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DIA

ORIGINAL RESEARCH

Seasonal and Secular Periodicities Identified in the Dynamics of US FDA Medical Devices (1976–2020): Portends Intrinsic Industrial Transformation and Independence of Certain Crises

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Abstract
The US Food and Drug Administration (FDA) regulates medical devices (MD), which are predicated on a concoction of economic and policy forces (e.g., supply/demand, crises, patents), under primarily two administrative circuits: premarketing notifications (PMN) and Approvals (PMAs). This work considers the dynamics of FDA PMNs and PMAs applications as an proxy metric for the evolution of the MD industry, and specifically seeks to test the existence [and, if so, identify the length scale(s)] of economic/business cycles. Beyond summary statistics, the monthly (May, 1976 to December, 2020) number of observed FDA MD Applications are investigated via an assortment of time series techniques (including: discrete wavelet transform, running moving average filter, complete ensemble empirical mode with adaptive noise decomposition, and Seasonal Trend Loess decomposition) to exhaustively seek and find such periodicities. This work finds that from 1976 to 2020, the dynamics of MD applications are (1) non-normal, non-stationary (fractional order of integration < 1), non-linear, and strongly persistent (Hurst > 0.5); (2) regular (non-variance), with latent periodicities following seasonal, 1-year (short-term), 5–6 year (Juglar; mid-term), and a single 24-year (Kuznets; medium-term) period (when considering the total number of MD applications); (3) evolving independently of any specific exogenous factor (such as the COVID-19 crisis); (4) comprised of two inversely opposing processes (PMNs and PMAs) suggesting an intrinsic structural industrial transformation occurring within the MD industry; and, (6) predicted to continue its decline (as a totality) into the mid-2020s until recovery. Ramifications of these findings are discussed.

Keywords Business cycles · Medical devices · FDA policy · Regulatory science · Economic dynamics

Introduction

The history of the United States (US) medical device (MD) industry is one of innovation—a complicated evolution encompassing a very broad everyday (e.g., general purpose thermometers) and specialized (e.g., human-embeddable systems) medical products. At some point in time, each registered MD—no matter how menial from today's vantage point—is an outcome of certain investments. On a company or sector level, these investments have not only included the demand / supply side variables (such as the various people, processes, and systems required of a research and development firm to idealize, actualize, market, and secure economic rents from the sale of a MD product) but also to meet the national policies enforced by one or more national health bodies to ensure the MD's safe intended use [1]. Thus, an important assignment would be to identify and investigate metrics of output that may be used as proxies to track certain aspects of the sector, including its innovativeness and its general health.

Globally, the MD development process requires supervision and registration with a local health agency, which in the US would be the Food and Drug Administration (FDA)'s Center for Devices and Radiological Health (CDRH).[1] Starting in 1976, CDRH received congressional mandates to ensure the safe and appropriate use of MDs via the Medical Device Amendments to the Federal Food, Drug, and

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1 Here, CDRH, FDA, or Agency may be used interchangeably.

Table 1 Some milestones in FDA device regulation since 1970)

Year	US Drug Regulation
1970	Cooper Committee is established, which "recommended that any new legislation be specifically targeted to devices because devices present different issues than drugs"
1976	Medical Device Amendments to the Federal Food, Drug, and Cosmetic (FD&C) Act
1990	Safe Medical Devices Act (SMDA)
1992	Mammography Quality Standards Act (MQSA)
1997	FDA Modernization Act (FDAMA)
2002	Medical Device User Fee and Modernization Act (MDUFMA)
2007	FDA Amendments Act (FDAAA), MDUFA II
2012	FDA Safety and Innovation Act (FDASIA), MDUFA III
2016	21st Century Cures Act
2017	FDA Reauthorization Act (FDARA), MDUFA IV

https://www.fda.gov/medical-devices/overview-device-regulation/history-medical-device-regulation-oversight-united-states

Cosmetic (FD&C) Act,[2] and subsequent legislation (see Table 1).

In total, the above laws allowed the FDA to develop regulations that offered an opportunity to regulate the industry while simultaneously promoting its development through applying a classification scheme to MDs based on patient risk via the intended use of a given MD. Simplistically, the greater the risk (and thus higher the class), the most stringent the requirements for receiving registration to market a specific MD in the US.[3] In a great part, this risk-based approach led to two key regulatory registration paths: the Premarketing Notification (PMN; otherwise, known as the 510(k)), and Premarketing Approval (PMA). The PMN process is relatively administratively simpler and results in a clearance [2], while that of the PMA is (typically) more complex (as it may require clinical data) and results in formal approval from the Agency.[4,5] One must keep in mind the importance that both circuits include an application from the Sponsor seeking registration: either a PMN or PMA. Thus, the application represents the sponsor's assertion of the merits of the MD and its potential viability in the marketplace. In many ways, the act of submitting the application for registration is the sponsor's belief that all of the various inputs (investments) have cumulated into an innovative product of interest to the marketplace. This is particularly true if the product attained registration status. Cumulatively, therefore, the total number of PMN and PMA Applications [and their sum Total MD (PMA + PMN)] over time would be a key piece of evidence (metric) supporting the evolution of innovativeness and/or other economies associated with the MD industry.

In this work, the three metrics of the regulated MD industry are considered: the number of PMN, PMA, and Total MD Applications. It is hypothesized that these metrics would be behave similarly to those of other economic variables, as each MD (and thus as a collective) is a resultant composite of various input—including those of the firm (e.g., people, processes, systems), those of the sector (e.g., supply/demand mechanics), as well as those of national policy and enforcement through a regulatory body. Unlike other economic variables, however, to the author's knowledge, little is known about the dynamics of these metrics and their potential importance to understanding the various factors that may have influenced their evolution (including its forecast). Importantly, in this case of MD development and the metrics selected, these factors include substantive economic activities (e.g., as crises) and/or health policy (e.g., laws) considerations.

