Supplementary Materials

I. Data Collection

The FDA website https://www.accessdata.fda.gov/scripts/cder/daf/ was accessed on July 16 and July 17, 2020. The data was culled from a monthly report and described as follows (see Figure 1):

“All Approvals and Tentative Approvals by Month.

Reports include only BLAs/NDAs/ANDAs or supplements to those applications approved by the Center for Drug Evaluation and Research (CDER) and tentative NDA/ANDA approvals in CDER. The reports do not include applications or supplements approved by the Center for Biologics Evaluation and Research (CBER).

Approvals of New Drug Applications (NDAs), Biologics License Applications (BLAs), and Abbreviated New Drug Applications (ANDAs), and supplements to those applications; and tentative approvals of ANDAs and NDAs.”

Upon entry into the data-repository via the website, the number of approvals from Jan. 1939 to Dec. 2019 was then determined by month (see Figure 2). The values were placed in Excel and then exported as a comma delimited CSV file for input into the data analysis routine.

Figure 1: The FDA web data-repository allowing search of drug approval reports as a function of month.
II. Statistical Analysis

Install R from: [https://cloud.r-project.org/](https://cloud.r-project.org/)
citation()

```
R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL [https://www.R-project.org/].
```

version

```
platform     x86_64-w64-mingw32
arch         x86_64
os           mingw32
system       x86_64, mingw32
status       
major        4
minor        0.2
year         2020
month        06
day          22
svn rev      78730
language     R
version.string R version 4.0.2 (2020-06-22)
nickname     Taking Off Again
```
#Step 1: Load data, convert to time series, perform descriptive statistics, and autocorrelation

```r
Input <- read.csv(file="c:\\Users/pzn6811\OneDrive - Takeda\Desktop\GLOC\read.csv", header=T, sep="",")
Input<-na.omit(Input) #excel seems to have some NAs at the end of column
time<-ts(Input$Number.of.Approvals,start=c(1939,1),end=c(2019,12),frequency=12)
time
```

```
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec
1939 0 4 1 1 0 1 0 2 0 1 0 0
1940 0 0 0 2 0 0 0 0 1 0 0 0
1941 1 0 0 0 0 1 1 3 0 0 0 0
1942 0 1 0 0 1 0 0 0 0 0 2 1
1943 0 0 1 0 3 1 0 0 0 0 0 1
1944 0 0 0 1 1 0 1 0 0 0 0 1
1945 0 1 0 0 0 0 0 0 1 1 0 0
1946 3 1 1 1 1 0 0 2 0 1 1 0
1947 2 1 1 1 0 2 3 2 0 1 0 1
1948 0 3 2 2 0 0 2 0 1 1 6 0
1949 0 0 1 1 2 1 2 1 1 2 0 1
1950 1 0 2 4 1 5 4 1 2 0 2 1
1951 1 0 2 2 4 4 2 1 1 0 2 2
1952 5 1 2 2 0 2 0 4 2 0 2 4
1953 8 3 2 7 5 1 7 0 7 1 6 9
1954 4 0 5 12 1 5 3 1 11 2 9 4
1955 3 3 6 6 8 4 8 13 5 2 4 3
1956 0 1 6 2 4 1 4 3 2 7 3 1
1957 2 5 2 13 8 4 3 3 4 5 6 5
1958 6 2 2 4 2 5 4 4 6 5 0 4
1959 3 6 3 5 8 4 4 8 7 3 6 5
1960 14 4 5 5 5 8 2 1 5 8 8 8
1961 4 2 25 13 11 8 6 13 6 10 1 5
1962 4 7 11 5 7 7 6 6 7 4 3 10
```
