Title: Since 1976, the Dynamics of US FDA Medical Device Premarket Notifications are Trending Downwards and Premarket Approvals are Trending Upwards, Yet Together There is a Clear Single 20-Year Period: Does this Represent a Structural Transformation for the Industry?

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Abstract: There has been concern that the severe acute respiratory syndrome coronavirus 2 (COVID-19) crises may have stifled medical device (MD) development. However, what if a decline was expected based on some non-COVID-19 force? Since 1976, it is shown that the number of FDA MD applications and registrations (comprised of the sum of premarket notifications (PMNs) and approvals (PMAs)) follow a clear 20-year periodic structure (with two well-defined peaks and a trough), while PMNs and PMAs are aperiodic: the former flowing downwards and the latter flowing upwards. It is hypothesized that the MD industry is undergoing a radical structural change and more needs to be done to not only understand these trends but – importantly – to do something to elevate the peaks and the troughs of these metrics of innovation.

Keywords: Schumpeter, structural change, medical devices, COVID-19, PMN (510k), PMA

The Context: United States (US) Food and Drug Administration (FDA) Medical Devices, COVID-19 Crisis, and Economic Cycles

In the US, the FDA (Agency) regulates medical devices (MD) (primarily under 21 CFR Parts 800-1299). Simplistically, the MD registration process is generally comprised of a submission of an application from the Sponsor followed by registration by the Agency: either as a Premarket Notification (PMN, 510k)¹ or approval (PMA)². Both of these administrative circuits take into regards the risk of the device in the intended population. A PMN requires that the applicant “demonstrate that the new device is ‘substantially equivalent [SE]’ to a predicate device in terms of intended use, technological characteristics, and performance testing, as needed³. The PMN numbers for use in this work also include those devices defined under De Novo Classification Scheme, wherein such an SE is not established as no predicate exists. A PMA, on the other hand, requires “valid scientific evidence demonstrating reasonable assurances of safety and effectiveness for the device’s intended use (*ibid*).” To give the reader a taste of the diversity of MDs under each scheme, examples of the former include catheters, blood pressure cuffs, pregnancy test kits, syringes, etc... and those of the latter include: contact lenses, dermal fillers, implantable systems.

A given application (and its final disposition) may thus represent the culmination of significant explicit (e.g., infrastructure) and tacit (e.g., know-how) investments by the Sponsor (and potentially other stakeholders) with the expectation of providing the market with a value-added, quality, FDA-reviewed MD for an expected return. Thus, the gross number of applications or registrations over a given time

¹ Note: MDs designated under the De Novo administrative cycle are integrated within PMNs.

² <https://www.fda.gov/medical-devices>

³ <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/how-study-and-market-your-device#step2>

may give significant insight into evolution (pro/egress) of the regulated MD industry in terms of economic and/or policy matters.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-19; HCoV-19; COVID-19) crisis affected all sorts of everyday activities from visiting to the grocery store to attending to medical concerns due to various factors including governmental action (Hale, 2021). This may lead some to wonder if the crises has affected innovative activities and capacities, including development of medical products. Recently, it was shown that there was little to no impact on the number of medicines produced at least in the US (and hopefully until at least 2022) (Daizadeh, 2021). Unfortunately, to the author's knowledge, there has not been an inquiry into the crises' potential effects, if any, on MD development.

Typically associated with some sort of radical exogeneous factor (such as a pandemic), it is known that a broad assortment of economic variables – such as rates of population growth, emi/immigration, construction intensity, interest rates, foreign trade, coal and pig iron production, climate, and so on – ebb and flow over time and space. Economists have attempted to define the various stages of such cycling phenomena: for example, Juglar defined this periodicity over three phases: prosperity, crisis, and subsequent liquidation, and suggested the length of the cycle with crisis/liquidation taking 1-2 years, followed by a 6-7 year phase of prosperity, with drivers to prosperity to crisis transition due to exuberance and thus over-speculation. Kitchin derived inventory cycles with wavelengths of 3.5 years. Kondratieff introduced the concept of the long-wave 50-60 year cycles and associated with inventiveness, while Kuznetz attributed medium-length cycles of 15-25 years to infrastructure concerns. Schumpeter argued (in part) via the 'creative destruction' hypothesis that a linear combination of technological transformations drove such medium-to-long cycles. While there are controversies still to be resolved, and other models have been proposed, in any case, it is generally understood that cycles seem to exist albeit their mechanics have yet to be fully understood (Daizadeh, 2020; Korotayev and Tsirel, 2010).

The Empirical Finding: Individually PMNs and PMAs Applications and Registrations are Aperiodic, but Collectively They are Periodic

Starting in May, 1976 until the present, US FDA MD data is readily available and include: the number of applications seeking PMN and PMA registration status (collectively termed MD Applications), and the number of FDA PMN Clearances and the number of FDA PMAs (collectively, termed MD Registrations). The reader is directed to the Electronic Supplementary Materials for all materials (the data source and preparation) and methods (statistical analysis). Independently, or collectively, all of these variables provide insight into the processes seeking and securing registration status in the US. For example, records comprising the number of MD Applications may reflect the innovativeness of developers, while that of MD Registrations may reflect the efficiency of the FDA in reviewing and approving the applications.