Specifically, the focus of this work is on one key characteristic of economic variables (particular those for which sufficient longitudinal data are available) is the appearance of so-called economic or business cycles in the FDA-regulated MD industry. Cycles are generally described in terms of wave mechanics in which a noticeable peak eventually leads to an trough and recycles—where the peak would be considered the pinnacle of economic prosperity (e.g., expansion) of some sort whereas the trough would be a temporally associated misery in productivity (e.g., contraction). From a certain perspective of exogenic strength, the ebb and flow of the variable would correspond to the time-varying strength of forces pressing on the metric. At least four broadly canonical cycles exist (beyond that of seasonal effects), although there has been advancements (see, e.g., [3]) summarized as:

2 Pub. L. 94-295 enacted on May 28, 1976.

3 Section 513(a)(1) of the FD&C Act [21 U.S.C. § 360c(a)(1)].

4 Section 515 of ibid.

5 https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma.

- Kitchin Short-Term Cycle [4]: 3.5 years in length. Derived as a generalization "supported by a wide range of, annual statistics for Great Britain and the United States, and especially by monthly statistics of clearings, commodity prices, and interest rates for the two countries (page 10)." Kitchin writes that he agrees with a "Mr. Philip Green Wright when he suggests: 'Business and price cycles are due to cyclical recurrences in mass psychology reacting through capitalistic production. The rough periodicity of business cycles suggests the elastic recurrence of human functioning rather than the mathematical precision of cosmic phenomena (page 14).'"
- Juglar Mid-Term Cycle [5, 6]: 6–7 years in length with a 1–2-year precipitous drop. Besomi ([5], page 3) captures Juglar's thoughts that—based on banking, population, price of corn, import and exports, rents and public revenue statistics across England, US, Prussia and Hamburg—there was a "a strict correlation … and that changes go through specific phases, always the same, and are in concordance in the countries where commerce and industry are more development. From this regularity, Juglar inferred that the common premise to all crises lies in the excesses of speculation and in the inconsiderate expansion of industry and trade (*ibid*, page 4)."
- Kuznets Medium-Term Cycle [7]: 15–25 years ([8] stated 15–20 years; Kuznets specified approximately (but equal to or greater than) 20 years [see Tables 3 and 4 on pages 204 and 205, respectively in Kuznets, 1930 across US and Europe and various goods and services (including with caveat trusts)]. Abramovitz [8] nicely summarizes this perspective in trichotomized phases: a rebound from depression ("growth rate of output was accelerating to maximum (page 351)"), steady growth ["smoothed growth rate was high enough to keep the labor force well employed. It was interrupted by short mild recessions, but at cyclical peaks the demand for labor pressed on supply (351/352)]", followed by a depression or stagnation ["actual output always fell sharply; smoothed output usually declined or at best grew very slowly (page 352)]."
- Kondratieff Long-Term Cycle ([9]: 50 years [± 5–7 years (*ibid*, page 111)]. Kondratieff derives 3 cycles each roughly 50 years (more or less) across a series of econometrics across France, England, Germany, the US, and the "whole world" (*ibid*, Table 1, page 110). Importantly, the author concludes the following proposals: (1) "long waves below … to the same complex dynamic process in which the intermediate cycles of the capitalistic economy with their principal phases of upswing and depression run their course (*ibid.* page 111);" (2) "during the recession of the long waves, agriculture, as a rule, suffers an especially pronounced and long depression (*ibid*);" (3) "during the recession of the long waves, an especially large number of important discoveries and inventions in the technique of production and communication are made, which, however, are usually applied on a large scale only at the beginning of the next long upswing (*ibid*);" (4) "at the beginning of the upswing, gold production increases as a rule… (*ibid*);" (5) "It is during the period of the rise of the long waves, i.e., during the period of high tension in the expansion of economic forces, that, as a rule, the most disastrous and extensive wars and revolutions occur (*ibid*)."

Here, the key hypothesis that is tested is: assuming PMN, PMA and the Total MD Applications are a proxy metric associated with the MD industry (and assuming therefore these variables act as other econometrics), do latent periodicities exists? If so, what are the time lengths of such periodicities. The hypothesis is tested via several statistical approaches, based on two objectives: (1) to understand the intrinsic nature of the 3 time series (viz., descriptive statistics) and, based on this information, (2) to resolve any identified periodicities accordingly. The statistical routines used to describe

- The data include typical distribution statistics (e.g., 1st, 2nd and higher moments), normality, seasonality, linearity, stationarity, long-range dependency, and structural break.

  The periodicities include Refined Moving Average Filter (RMAF), Seasonal Trend Loess (STL), wavelet power spectra, and the Complete Ensemble Empirical Mode with Adaptive Noise decomposition (CEEMDAN).

An explanation of each of the algorithms and why they were selected are part of the Materials and Methodologies section. Thereafter, *prima facie* results are presented. The manuscript closes with an interpretation of the results and key conclusions including limitations of the study and future directions for continued research.

Materials and Methodologies

While details of the materials (including data acquisition and preparation) and methodologies (including R programming code) are presented in the accompanying Supplementary Materials as a means to fully replicate and/or extend this analyses, this section summarizes the data sources and its preparation, as well as the rationale and statistical methodologies used in performing the analyses.

Data Sources and Data Preparation

The data were focused on applications (and not registrations) as the key hypotheses surrounding efficiencies associated with the MD industry (and not, e.g., those of the FDA registration process). The US FDA data are considered in this report as the 'authorized system of record;' thus, PMN and PMA data were obtained from the US FDA repository, as there is no known repository containing failed (that is, non-authorized for sale) MDs.

- PMNs: The data were obtained from the FDA site: https://www.fda.gov/medical-devices/510k-clearances/downloadable-510k-files on June 30, 2021. The files included PMN7680.ZIP (1976–1980), PMN8185.ZIP (1981–1985), PMN8690.ZIP (1986–1990), PMN9195.ZIP (1991–1995), and PMN96CUR.ZIP (1996-Current).
  - Date Range: May, 1976 to Dec, 2020
  - Total Number of Records: 158,961
- PMAs: The data were obtained from the FDA site: https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals#pma (under section "PMA/PDP Files for Downloading" on June 30, 2021. The files included pma.zip, "which contains information about the releasable PMAs (ibid)."
  - Date Range: Oct., 1960 to Dec., 2020 (Note: The data were truncated to May 1976 to Dec 31, 2020 to allow direct comparison of the earliest PMN record. A negligible deletion of 178 records.)
  - Total Number of Records: 44,831 (44,805 with the truncation)

These data sources were culled for "DATERECEIVED" (Application); that is, the date the application was received by FDA; and imported into Excel, wherein the dates were counted on a monthly scale and then exported as Comma-Separated Values (CSV) file for input into the R programming environment.