| Year | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|------|---|---|---|---|---|---|---|---|---|----|----|----|
| 1963 | 7 | 1 | 3 | 6 | 12 | 9 | 20 | 3 | 15 | 14 | 7 | 11 |
| 1964 | 7 | 1 | 10 | 8 | 9 | 24 | 9 | 11 | 9 | 9 | 14 | 11 |
| 1965 | 14 | 9 | 12 | 10 | 9 | 13 | 3 | 12 | 11 | 17 | 12 | 13 |
| 1966 | 15 | 13 | 19 | 8 | 20 | 5 | 13 | 9 | 12 | 9 | 8 | 20 |
| 1967 | 9 | 8 | 19 | 41 | 8 | 11 | 17 | 12 | 7 | 8 | 9 | 17 |
| 1968 | 9 | 6 | 12 | 9 | 3 | 8 | 10 | 13 | 6 | 7 | 16 | 10 |
| 1969 | 10 | 8 | 12 | 7 | 4 | 12 | 16 | 10 | 12 | 7 | 24 | 15 |
| 1970 | 10 | 11 | 11 | 30 | 13 | 17 | 11 | 13 | 9 | 13 | 14 | 27 |
| 1971 | 16 | 14 | 20 | 23 | 28 | 21 | 17 | 24 | 24 | 18 | 19 | 21 |
| 1972 | 26 | 30 | 15 | 30 | 23 | 28 | 29 | 33 | 34 | 34 | 21 | 20 |
| 1973 | 23 | 24 | 27 | 17 | 28 | 30 | 35 | 20 | 19 | 44 | 36 | 33 |
| 1974 | 48 | 37 | 38 | 40 | 66 | 55 | 50 | 52 | 39 | 43 | 73 | 70 |
| 1975 | 62 | 44 | 87 | 61 | 138 | 102 | 140 | 98 | 157 | 72 | 77 | 90 |
| 1976 | 145 | 87 | 143 | 87 | 251 | 185 | 149 | 124 | 250 | 124 | 145 | 128 |
| 1977 | 121 | 164 | 81 | 139 | 158 | 169 | 150 | 158 | 131 | 120 | 68 | 185 |
| 1978 | 164 | 193 | 224 | 170 | 144 | 190 | 242 | 223 | 172 | 230 | 234 | 116 |
| 1979 | 145 | 213 | 153 | 203 | 164 | 213 | 208 | 252 | 163 | 295 | 168 | 180 |
| 1980 | 254 | 275 | 135 | 179 | 290 | 462 | 293 | 310 | 219 | 191 | 119 | 178 |
| 1981 | 331 | 163 | 238 | 292 | 243 | 297 | 158 | 222 | 195 | 329 | 309 | 273 |
| 1982 | 183 | 323 | 356 | 391 | 328 | 536 | 449 | 247 | 267 | 180 | 224 | 312 |
| 1983 | 261 | 218 | 246 | 201 | 180 | 263 | 356 | 210 | 170 | 176 | 256 | 223 |
| 1984 | 274 | 322 | 439 | 247 | 217 | 272 | 226 | 249 | 359 | 463 | 270 | 211 |
| 1985 | 362 | 190 | 276 | 498 | 408 | 570 | 438 | 503 | 344 | 530 | 347 | 344 |
| 1986 | 509 | 421 | 238 | 303 | 328 | 326 | 353 | 369 | 314 | 354 | 359 | 292 |
| 1987 | 289 | 290 | 378 | 408 | 375 | 291 | 565 | 287 | 256 | 271 | 260 | 310 |
| 1988 | 290 | 446 | 522 | 459 | 399 | 498 | 344 | 482 | 303 | 360 | 511 | 498 |
| 1989 | 463 | 434 | 422 | 379 | 518 | 397 | 551 | 262 | 236 | 341 | 301 | 231 |
| 1990 | 441 | 323 | 269 | 303 | 245 | 290 | 203 | 222 | 410 | 214 | 302 | 241 |
| 1991 | 363 | 491 | 490 | 404 | 339 | 229 | 294 | 490 | 375 | 274 | 300 | 395 |
| 1992 | 399 | 367 | 283 | 649 | 395 | 326 | 294 | 343 | 389 | 241 | 283 | 412 |
Persistency and cyclicity in US drug approvals

Author: Daizadeh, I.

plot(time)
summary(time)

Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.0     5.0   164.0   186.4   329.2   858.0

library(moments)
citation("moments")

Lukasz Komsta and Frederick Novomestky (2015). moments: Moments, cumulants, skewness, kurtosis and related tests. R package version 0.14. https://CRAN.R-project.org/package=moments

sd(time)

190.9333

Kurtosis(time) #platykurtic (excess kurtosis = kurtosis – 3)

2.598539

Skewness(time)

0.6980762

acf(time);pacf(time)

ndiffs(time)

