



Correlates of time to approval and other clinical development periods

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The drug development cycle is classically divided into a clinical phase and review phase, with the clinical phase typically being further partitioned based on the planning and conduct of adequate and well controlled trials. Factors affecting the duration of the development intervals have not previously been systematically investigated. Here, we analyze a large population ($N = 825$) of New Drug Applications (NDAs) approved between 2008 and 2017 to characterize the typical duration of these intervals and the development factors associated with their duration. These data and analyses will help those involved in pharmaceutical development by enabling data-driven planning and by providing insight into the effect of certain factors on the duration of drug development programs.

Introduction

Time is the most valuable of all nonhuman resources in drug development. Time lost affects patient care, erodes patent coverage and opportunities to study other assets, and results in the loss of valued employees to retirement or other firms. For some of the top-selling therapeutics of the past two decades, a single day lost on the market might equal a loss of US\$25–50 million in sales [1]. In-depth analysis of the clinical development and review cycles could reveal the expected duration of these periods under typical circumstances or for programs with an Expedited Program designation or after nonapproval outcome. Our objective was to determine how the duration of development varies between different types of therapeutic, those with distinct presubmission characteristics, or with different outcomes from the first cycle of regulatory review.

An overview of clinical development milestones and periods

The time in development has classically been described as having a clinical phase, extending from the beginning of activities to the initial submission of the NDA followed by the review phase, which

ends with approval [2] (Fig. 1). The clinical phase can be divided into periods, based on major milestones; the definitions of major milestones and the events and conventions used to define and analyze development periods are shown in Table 1. In keeping with the granularity of our terminology, the classically termed review phase corresponds to our ‘review period’ because it is not further subdivided in our analyses.

Time to market in the typical paradigm of drug development starts at the point where an idea is generated. For first-in-class molecules and new chemical entities (NMEs), the project often begins with a multidisciplinary team of marketing, clinical, and pharmacology expertise crafting a value proposition in a target product profile with the sentinel idea at its core [3]. Many early development activities for a drug are not readily traceable until an application is made to study the drug in humans. In the USA, this application is the Investigational New Drug Application (IND). Other projects, such as a development program for a pediatric dosing regimen following an approval, might arise from regulatory interactions, such as the Pediatric Written Request. Evidence for the initiation of a modified-release development program might be suggested by the initiation of a clinical pharmacology study. In 5% of approvals, which are mostly modifications in formulation or dosage form, an IND is not submitted because there is no plan to

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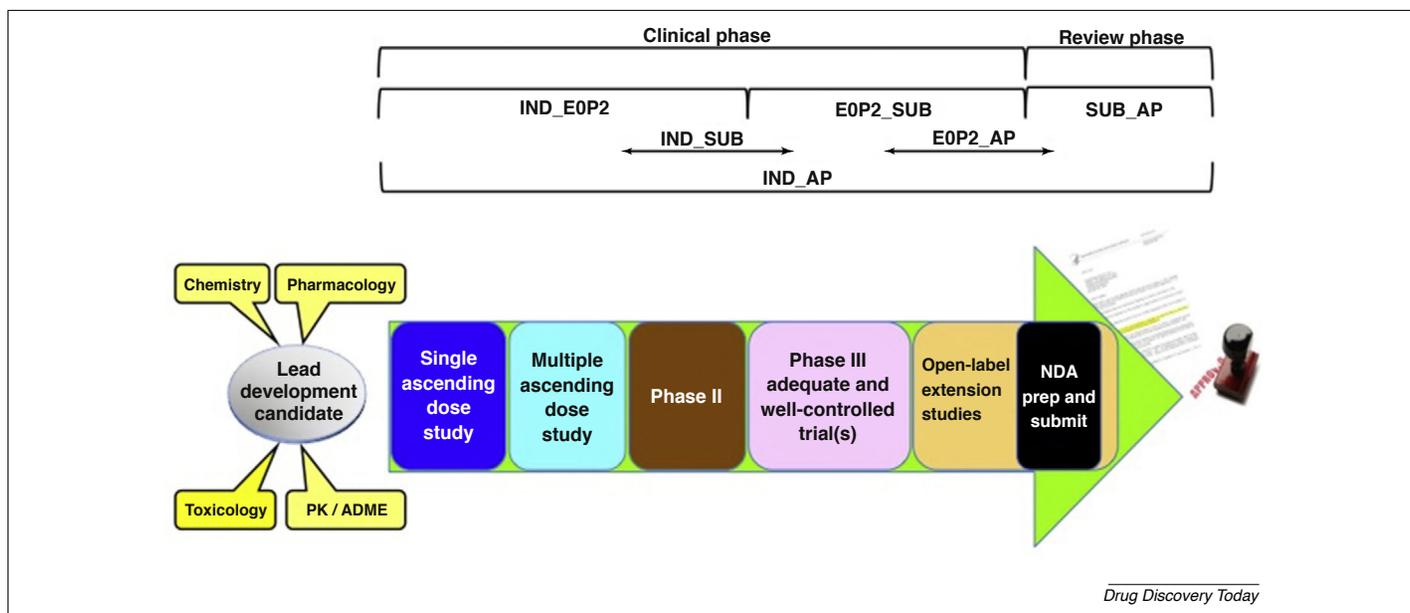