In total, 3 variables comprised the complete dataset: PMN Applications, PMA Applications, and Total MD Applications (that is, the monthly number of PMNs and PMAs were simply summed)—each with 536 values (the sum of all observations within a given month from May 1976 to December 2020). To summarize, the 3 time series were:

- Time Series #1: PMN Applications: MDs seeking PMN (510(k)) registration.
- Time Series #2: PMA Applications: MDs seeking PMA registration.
- Time Series #3: Total MD Applications: MDs seeking either PMN or PMA registration.

Statistical Analyses

The general intent of the statistical analyses were two-fold: (1) to understand the intrinsic nature of the 3 time series (viz., descriptive statistics) and, based on this information, (2) to resolve periodicities accordingly. Note: As discussed further below, certain data attributes elucidated from certain tests necessitated further analysis (see Results) specifically around non-stationarity and long-term memory.

There are many statistical approaches with a capability to characterize a given dataset including decomposition (viz., reduction to seasonal, trend, and random (stochastic) contributions and inversely reconstructing the time series (within some sort of acceptable error) through some additive or multiplicative combination), structural changes (viz., identification of meaningful changes in certain distribution attributes), data (e.g., correction denoising and/or missing data), and dimensionality reduction (e.g., techniques to reduce or identify the variables that would represent key properties of the original variable space) and so on. Here, the algorithms selected were a result of: appropriateness based on the time series structure (e.g., non-linearity and non-stationarity), accessibility to the algorithm (access via the R Project), as well as the nature of the signal to be resolved (periodicity). Thus, an effort has been made to use known methodologies (where possible) and cross-validating the results through either using different approaches (ideally with limited theoretical overlap) or exploring the parameter space of a given algorithm. As this work is a result of applying known methodologies, all supportive mathematical formulae are deferred via citation. Unless specified otherwise, all methods presented followed standard implementation and default parameters were used (as appropriate) throughout the analyses.

Step 1: Statistical characteristics of the data.

This step simply explores the distribution of the data from a time series perspective, estimating its general characteristics (e.g., moments) as well as outlining its dynamics [e.g., its stationarity and long-range dependency (LRD)]. Either the characteristics of the distribution or properties of the dynamics may alter the calculations, since—for example –a stationary or non-LRD time series may allow for 'simpler' approaches to the analysis, as the moments would be time invariant or individual signals separable, respectively. The analyses followed the following prescription:

Time series loaded and descriptive statistics performed([10, 11]: R Package: 'fBasics'; [12]: R Package: 'forestmangr'): In this step, the data were read as a time series into the R program, and descriptive statistics were assessed via the following tests:

- Normality ([13]: R package: 'foreach'; [14]: R package: 'nortest'): Anderson–Darling (A–D), Cramer-von Mises (CvM), and Lilliefors (Kolmogorov–Smirnov) (K–S) normality tests
- Seasonality ([15]: R package: 'seastests'): WO, QS, Friedman and Welch tests
- Nonlinearity ([16]: R package: 'nonlinearTseries'): Teraesvirta's and White Neural Network tests, and Keenan, McLeod-Li, Tsay, and Likelihood Ratio tests
- Stationarity ([17]: R package: 'aTSA'): Augmented Dickey–Fuller (ADF), Kwiatkowski-Phillips-Schmidt-Shin (KPSS), and Phillips–Perron (PP) Unit Root Tests
- LRD: Qu and Multivariate local Whittle Score type (MLWS) tests ([18]: R package: 'LongMemoryTS'), autocorrelation function (ACF) ([10]: R package 'stats'), and Hurst Exponent ([19]: R Project: 'pracma' (hurstexp); [20]: R Project: 'tsfeatures' (hurst)]
- Order of integration ([18]: R package: 'LongMemoryTS']: Geweke-Porter-Hudak (GPH) estimator of fractional difference

Given that 2 tests (viz., MLWS and Qu test) suggested 'spurious' LRD, yet the Hurst Exponent and the existence of non-zero/non-unity (fractional) order of integration existed; thus, statistical estimation of structural breaks was performed using the standard dynamic programming model of Bai and Perron as implemented by ([21–23]: R Project: 'strucchange'; [24]: R Project: [tseries']). In this approach, the definition of structural break is one in which there is a some sort of significant change in the parameters of a (linear) regression model. The existence of breaks would strongly affect the selection of statistical algorithms.

Step 2: Statistical determination of periodicities latent in the data.

Shorter-term Periodicities: Seasonal trend decomposition via Loess method (STL) ([10]: R Package: 'stats'), Refined Moving Average Filter (RMAF) ([25]: R Package: 'rmaf'), and the wavelet power spectrum using a Morlet wavelet under a smoothing (Loess) reconstruction ([26]: R Package: 'WaveletComp') were used to investigate the short-term structure of the time series data. For the latter, the average period versus the average power for each method was then calculated to elucidate the main periodicities (*ibid*). The dominant frequencies identified were then re-confirmed via spectral analysis ([27, 28]: R Package: 'forecast'). This approach allowed for cross-validation as these methods are orthogonal—that is, there limited-to-no methodological overlap between the methods chosen.

Longer-Term Periodicities: STL, RMAF, and the Complete Ensemble Empirical Mode with Adaptive Noise decomposition (CEEMDAN) ([29, 30]: R Project: 'Rlibeemd') were used to determine the longer trend. The challenge of resolving longer periodicities were multi-factorial and rested with the non-stationary, non-linear, and multiple structural break nature of the data over the duration of the data series. Thus, the CEEMDAN method, which utilizes an adaptive decomposition, has been considered the method of choice to tackle such programs given its flexibility with this type of data [31].

Results:

Objective 1: Statistical Properties of US MD Applications

The evolution of PMN and PMA Applications seem to follow inverse trajectories, while that of Total MD Applications resembles the sum of the two qualitatively (Fig. 1). The trendline for PMNs (Fig. 1a) suggests a significant decay since the peak in the early 1990s, while for PMAs there has been an acceleration since 2000 (Fig. 1b). While PMA Applications (Fig. 1c) show a somewhat relative decline in peak in 2020, it is relatively small. The evolution of Total MD Applications is notable due to the clear presence of a single period with a decline prior to the year of COVID-19 (2020). Note: The scales of the trendlines (Fig. 1—right in green) are slightly different than that of the original observations to better resolve the yearly distributions.

