CHAPTER 1 – OVERVIEW of DDEP CLINICAL DEVELOPMENT AND APPROVAL TIMES

Introduction

Faster development is one of the key claims made by drug delivery companies in promoting their products and their services. One company's annual report had the following cover statement regarding their drug delivery product activities.

“Shorter development timelines
   Faster market penetration
   Lower development costs”

Another company that provides drug delivery technology platforms and services to the industry stated: “[our] approach to new-product development through application of drug delivery technology to known drugs is faster and less risky than research of new molecular entities.”

These are two variations on the oft-repeated claims made by drug delivery companies concerning the benefit of drug delivery products and technologies. But are there figures that support these claims? What are the actual development parameters for Drug Delivery Enabled/Enhanced Products (DDEP) and how do they compare with the figures for new chemical entity (NCEs) products?

The issue of clinical development and approval times for DDEP is addressed in this and the following chapters. By looking at a large cohort of drug delivery enabled and enhanced pharmaceuticals (DDEP) approved in the USA during the period of 1996 through the end of 2010 it’s possible to definitively determine the clinical development and approval times for DDEP. Chapter 1 looks at the overall data, the bigger picture, while Chapters 2 and 3 examine how various clinical development and regulatory strategies, technology approaches and other product specific parameters impact approval times. The differences are remarkably large. Understanding these figures can help companies developing DDEP better understand how comparable products have performed and better forecast their own portfolio development and approval timelines. Despite the belief that all products are unique, and past performance is not necessarily indicative of future results, reality suggests that it is often harder to deviate from the mean and median than it is to approach it. Known as ‘regression to the mean’, and powerfully impacts all new products that follow traditional development paths. Knowing what the mean actually is can be important is setting timelines and managing expectations.
**Methodology**

The methodology for all aspects of this report is outlined in “Appendices – Introduction”. Points of methodology specific to Chapter 1 are summarized in Appendix 1 (available upon request). The core product group used for this analysis consists of 202 drug delivery enabled and/or enhanced products (DDEP) approved by the US FDA between 1996 and 2010. This represents approximately 85% of all DDEP approved in this period. The coverage rises to more than 90% for the group of products approved in the period 2000 to 2010. In essence this is a full population analysis rather than a sampling. FDA review and approval time coverage approaches more than 95% for DDEP approved in the period of 1996 to 2010. A full list of the products included in the analysis is available upon request.

Excerpt:

Unless otherwise stated, all development times in this chapter and report refer to clinical stage development times. Preclinical development times are not factored into any of the development times presented in this report.

Regulatory and Approval times are calculated from the date a product NDA was first filed with the FDA until the date it was approved for marketing. No adjustments are made for time that may have been taken by the sponsoring company to provide remedial information, perform additional data analyses, or conduct additional studies that may have been requested by the FDA.
Background

Pharma Product Development Times

Historical product development times for Big Pharma products, almost always new chemical entities, have been reasonably well established in a series of articles by Joseph DiMasi, Ronald Hansen and Henry Grabowski. In their 2003 article [Journal of Health Economics, 22 (2003) 151-185] they wrote that the average clinical development and approval time for an NDA product was 90.3 months or about 7.5 years. This estimate applied to pharmaceuticals that had entered clinical development in the period 1983 to 1994. This body of information has been updated by the Tufts Center for Drug Development (Tufts CSDD), where J. DiMasi is Director of Economic Analysis, in a series of press releases, publications, subscription reports and opinion pieces. A recent report from Tufts CSDD, OUTLOOK 2010, provides updated figures on general development and approval times as well as success rates for pharmaceutical products. These figures will be used for comparison with the DDEP2011 findings covering drug delivery enabled/enhanced product. Although methodology differs somewhat, the figures are comparable as the basic outcome being studied, time elapsed between the start of clinical trials and FDA approval, is the same. The reader is urged to read the public and subscription-only materials from Tufts CSDD to better understand the general parameters impacting new chemical entity drug development and approval timelines.

Defining DDEP

This report uses the acronym DDEP for drug delivery enabled/enhanced product. We define a DDEP as a pharmaceutical product used for the treatment of humans that incorporates a drug delivery technology to alter the absorption, distribution, metabolism and/or excretion of a pharmaceutical active with the intention of enabling and/or enhancing its therapeutic benefits. DDEP are restricted to products that utilize non-toolbox formulation technologies. By non-toolbox we refer to drug delivery and formulation technologies that are proprietary, if not patented, and are not generally accessible to all companies. Examples of these non-toolbox technologies are PEGylation, Oral Dissolution Technologies (ODT) and Transdermal Patches, all of which in the period covered by this report are available from multiple sources but generally require certain proprietary materials or know-how. One technology not included in our definition of DDEP is enteric coating as used to avoid gastric degradation. Accordingly, products such as proton pump inhibitors are excluded from this analysis. The purpose of defining a DDEP in this manner is to provide a reasonable break between drug delivery and simple formulation impacted pharmaceutical products. This is a sliding definition. What was considered a breakthrough drug delivery technology when first introduced is often considered a toolbox or formulation technology a decade or two later.
**Analysis and Results**

**Clinical Development and Approval Times**

The overall average development and approval time for all DDEP in the period 1996 through 2010 is 6.2 years. This is the mean average time it has taken for a DDEP to progress from IND approval through to FDA approval. Any development time required before the start of IND approval is not included. This 6.2 year mean average covers all 202 DDEP included in the DDEP 1996-2010 development product database. The median average development and approval time for this group is 5 years.