FIGURE 1 Schematic diagram of the full development cycle for therapeutics. Please see main next for definitions of abbreviations.

include new studies in patients [4]. Although not typical for drugs aiming for marketing in the USA, it is possible for a program to go through development with little interactions with the FDA up to the NDA or Biologic License Application (BLA) marketing application [e.g., the NDA review of Radicava (edaravone) [5].

The End-of Phase 2 meeting (EOP2) is a milestone heralding the end of the ‘learning phase’ and onset of larger adequate and well-controlled trials (AWCTs). Its name infers having Phase II studies evaluating dose effect on efficacy and safety, but programs occasionally go directly from clinical pharmacology trials (Phase I) to the AWCTs of Phase III without the benefit of Phase II studies or the meeting before Phase III. This consultation is most useful for a program evaluating an NME to vet ideas for the large, expensive trials of Phase III, and less so for a modified-release drug or reformulation, which might not need any clinical trial for approval. Having an EOP2 is associated with more efficient development in the USA and Japan [6,7].

The review period refers to the interval following completion of the AWCTs and preparation of the marketing application [8]. This period extends from the initial submission of the marketing application (SUBi), to the Approval (AP). The SUBi_AP period has potential for variability because there are several reasons why an application might be shorter or longer than another that occurs at this time. The reasons for this variability most relevant to all programs are their review status and first review cycle outcome. Programs with a Review Status of Priority, which is granted for drugs treating serious diseases that would ‘... provide a significant improvement in safety or effectiveness’, have a review period of 8 months, whereas the Standard Review period is 12 months from the initial submission of the application [9]. As a consequence, analysis of any phase including SUBi_AP, such as the IND_AP or EOP2_AP, should contrast programs having Priority separately from those with Standard Review status, in addition to calculation of the collective group. The SUBi_AP period includes

TABLE 1 Events and conventions related to clinical development periods

Period	Abbreviation	Events and conventions
IND → end of Phase II meeting	IND_EOP2	From the beginning of development to before AWCT; essentially the duration of clinical pharmacology studies; [Convention 1] Not included in programs without EOP2 Meeting; [Convention 2] Milestones other than IND submission used to indicate beginning of development if e.g., no IND, major event more appropriate (pediatric written request), or extensive planning communication with Division before IND
IND application → NDA initial submission	IND_SUBi	From beginning of development to initial submission of NDA; includes Phase I, II, and III studies and preparation of NDA; classically referred to as the ‘Clinical Phase’
IND application → approval	IND_AP	From beginning of clinical pharmacology studies to NDA; classically referred to as ‘Time to Approval’ or ‘Full Development Cycle’: [Convention 3] Priority and Standard Review NDAs evaluated separately for this period
End of phase II meeting → initial NDA submission	EOP2_SUBi	From EOP2 Meeting/Beginning of AWCT to initial submission of NDA; measures length of Phase III clinical trial program and NDA preparation; See Convention 1
End of Phase 2 meeting → AP	EOP2_AP	From EOP2 Meeting/Beginning of AWCT to AP; See Conventions 1 and 3
Initial NDA submission → AP	SUBi_AP	From submission of NDA to approval; classically referred to as the ‘Review Phase’; See Convention 2

the first cycle review of the marketing application and, in the case of applications not approved, the correction of deficiencies and subsequent review cycle(s) through approval. As a consequence, the second reason for differing durations of the Review Period is that this interval will obviously be longer if the first cycle action is a Complete Response (CR), the current term for a nonapproval action at the end of the review cycle, instead of an AP. A related, third reason for prolongation of the review period is that an extension of this period might be triggered by submission of a Major Amendment (MA) that will add 90 days to the SUBi_AP.