Shifting our attention to the distribution properties, Tables 2, 3 and Figs. 2 presents the results of the various tests and finds that all three time series are non-normal (skewed with differences in tail thickness: PMN-leptokurtic, PMA-mesokurtic, and total MD- platykurtic relative to a normal distribution, but similar in spread), non-stationary, seasonal, non-linear, with considerable long-memory (see Fig. 2 in which there is a long decay to zero) with fractional order of integration, significant persistency, and the existence of structural changes.

Objective 2: Periodicity Latent within US MD Applications

Short-term Cyclicity: STL, RMAF, the wavelet power spectrum using a Morlet wavelet, and spectral analysis reconfirmed seasonality as well as elucidated short-term periodicity. Seasonality (Fig. 3) pictographs suggest multiple short-term cyclicity at the 1-year mark or less; spectral analysis resolved dominant peaks at 1-year (PMN), third-year (PMA), and quarter-year (TotalMD), seemingly mapping against business quarters. Where red represents increased foci of energy, the wavelet power spectra (Fig. 4) presents conceptually near similar results, with a 1-year period or less oscillating over the full reporting period for all three time series. Of interest, there is a concentration of energy (red) around 1-year from 1985–1990 for PMNs, 2003–2020

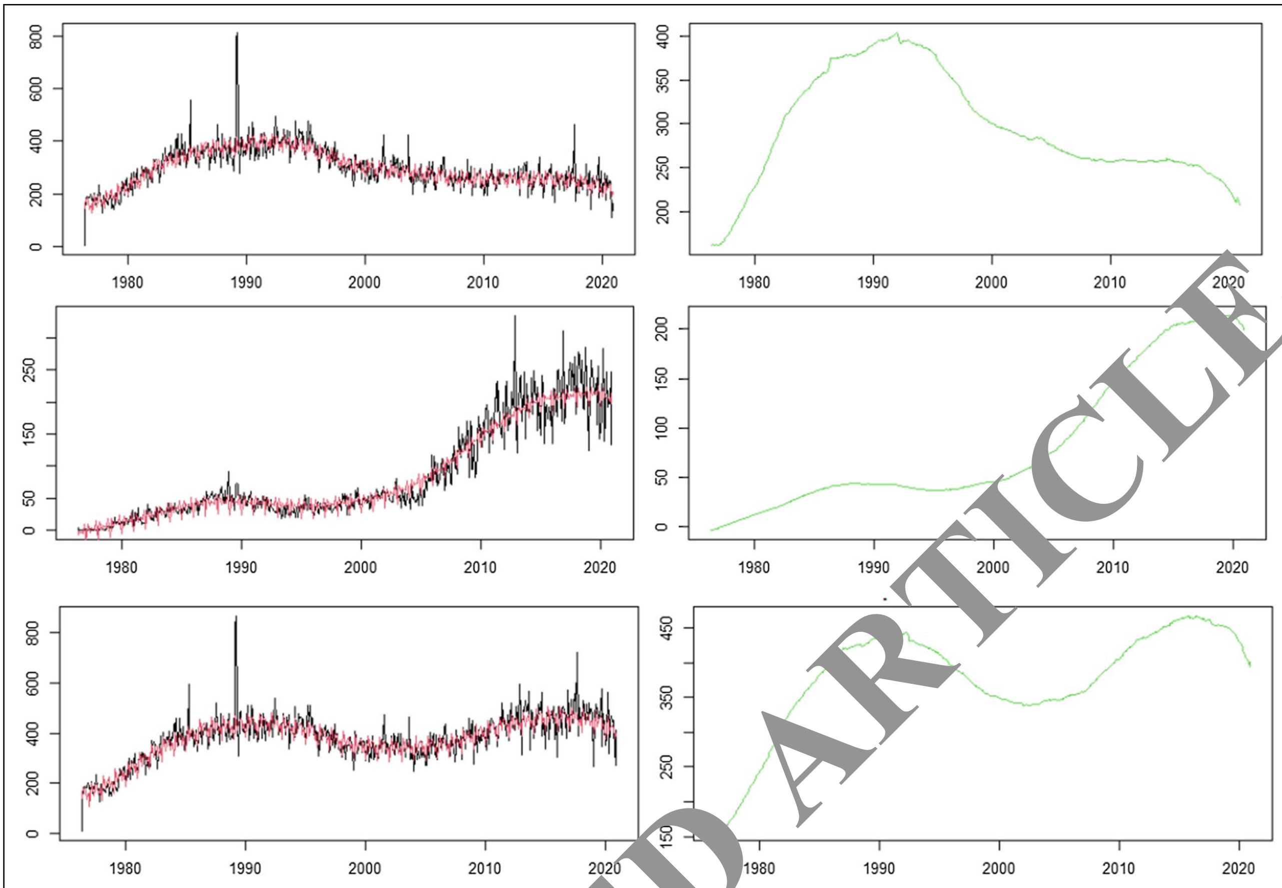

Fig. 1 Time evolution of PMN applications (top), PMA applications (middle), and total MD applications (bottom): observed number of applications (red); estimated trend (left) and estimated trend only (right) (defined moving average with a period of 12 months)

Table 2 Summary statistics of US FDA MD applications

Statistic	PMN applications	PMA applications	Total MD applications
Minimum	3	0	7
Maximum	813	335	869
1st Quartile	247	32	327
3rd Quartile	347.25	135.25	437.25
Mean	296.11	83.59	379.7
Median	286	50	388
Standard error (mean)	3.45	3.25	4.11
Lower confidence limit (mean)	289.33	77.21	371.62
Upper confidence limit (mean)	302.89	89.98	387.78
Variance	6389.99	5665.03	9058.6
Standard deviation	79.94	75.27	95.18
Skewness	1	1.06	-0.02
Kurtosis	5.14	-0.11	2.34
Total records	158,714	44,805	203,519

Total number of observations = 536 per time series; rounded to 2 significant digits; units in months

Table 3 Summary of normality, stationarity, seasonality, long-memory, and non-linearity test results of US FDA MD (rounded to tenths; units in months; rejection of the null hypothesis was based on *p*-value < 0.01; results are presented in Supplementary Materials)