[1] 1
#Step 2: Perform normality, stationarity, seasonality, long-memory, and non-linearity tests

#normality test

library(nortest) #all normality tests rejected hypothesis of normality – presenting two

citation("nortest")
Juergen Gross and Uwe Ligges (2015). nortest: Tests for Normality. R package version 1.0-4. https://CRAN.R-project.org/package=nortest

ad.test(time) #null normality

Anderson-Darling normality test
data:  time
A = 48.166, p-value < 2.2e-16

Cvm.test(time)

Cramer-von Mises normality test
data:  time
W = 7.5428, p-value = 7.37e-10
Warning message:
In cvm.test(time) :
p-value is smaller than 7.37e-10, cannot be computed more accurately

#stationarity test

Library(aTSA)

Citation("aTSA")

Debin Qiu (2015). aTSA: Alternative Time Series Analysis. R package version 3.1.2. https://CRAN.R-project.org/package=aTSA

stationary.test(time,method="kpss")

KPSS Unit Root Test
alternative: nonstationary
Type 1: no drift no trend
  lag  stat  p.value
  7  6.32   0.01
-----
Type 2: with drift no trend
  lag  stat  p.value
  7    7   0.01
-----
Type 1: with drift and trend
  lag  stat  p.value
  7 0.671   0.01
-----------
Note: p.value = 0.01 means p.value <= 0.01
  : p.value = 0.10 means p.value >= 0.10

stationary.test(diff(time),method="kpss")

KPSS Unit Root Test
alternative: nonstationary
Type 1: no drift no trend
lag   stat   p.value
7  0.0776   0.1
-----
Type 2: with drift no trend
lag   stat   p.value
7  0.0281   0.1
-----
Type 1: with drift and trend
lag   stat   p.value
7  0.0162   0.1
-----------
Note: p.value = 0.01 means p.value <= 0.01
: p.value = 0.10 means p.value >= 0.10

#long-memory test

library(LongMemoryTS)
citation("LongMemoryTS")

Christian Leschinski (2019). LongMemoryTS: Long Memory Time Series. R package version 0.1.0. https://CRAN.R-project.org/package=LongMemoryTS

m<-floor(1+500^0.75)

# Qu test

Qu.test(diff(Input$Number.of.Approvals),m)
$W.stat
[1] 1.033545

$CriticalValues
eps=.02 eps=.05
alpha=.1  1.118  1.022
alpha=.05  1.252  1.155
alpha=.025  1.374  1.277
alpha=.01  1.517  1.426

#Multivariate local Whittle Score

MLWS(diff(Input$Number.of.Approvals), m=m)

$B
[1]
[1,] 1

$d
[1] 0.9172231
$W.stat$
[1] 0.9172231

$\text{Critical Values}$

\begin{align*}
\text{alpha} = .1 & \quad \text{1.118} \\
\text{alpha} = .05 & \quad \text{1.252} \\
\text{alpha} = .025 & \quad \text{1.374} \\
\text{alpha} = .01 & \quad \text{1.517}
\end{align*}

# Seasonality tests

library(seastests)
citation("seastests")

Daniel Ollech (2019). seastests: Seasonality Tests. R package version 0.14.2. https://CRAN.R-project.org/package=seastests

# Webel-Ollech overall seasonality test

summary(wo(time))

Test used: WO
Test statistic: 0
P-value: 1 1 0.05105411
The WO - test does not identify seasonality

# calculate through variety of tests

isSeasonal(time, "qs") # QS test
[1] FALSE

isSeasonal(time, "fried") # Friedman test
[1] FALSE

isSeasonal(time, "welch") # Welch test
[1] FALSE

# Nonlinearity tests

library(nonlinearTseries)
citation("nonlinearTseries")

Constantino A. Garcia (2020). nonlinearTseries: Nonlinear Time Series Analysis. R package version 0.2.10. https://CRAN.R-project.org/package=nonlinearTseries

> nonlinearityTest(time)

** Teraesvirta's neural network test **
Null hypothesis: Linearity in "mean"
X-squared = 227.9227 df = 2 p-value = 0
** White neural network test **
Null hypothesis: Linearity in "mean"
X-squared = 227.1936 df = 2 p-value = 0

** Keenan's one-degree test for nonlinearity **
Null hypothesis: The time series follows some AR process
F-stat = 17.08669 p-value = 3.888728e-05