Evaluation of clinical periods for approved NDAs

We created a database of critical milestones of 825 NDAs approved from 2008 to 2017 to derive the average duration of periods and phases described in Table 1. These and other data were extracted from publicly available review packages from the Drugs@FDA website (www.accessdata.fda.gov/scripts/cder/daf). A full description of the methodology of data extraction and database are available elsewhere [4]. Given the differences in the regulations [e.g., the 505(b)(2) pathway] and in important descriptive factors (e.g., the NDA classification system), BLAs were not included in this study. Considering that the Review Status and first cycle review outcome affect the time to market of all applications, our review of these factors are described first.

Evaluating the influence of the Review Status and First Cycle Outcomes with the Duration of Periods

Review Status

It is not surprising that the applications with Priority Review status had a significantly longer full development cycle (IND_AP) than those with Standard Review status, because Priority Review programs have a larger percentage of NMEs than those with Standard Review (63% versus 22%) that are more complicated and have longer trials. Standard Review designations that might not require Phase III trials predominate for new dosage forms (33% versus 19%) and reformulations (26% versus 9%) versus Priority Review (Table 2). Following this reasoning, it is not unexpected that programs having a Priority Review status had a median Clinical Phase (IND_SUBi) duration that was significantly longer than those with Standard Review status.

Of the intervals containing the Review Phase outside of the full Development Cycle (IND_AP), there were no meaningful differences between the duration of programs having Priority and Standard Review Status. The median difference for Priority and Standard programs in the SUBi_AP period was only 1 month more than the expected 4-month review cycle difference. In summary, whereas the Review Status had the expected association with the shorter Review Period for programs with Priority Review, the more significant association was with a longer IND_EOP2 period.

First cycle outcome

The duration of periods evaluated based on the first cycle regulatory action, or outcome, would intuitively appear to be longer for programs having nonapproval outcomes, such as the CR, a Refuse to File (RTF; or Withdrawn) status, or those with review extensions based on a MA, although this is not always the case. Whereas the full development cycle (IND_AP) demonstrated a significant level of difference between programs based on the first cycle regulatory outcome, only those with an outright approval were different than the overall group average, less by 650 days (Table 2). Those receiving a CR,MA were marginally more than the group average by 325 days. The duration of the Clinical Phase (IND_SUBi), was longer in programs having an AP,MA than those with other actions. This trend appeared to be related to a particular cluster of longer studies being conducted in this group.

For intervals containing the Review Cycle, EOP2_AP and SUBi_AP, significant differences occurred in the duration of programs with different outcomes. Programs with a CR had a duration of the EOP2_AP period longer than the overall average on the order of 200–350 days if they also had a MA. Programs with a first cycle approval were shorter than the overall average by 575 days. During the SUBi_AP, or Review Period, programs with an AP or AP,MA had a duration of 490 or 400 days shorter than the overall average, respectively. Programs having a CR or CR,MA had a SUBi_AP duration 260 or 350 days longer than the overall average. These differences in the Review Period were among the statistically significant associations with the greatest magnitude of effect size (Fig. 2).

TABLE 2

Median (Interquartile Range) duration of epochs by Review Status and First Cycle action