Figures 1 presents the dynamics of the monthly number of MD Applications (Figure 1a (PMN), c (PMA), and e (total)) and MD Registrations (Figures 1b (PMN), d (PMA), and f (total)) over time. Importantly, Figures 1a (PMN Applications), 1b (PMN Registrations), 1c (PMA Applications), and 1d (PMA Registrations) illustrate the dichotomous nature of the PMN and PMA dynamics, which effectively move inversely to each other. The number of PMAs have been growing over the recent years, while that of PMNs have been relatively decreasing or dynamically stagnate over the last decade. This is acutely observed in the trend-line depictions (left in red and right in green) estimated from a moving average calculation with a 12-month period (Qiu, 2015; R Core Team, 2020; Trapletti and Hornik, 2020; Borchers, 2021).

Of particular interest here is the clearly periodic (double-humped) structure that manifests when both PMNs and PMAs are considered collectively – that is, the total number of MD Applications or

Registrations (Figures 1e and f, and Figure 2). Figure 2 presents and defines a single period (that is, the date and amplitude of the two peaks and a trough) as:

- FDA MD Applications: Period: 20.5 years; Peak-to-Trough Relative Percent Decrease: ~24%
 - Peak 1: Date: Apr 1992; Amplitude: 444
 - Peak 2: Date: Oct 2012; Amplitude: 442
 - Trough: Date: Feb 2002; Amplitude: 339
- FDA MD Registrations: Period: 26.5 years; Peak-to-Trough Relative Percent Decrease: ~28%
 - Peak 1: Date: Sept 1992; Amplitude: 433
 - Peak 2: Date: Mar 2019; Amplitude: 470
 - Trough: Date: Apr 2003; Amplitude: 340

The Two Key Questions: Why and What Does This Mean for the Future of MD Development?

Over the last 40 years, US MD development has evolved over a backdrop of potentially significant economic and policy events (Daizadeh, 2021b). These have included: The 1981 recession, the 1987 Black Monday, the 2001 Dot-Com Crash, the 2007-2009 recession, and the 2020 COVID-19 crisis and corresponding recession. Concomitantly, US FDA MD-related policy changes have included: the 1976 amendments to the Federal Food, Drug, and Cosmetic (FD&C) Act, the 1990 Safe Medical Devices Act (SMDA), the 1992 Mammography Quality Standards Act (MQSA), 1997 FDA Modernization Act (FDAMA), the 2002 Medical Device User Fee and Modernization Act (MDUFMA) and its Reauthorization in 2007, 2012, and 2017, the 2016 21st Century Cures Act, the 2012 FDA Safety and Innovation Act (FDASIA).

So how should one consider the unique 20-year period for total number of PMNs and PMAs, the downward-to-stagnation trend of the PMNs or the upward trend of the PMAs – through the lens of FDA MD policy, domestic economics, a combination of both (with/without additional exogenous factors)?

While many hypotheses may exist, based on the empirical data presented in Figures 1 and 2, the author proposes that the 20-year period may represent a structural transformation potentially not related to (or a variation of) so-called Schumpeter's 'creative destruction,' wherein simply one asset replaces another *in toto* (e.g. digital streaming services versus that of Digital Video Disc) (Bernard, et al., 2014). In the context of MDs, generally, PMAs do not straightforwardly replace PMNs. We still need sterile hospital bags, heart pressure cuffs, and so forth, even though such devices do not meet the hurdle of the PMA; viz., life supporting or life sustaining devices and general and special controls are insufficient to provide assurance of safe use.

The rise in PMAs starting in 2000 and the decline-to-stagnation for PMNs starting in the 1990s implies another type of paradigm shift: One that may be due to technological inventiveness driving the growth of complex devices that are embedded within the human system and intended to alter the biological mechanism in a fundamental and clinically meaningful way (PMAs). It is interesting that the rise of PMAs is concomitant to the rise of the 21st century technology patterns observed in other contexts (e.g., see Daizadeh, 2021). While more speculative, it may be that the investment required for a PMA (e.g., human studies, etc...) offers higher relative returns or a different reimbursement strategies than PMNs; and, thus, more attractive to firms in the industry.

Now, assuming the economics and policy landscape continues its dynamism, including accommodations of additional crises of similar strength as that of COVID-19, with all other things being equal, it would be anticipated that the next minima would occur roughly at 2024, when the growth cycle occurs. With the above in mind, and while needed theoretical work requires development in the context of MDs, US policy makers should be aware of the ebb, which may be significant (up to 30%), and potentially adjust, depending on how the numbers evolve. For example, a hand's-off approach may be appropriate for PMNs, as recent legislation – such as that of the De Nov designation promulgated in 2018 for low risk,

unpredicted devices – may spur continued interest in PMN development; or, alternatively, mechanisms to increase the efficiency of PMAs may also be used to elevate the trough.

In any case, what we learned from this particular experiment is that COVID-19 did not leave an indelible mark on MD development. It did, however, raise interest into a remarkable metric, which may be of significant interest as a proxy for innovativeness in MD development. Alongside medicinal development, something to consider as a means to further medical product development.

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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. See Electronic Supplementary Materials for all data and methods to replicate (and hopefully extend) the results presented herein.

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Figure 1: The Observed Number (Black) of (a) FDA PMN Applications, (b) FDA PMN Clearances, (c) FDA PMA Applications, (d) FDA PMAs, (e) FDA MD (PMN + PMA) Applications, and (f) FDA MD (PMN + PMA) Registrations with Respective Estimated Trendlines (Red on Left, and Green on Right)

c)

d)

e)

Figure 2: Periods Resolved from Trends of the Number of FDA MD Applications (Red) and FDA MD Registrations (Blue): The Vertical (Horizontal) Lines Represent Date (Amplitude) of Local Maxima and Minima. Two Periods Identified are 20.5 Years (Red): Oct 2012 [442] - Apr 1992 [443], and 26.5 Years (Blue): Mar 2019 [470] - Sept 1992 [432].