Test category	Tests*	Test Result Against Null		
		PMN Applications	PMA Applications	Total MD Applications
Normality	A-D, CvM, KS	Reject normality	Reject normality	Reject normality
Seasonality	WO, QS, Friedman	Seasonality	Seasonality	Seasonality
Linearity	TNN, WNN	Reject linearity +	Reject linearity	Reject linearity
Stationarity	ADF, KPSS, PP	Reject stationarity	Reject stationarity	Reject stationarity
Order of integration (fractional differencing order *d*)	GPH	0.39	0.65	0.44
Long-memory	ACF	Yes	Yes	Yes
Hurst exponent	(1) Simple R/S hurst estimate (2) 0.5 plus the maximum likelihood estimate of the fractional differencing order d#	(1) 0.83 (2) 0.93	(1) 0.86 (2) 1.0	(1) 0.77 (2) 0.92
Structural breaks	Significance testing of EFP with OLS-CUSUM, OLS-MUSUM, Rec-CUSUM, and Rec-MOSUM$	Reject no structural changes	Reject no structural changes	Reject no structural changes

A–D: Anderson–Darling; CvM: Cramer-von Mises; KS: Lilliefors (Kolmogorov–Smirnov); ADF: Augmented Dickey-Fuller; KPSS: Kwiatkowski-Phillips-Schmidt-Shin; PP: Phillips-Perron MLWS: WO: Webel-Ollech; TNN: Teraesvirta Neural Network; WNN: White Neural Network; GPH: Geweke and Porter-Hudak; ACF: autocorrelation function

+ Null hypothesis of linearity (in 'mean') rejected at the *p*-value < 0.0.8[illegible] (TNN) and 0.0087 (WNN)

#Calculation is difference than that above, see Haslett and Raftery, 1989. Generally, the Hurst Exponent is related to the fractional dimension, *d*, by the equation: $d = 2\text{-}Hurst$

EFP empirical fluctuation processes, OLS-CUSUM:; OLS-MOSUM:; Rec-CUSUM:; Rec-MOSUM:

for PMAs, and similarly both 1985–1990 and 20[illegible]3–2020 for Total MDs.

Longer-Term Cyclicity: RMAF (Fig. [illegible]), and CEEMDAN (Fig. 5) algorithms elucidated longer trends. Its challenging to view a periodic structure in the RMAF with the exception of Total MD, in which a clear single periodic structure (with two peaks and a trough) is resolved (Fig. 1 bottom). The two respective peaks are located at: April, 1992, July 2016, respectively; a period of 2[illegible] years and 3 months. The result of the CEEMDAN methodology depicts peaks at around 5 years across time lengths and time series data.

A summary of the periodicities for ease of reference along with the sources is presented in Table 4:

Discussion and Conclusion

This work concerns itself with the FDA-regulated MD industry and select metrics (PMN, PMA, Total MD) that may be used to explore its evolution. The behavior of the proposed metrics are presumed to be similar to that of other econometrics (e.g., labor, pricing, and production), given the diversity of inputs of varying strengths used to develop a specific MD (output). A specific property of econometrics is the presence of periodicities. This work continues to add support for the existence of such periodicities, as several were found via these proposed metrics. The robust finding of periodicities across a broad assortment of econometrics data (including that of FDA-regulated medicines [32]) strongly suggests the existence of potential laws (akin to those identified in physical systems) that may reflect (or indeed govern) aspects of growth and ebb dynamics observed in these curvilinear structures. Future work may consider using these data (and/or those of FDA-approved medicines) to build such a theory, as the data are robust, easy to collect, and relatively granular (daily values that can be aggregated).

Additionally, this work also sought to identify the time lengths of the latent time series periodicities. Importantly, both seasonal and secular cyclicities were identified. These included: seasonal and yearly, mid-term (Juglar), and medium-term (Kuznets) cycles. A longer (Kondratieff) term (> 20) year cycle was not observed from the methods used. The seasonal/yearly periodicities as well as a Kuznets 24-year medium--term cycles were the most easily elucidated, based on the selected methods; indeed, the Kuznet