First Cycle action	Review Status	N Pts	IND_EOP2 (<i>P</i> = 0.0062)	IND_SUB (<i>P</i> < 0.001)	EOP2_SUB (<i>P</i> = 0.6229)	EOP2_AP (<i>P</i> = 0.1011)	SUB_AP (<i>P</i> = 0.0037)	IND_AP (<i>P</i> = 0.0003)
All First Cycle actions								
All	All	825	847 (1059)	1473 (1688)	1074 (718)	1549 (928)	361 (327)	1950 (1794)
	P	188	1054 (981)	1890 (1670)	1081 (772)	1412 (1012)	242 (171)	2266 (2011)
	S	637	756 (1018)	1292 (1616)	1074 (657)	1643 (955)	393 (377)	1845 (1719)
First Cycle action	Review Status	N Pts	IND_EOP2 (<i>P</i> = 0.3674)	IND_SUB (<i>P</i> = 0.0229)	EOP2_SUB (<i>P</i> = 0.0003)	EOP2_AP (<i>P</i> < 0.001)	SUB_AP (<i>P</i> < 0.001)	IND_AP (<i>P</i> < 0.001)
Individual First Cycle actions								
AP	All	446	847 (989)	1431 (1509)	1061 (639)	1340 (668)	303 (62)	1765 (1537)
AP,MA		88	1006 (1273)	1792 (1805)	1426 (907)	1850 (881)	395 (61)	2215 (1741)
CR		205	803 (1012)	1287 (1794)	1088 (719)	2013 (979)	757 (639)	2372 (1989)
CR,MA		35	837 (1166)	1475 (1581)	947 (381)	2279 (828)	853 (846)	2750 (2207)
RTF/WD		51	912 (1648)	1238 (2404)	1267 (1415)	1947 (1400)	851 (802)	2086 (2558)

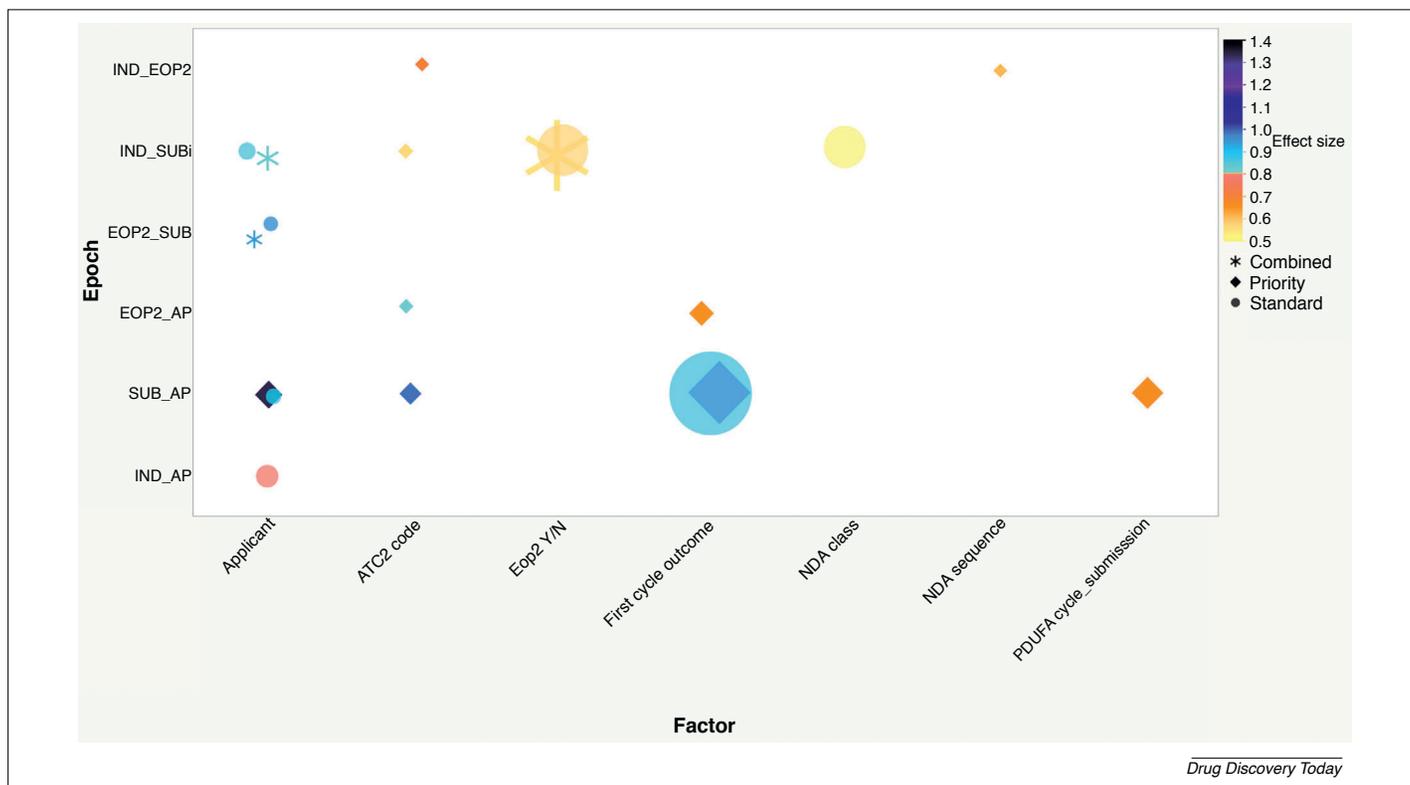


FIGURE 2

Effect size of significant development epoch and factor associations. Please see main text for definitions of abbreviations.