** McLeod-Li test **
Null hypothesis: The time series follows some ARIMA process
Maximum p-value = 0

** Tsay's Test for nonlinearity **
Null hypothesis: The time series follows some AR process
F-stat = 2.733688 p-value = 6.342547e-14

** Likelihood ratio test for threshold nonlinearity **
Null hypothesis: The time series follows some AR process

Alternative hypothesis: The time series follows some TAR process
X-squared = 47.58834 p-value = 0.0004552571

**Step 3: Develop Hurst over time**

library(tsfeatures)
citation("tsfeatures")

Rob Hyndman, Yanfei Kang, Pablo Montero-Manso, Thiyanga Talagala, Earo Wang, Yangzhuoran Yang and Mitchell O'Hara-Wild (2020). tsfeatures: Time Series Feature Extraction. R package version 1.0.2. https://CRAN.R-project.org/package=tsfeatures

hurstApprovals=0
end<-length(time)
for (i in 1:end) { hurstApprovals[i] <- hurst (time[1:(1+i*1)]) }
hurstApprovals<-ts(hurstApprovals,start=c(1939,1),end=c(2019,12),frequency=12)
plot(hurstApprovals)
# Identify periods

# Method 1: The Wavelet Power Spectrum Of A Single Time Series
# Note: Loess smoothing as default is 0.75 for this parameter

library(WaveletComp)
citation("WaveletComp")

Angi Roesch and Harald Schmidbauer (2018). WaveletComp: Computational Wavelet Analysis. R package version 1.1. https://CRAN.R-project.org/package=WaveletComp

monthyear <- seq(as.Date("1939-01-01"), as.Date("2019-12-31"), by = "month")
monthyear <- strftime(monthyear, format = "%b %Y")
c <- analyze.wavelet(data.frame(time), "time", dt=1/12, dj=0.1)
wt.image(c, main = "wavelet power spectrum", periodlab = "Period (Years)", timelab = "Month /Year", spec.time.axis = list(at = 1:length(monthyear), labels = monthyear))
Persistency and cyclicity in US drug approvals

Author: Daizadeh, I.

wt.avg(c)

wavelet power spectrum

Month / Year

wt.avg(c)
#Method 2: Continuous Morlet Wavelet Transform

Library(dplR);citation("dplR")

Bunn AG (2008). “A dendrochronology program library in R (dplR).” _Dendrochronologia_, *26*(2), 115-124. ISSN 1125-7865, doi:10.1016/j.dendro.2008.01.002 (URL: https://doi.org/10.1016/j.dendro.2008.01.002).

Bunn AG (2010). “Statistical and visual crossdating in R using the dplR library.” _Dendrochronologia_, *28*(4), 251-258. ISSN 1125-7865, doi: 10.1016/j.dendro.2009.12.001 (URL:https://doi.org/10.1016/j.dendro.2009.12.001).

Andy Bunn, Mikko Korpela, Franco Biondi, Filipe Campelo, Pierre Mérian, Fares Qeadan and Christian Zang (2020). dplR: Dendrochronology Program Library in R. R package version 1.7.1. https://CRAN.R-project.org/package=dplR

wave.out <- morlet(time, p2 = 8, dj = 0.1, siglvl = 0.95)
wave.out$period <- wave.out$period/12

wavelet.plot(wave.out)

wave.avg <- data.frame(power = apply(wave.out$Power, 2, mean), period = (wave.out$period))

plot(wave.avg$period, wave.avg$power, type = "l")

# Confirm time series frequency
library(forecast); citation("forecast")

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Hyndman R, Athanasopoulos G, Bergmeir C, Caceres G, Chhay L, O’Hara-Wild M, Petropoulos F, Razbash S, Wang E, Yasmeen F (2020). forecast: Forecasting functions for time series and linear models. R package version 8.12, <URL: http://pkg.robjhyndman.com/forecast>.

Hyndman RJ, Khandakar Y (2008). “Automatic time series forecasting: the forecast package for R.” _Journal of Statistical Software_, *26*(3), 1-22. <URL: http://www.jstatsoft.org/article/view/v026i03>.

findfrequency(time) # dominant frequency is determined from a spectral analysis of the time series

[1] 17