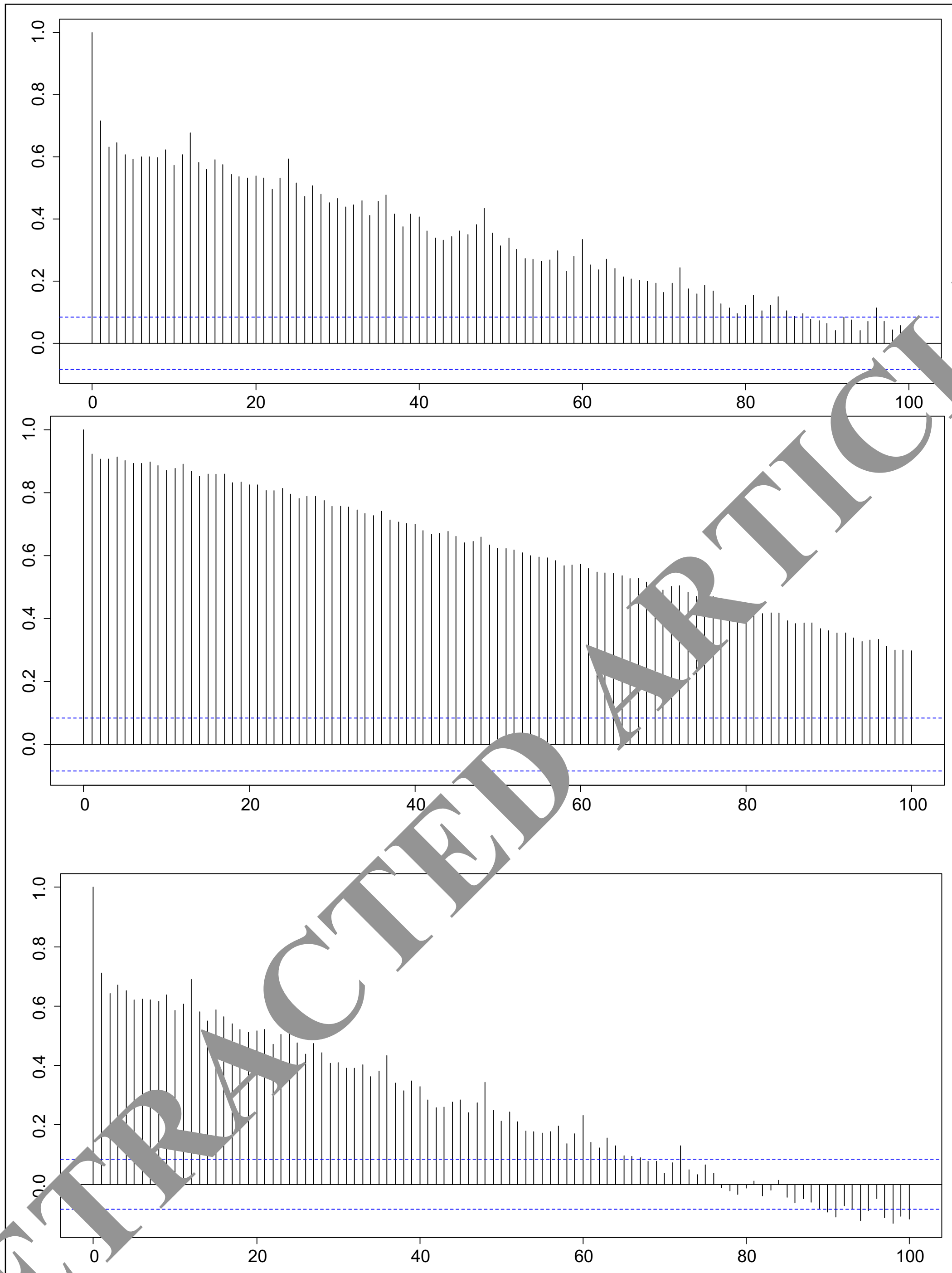

Fig. 2 Auto (serial) correlation function versus lag (months): PMN applications (top), PMA applications (middle), and total MD applications (bottom) [95% Confidence Levels denoted in Blue]

cycle was derived from simple observation (albeit much more clearly post-RMAF).

Theoretically, how would one translate the theorists conjectures of periodicities to the MD industry? For the medium-term (24-year) cycle, and leveraging Kuznets theory, the author speculates that the existence (and use) of the substructures of the PMN and PMA Application curves (metrics) give us a unique insight into the MD industry from a periodicity perspective. Apparently from the simple PMN and PMA plots (Fig. 1), it would seem that the industry is undergoing a potential transformation. The number of PMNs since at least 2000 has been stagnate to trending downward

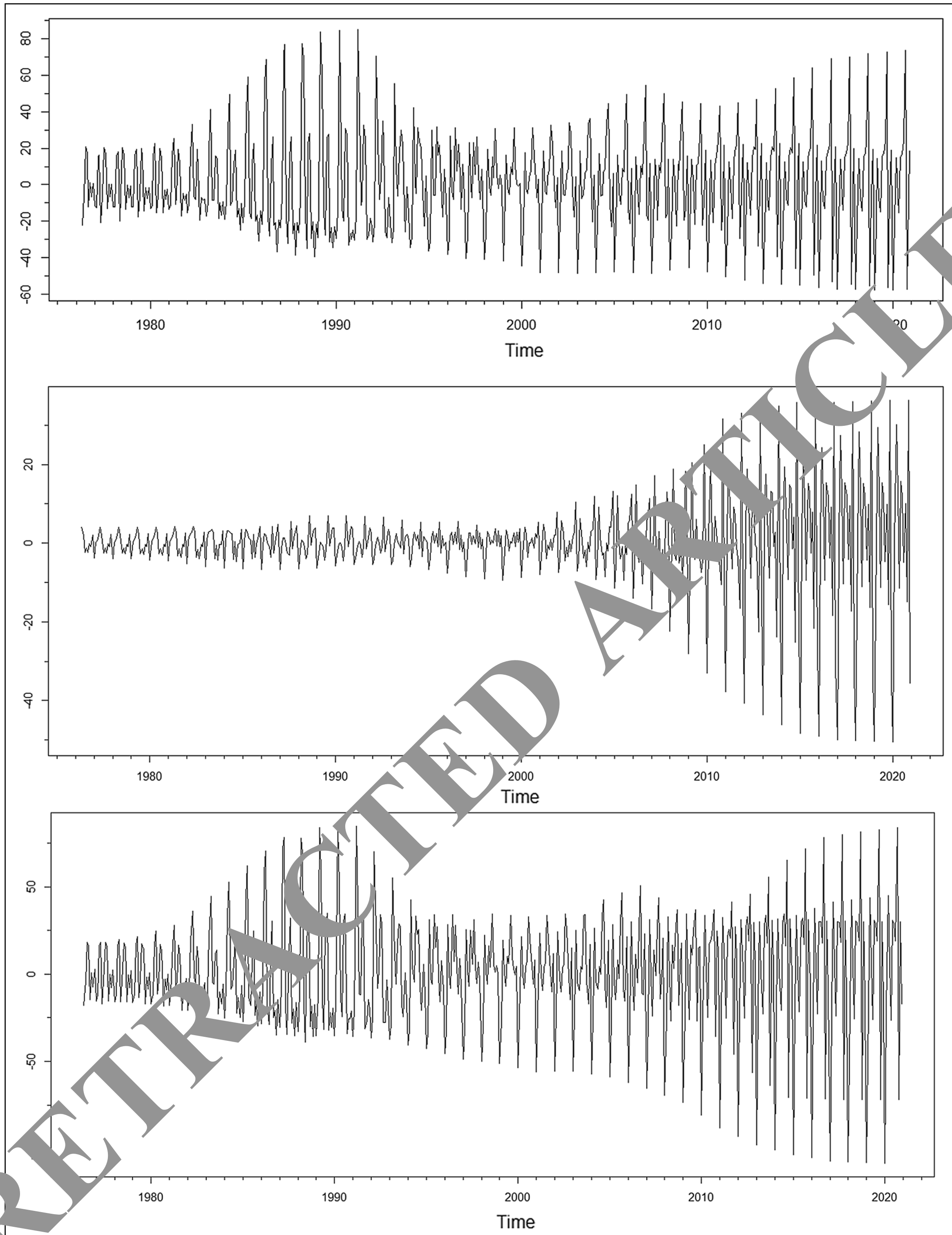

Fig. 3 Seasonal periodicity (via STL) for PMN (top), PMA (mid), and total MD applications (bottom)

from a relative peak in the early 1990s, while PMAs since 2000 has been clearly growing in a striking-cobra-like pattern. Taken together, the collective metric (Total MD) resembles a clear Bactrian-camel-like structure with two clear peaks and a trough in the-1990s and mid-2010s. This would suggest an industry oriented movement from simple