Significant associations between epoch durations and other development factors of interest

In the second phase of our analyses, periods were cast as dependent variables and demographic characteristics as model effects, or factors. The association of these factors with the interval durations was initially tested with the Response Screening platform of the JMP software, which calculates the effect size and a multiplicity-adjusted P value ('FDR PValue') of the association (Table 3). Detection of significant associations were followed by ANCOVA analyses to further evaluate individual factors.

Significant effects of large magnitude irrespective of Review Status were observed between the factor of Applicant and the duration of most intervals, including the Full Development Cycle (Fig. 2 and Table S1 in the supplemental information online). A large (\geq Cohen's 0.8) effect size [11] occurred between the First Cycle Outcome and intervals containing the Review Period. Other notable associations with the duration of intervals included the ATC2 class, EOP2 Y/N, Fast Track, and NDA Class. These associations are described in further detail below.

Applicant

Applicant is a complex factor with key characteristics, such as number of employees and market capital, that go beyond the scope of this study. The importance of this factor is reflected by numerous significant associations of large effect size with almost every interval duration. We evaluated the interaction of Applicant with all of the other demographic factors in our data set to better understand this element. The NDA rank order (i.e., the order of NDA in the series for each applicant) had the most

significant interaction with Applicant and also the greatest effect size. Of all of the development epochs, the Review Period (SUB_i_AP) had the most robustly significant association with the Applicant ($P = 0.003$) and the Applicant/NDA rank order interaction ($P = 0.009$). The inverse relationship between the Review Period duration and Applicant's NDA rank order was likely because of the decrease in the number of nonapprovals with increasing experience.

EOP2 Y/N

It appears logical that one of the strongest associations of an interval duration for the factor EOP2 Y/N would be with the IND_SUBi, the 'Clinical Phase', the interval that contains the AWCTs. The median duration of this interval was shorter in programs without the EOP2 meeting [$N = 440$; 808 days (1182)] than in those with the meeting [$N = 384$; 2066 days (1289)], reflecting the lack of Phase III or less complex registrational studies.

NDA class

The association of NDA class with the time for development appears intuitive; Class 1 drugs, or NMEs, would appear to take the longest to develop, because most need a comprehensive clinical pharmacology program, Phase II studies to explore the relationship of dose or exposure to efficacy and safety, and at least one but usually two adequate and well-controlled trials to confirm efficacy. By contrast, Class 5 drugs would appear to be the most abbreviated because many programs use bioequivalence studies as their basis of evidence for approval. In this analysis, only epochs