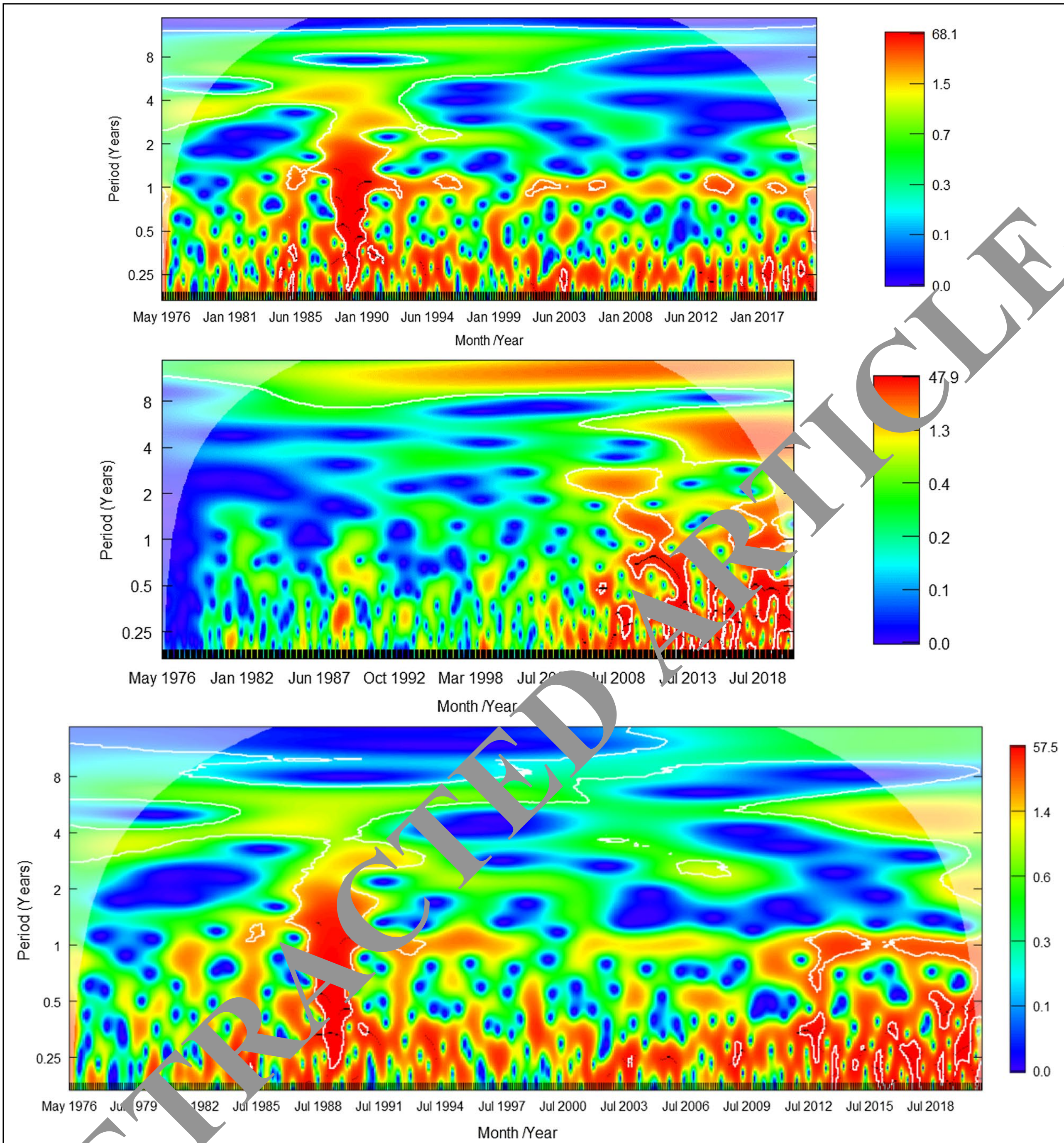

Fig. 4 Wavelet power spectra for PMN (top), PMA (middle), and total MD (bottom) applications

(lower risk, lower class) MDs to ones that are more complex (higher risk, higher class). Entrepreneurial tendencies grew as of 2000 to build complex MDs (e.g., human embedded systems) requiring additional health authority review and oversight (PMA); presumably driving economic rents given the increase in production costs. PMN activity stagnated due to lack of innovative creativity. Unlike other industries, however, PMAs would not generally replace PMNs—that is, we still need thermometers; thus, there is a floor to PMN Applications, whereas there is no limit to those of PMAs.

The seasonal/1-year and Juglar cycles are also of considerable interest. The latter specifically as the 5–6-year cycle was persistent via both PMAs and PMNs and throughout the data reporting duration of 44 years. An explanation for these