TABLE 3

Variables used as factors for analysis

Variable	Definition ^a	Conventions for Analysis
Drug characteristics ATC2 Code ^b	WHO/ATC Level 2 Code for Therapeutic Class	
Applicant characteristics Applicant	Sponsor submitting NDA or that performed most of development activity if applicable	Original Applicant used, irrespective of subsequent mergers
NDA characteristics Legal Basis	Whether NDA was submitted according to Section 505(b)(1) (applicant owns or has right of reference to all materials) or 505(b)(2) (applicant has referenced materials not owned or did not have right of reference)	
PDUFA Cycle of Submission	The 5-year cycle, established in the Prescription Drug User Fee Act (starting from 10/1/1992), in which NDA was originally submitted	Only Cycles 4, 5, and 6 were used because those submitted in earlier cycles only included drugs not approved in first cycle of review and those submitted after only included applications approved in first cycle of review
PDUFA Cycle of AP	The 5-year cycle, established in the Prescription Drug User Fee Act, in which NDA was approved	
NDA rank order	Rank order of NDA for each applicant in database	
Applicant characteristics Applicant	Sponsor submitting NDA or that performed most of the development activity if applicable	Original Applicant used, irrespective of subsequent mergers
Expedited Programs ^c Accelerated AP	Approval based on surrogate endpoint reasonably predicting clinical benefit	
Fast Track	Program for serious conditions with data demonstrating potential to address an unmet need	Programs approved before 11/21/97 designated as Not Applicable (NA) Programs with Breakthrough Designation but not Fast Track, analyzed as having had Fast Track designation (FTD) because they had all of the functional benefits of Breakthrough Therapy designation (BTD)
Breakthrough Designation	A program for serious conditions with clinical data demonstrating substantial improvement on clinical endpoints over other therapies	Programs submitted before 1/3/12 designated as Not Applicable (NA)
Review Status	An Expedited Program that determines length of period of review: Priority, 6 months; Standard, 10 months	All intervals containing the Review Period were analysed by Review Status (Priority or Standard) and with the unseparated groups (Priority + Standard)
Regulatory Features IND Application End of Phase II Meeting	Application to study new drug in USA Meeting typically held before Phase III studies to discuss design, conduct, and analysis of these studies	
Regulatory Outcomes First Cycle RTF/Withdrawal	When Review Division does not file NDA submission or Sponsor withdraws NDA (for any reason)	RTF and NDA Withdrawals grouped because most withdrawals in this database happened immediately before NDA filing was to occur and the Division noted a potential for RTF ^d
First Cycle MA	Extension of review cycle by 90 days based on submission of significant materials for review after initial submission	
First Cycle AP	Regulatory Action of First Cycle: AP (+/- MA) or Non-Approval	
First Cycle outcome	Regulatory Action of first cycle of review: AP OR AP +/- MA OR CR +/- MA OR RTF/Withdrawal ^a	

^a Descriptions are intended to clarify use of these variables and are not intended as regulatory definitions.

^b www.whocc.no/atc_ddd_index/.

^c [9].

^d [10].

from programs with Standard Review Status demonstrated a significant association with at least a moderate effect size, with the exception of the Review Period (SUBi_AP). In these programs, the duration of the period generally reduced with increasing NDA Class [i.e., longest for NDA Class 1 (NMEs) and shortest for NDA Class 7 (Marketed, Unapproved)]. In the Review Period, all NDA classes had about the same duration.

Expedited programs

Based on their program objectives, Expedited Program designation would appear to be associated in some manner with the duration of development periods. Fast Track and Breakthrough therapy purport to expedite development and review, or make them more efficient. All other factors being equal, Priority Review was shorter than Standard Review by 4 months. The path through Accelerated

Approval intuitively appears shorter than the standard NDA AP based on clinical benefit; however, this comparison is only necessarily true for the same indication.

Following the screening for association of the four expedited programs with the duration of all of the development intervals with and without partitioning by Review Status, no significant associations were found with a moderate or greater effect size.

PDUFA cycle of submission

The PDUFA Cycle of Submission was most significantly associated with the duration of the Review Period (SUBi_AP) of programs granted Priority Review ($N = 174$; FDR $P = 7.3 \times 10^{-10}$, ES = 0.7). The effect on Standard Review submissions was also nominally significant, although the effect was smaller ($N = 618$; FDR $P = 3 \times 10^{-14}$, ES = 0.3). One can observe a trend in the reduction of the Review Period for each of the major NDA classes (i.e., NMEs, New Dosage Forms, and Reformulations) with each subsequent PDUFA Cycle.

Concluding remarks and future perspectives

Ample pharmaceutical experience has provided a foundation of data to inform developers and regulators about the expected duration of therapeutic development. Of all factors associated with development, the Applicant has significant associations with the most intervals with the greatest effect size of all the factors we

evaluated. Although the full scope of this association is probably complex and multifactorial, the interaction of the Applicant with the NDA rank order appears to explain an important aspect of the relationship. Future studies evaluating Applicant characteristics in more depth would be useful to further assess this issue. The period with the greatest variability appeared to be that from SUBi_AP, the Review Period. This interval had significant associations with expected factors such as the Review Status and First Cycle Review outcome, as well as whether programs had EOP2 meetings and the NDA class. Less tangible factors, associated with different therapeutic or ATC2 classes as well as the changing regulatory landscapes of succeeding PDUFA cycles had a substantial effect on the duration of much of the development cycle, with a peak influence on the Review Period. Detailed evaluation on the role of Applicant, ATC2, and changes with successive PDUFA Cycles will provide insight into meaningful effects on the duration of therapeutic development periods.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drudis.2019.05.027>.

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