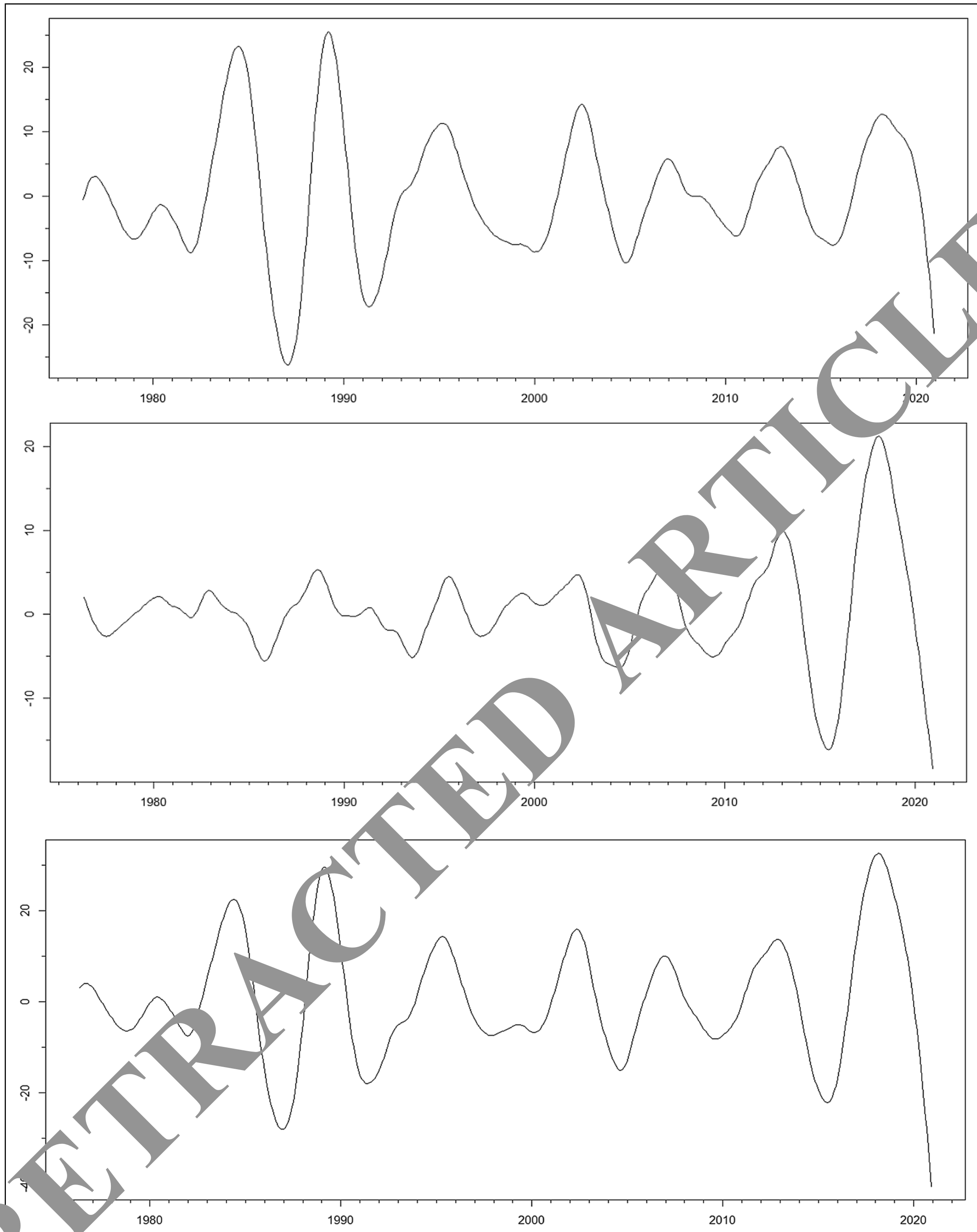

Fig. 3 CEEMDAN trends for PMN (top), PMA (mid), and total MD (bottom) applications

is outstanding but may be speculated to reflect time lengths required for implementing simple to moderate innovation design changes. Imagine a MD in which a specific correction or addition to functionality was made. The updated (new) MD would be subsequently tested, placed into production, an application sought and registration granted by the HA. The rate of MD development in this context would be relatively much shorter than an industry transformation.

As noted by the periodicity theorists, there is little impact of crises to long-term tendencies. Consistent with

Table 4 Mapping of Broad Canonical Economic Cycles with that of periodicities associated with FDA Medical Devices (units in years) as identified in this study (see text for details)

Theory	Canonical periodicity	PMN	PMA	Total MD
Seasonal/yearly Cycle*	0.25/1	1	0.3 / 1	0.25 / 1
Kitchin Short-term cycle	3.5			
Juglar Mid-term cycle#	7–11	5–6	5–6 / 8	5–6
Kuznets Medium-term cycle^	15–25			24
Kondratieff Long-term cycle	40–60			

^Fig. 1 (total MD) [as well as CEEMAD (see Supplementary Materials)]

Reference: *Table 3, Figs. 3 and 4, and dominant peaks of spectral analysis (see Supplementary Materials# Figure 4 (middle), Fig. 5

^Figure 1 (total MD) [as well as CEEMAD (see Supplementary Materials)]

the medium-term findings of Kuznets, there is no obvious impact of economic crises on Total MD Applications. There was a subsequent decrease in Total MDs prior to the recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-19; HCoV-19; COVID-19) crisis. In fact, there has not been any noticeable change at least in this study due to the crises on the cycles; the author also did not notice any blatant impact of the COVID-19 crisis on medicines development at least as of Aug 2020 [33]. it would be anticipated from the data that Total MD Application will continue a downward ascent until the mid-2020s prior to rising again, with a potential drop of at least 25% anticipated. PMNs will continue to drift seemingly. It therefore seems reasonable that PMAs would fall, assuming the continued structure.

Lastly, this work also has provided insight into the data themselves. We learn that the data are non-normal, non-linear, and non-stationary with specific characteristics (lop-sided and fat tailed). We also learned that there is an intrinsic long-range dependency (LRD) reflecting memory dynamics as well as multiple structural breaks. Both of these features suggest statistical avenues to generate and investigate hypotheses related to exploring the impact of specific exogenous influences. The Chronological Hurst Exponent, which algorithmically leverages LRD, and Structural Breakpoint Analysis have been used in this way for FDA US medicines as an attempt to link economic events (e.g., crises) and policy interventions to changes in either LRD or structural breaks accordingly [34]—a similar experiment could be performed for MDs [35, 36].

This work concludes that (1) PMA and PMN data may be viewed as a proxy measure of innovativeness and certain economies in the MD industry; (2) similar to other econometrics in that periodicities exist are present in these metrics; (3) seasonal/1-year, Juglar and Kuznets periodicities are present in the metrics; (4) these metrics do not seem affected by specific crises (such as COVID-19); (5) PMNs and PMAs evolve inversely and suggest a structural industrial transformation; (6) Total MDs are predicted to continue their decline into the mid-2020s prior to recovery (thus, these metrics may play a greater role in predicting the evolution of the MD industry).

Disclosures

The author is an employee of Takeda Pharmaceuticals; however, this work was completed independently of his employment. 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 Supplementary Materials for all data and methods to replicate (or extend) the results presented herein.

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Supplementary Information

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