The average development and approval time for DDEP approved in the five-year period 2006 to 2010, a period perhaps more relevant to the present, is 6.7 years. The median development and approval time for this same period is 6 years. There are 80 products in this 2006 to 2010 approval group.

It is worth noting the difference between the mean and median averages for both of these periods. These figures suggest a skewed distribution of development and approval times. This becomes obvious when development and approval times are plotted, Chart 1-1. While it is hard to imagine developing a DDEP through to approval in less than two years (IND approval through conducting all clinical trials, filing an NDA and FDA review), it is certainly possible to take much longer than 5 years. The longest development and approval time is 16 years, a feat shared by two products.

**Chart 1-1: Development & Approval Times, Distribution by Total Time (1996-2010)**

![Chart 1-1: Development & Approval Times, Distribution by Total Time (1996-2010)](image-url)
Looking more closely at the data presented in Chart 1-1 one finds that almost one-tenth (9.5%) of all DDEP are developed and approved in two years or less, and about one-third (34%) in four years or less. Almost two-fifths (39%) of all approved DDEP in the period 1996 to 2010 took more than six years to progress from the start of clinical development through to approval.

**Evolution of DDEP Clinical Development and Approval Times**

The analysis to this point has covered clinical development and approval times for DDEP approved between 1996 and 2010. This fifteen-year period provides a broad overview of DDEP clinical development and approval times, and includes a large number of products. It is worth looking at how clinical development and approval times have evolved over this period. Chart 1-2 presents the rolling three-year average clinical development and approval times, i.e., 1996-1998, 1997-1999 and so on, for approvals between 1996 and 2010.

There is an increase of about one year in the mean average clinical development and approval time for DDEPs over the past decade and a half, growing from 5.3 to 6.5 years. The following chapters examine subsets of the full DDEP population to better understand what parameters are responsible for the increased clinical development and approval times.

**Chart 1-2: Development & Approval Times, Rolling Three-Year Average (All DDEP 1998-2010)**

![Chart 1-2: Development & Approval Times, Rolling Three-Year Average (All DDEP 1998-2010)](image-url)
Regulatory (FDA) Review and Approval Times

We can quite accurately determine the FDA review times for DDEP approved in the US using publicly available information that provides submission and approval dates. The mean average review and approval time for all drug delivery enabled/enhanced products (n=220) was 21.7 months with a median of 14.8 months. The range of review and approval times was very wide, ranging from 6 to 116 months.

The review period as reported here is the time from when the NDA was first filed with the FDA to the point it was approved for sale in the USA. This includes both the actual time spent by the FDA on the review process and any additional time taken by the filing company to address issues raised during the review. There is no accounting made for NDAs that were withdrawn by a company and later resubmitted, NDAs that required review by FDA advisory panels, or those that required additional clinical trials. Once a company filed an NDA the clock was considered to have started ticking. This approach can reflect poorly on the FDA as excessive review times, the period between initial filing and approval, may not be related to FDA performance but rather result from the submission of an incomplete NDA in terms of content or format, that required additional time on the part of the company to satisfactorily rectify.

In this light then the 15-month median review and approval time seems to be a reasonable real world estimate of how long an FDA review has taken assuming a limited number of questions asked of the filing company. This point seems to be supported by looking at the distribution of DDEP review and approval times between 1996 and 2010, Chart 1-3.

About one-eighth (13%) of all DDEP were reviewed and approved within the proscribed 10-month period for a standard review. Almost half (49%) of all DDEP were reviewed and approved in less than fourteen months, and more than two-thirds (70.7%) in less than two years. The FDA review and approval times presented in Chart 1-4 include all 220 products in the report database (1996-2010). For comparison, the Tufts Center for the Study of Drug Development estimated the mean average FDA review time for products included in their 2005-2007 cohort was 13 months.

Chart 1-3: Review & Approval Times in Months, All DDEP (1996-2010)
Evolution of Regulatory Review and Approval Time

The figures in Chart 1-3 present the distribution of review and approval times for the full 1996 to 2010 period. It’s worth considering how review and approval times have evolved over this period. Chart 1-4 presents the rolling three-year mean (bars) and median (line) review and development times for DDEP over the 1996 to 2010 period.

The difference between the mean and median review and approval times is obvious when looking at Chart 1-4. Also obvious is the increase in review and approval times over this period, about four to eight months in terms of mean average, and one to five months in terms of the median. Less obvious are the causes for the increase in review and approval times. Had the FDA slowed down the review process, had DDEP submissions become more complex, or were the submissions increasingly incomplete? Regardless of the cause the steady increase in review and approval times is an issue that needs to be factored in when estimating development and approval timelines. On the positive side, in the period of 1998 to 2010 the FDA approved about 30% of all submissions in thirteen months or less.

Chart 1-4: Review & Approval Times, Rolling Three-Year Mean and Medians (all DDEP 1996-2010)
DDEP Development Times

With firm estimates of the overall clinical development and approval times, and review and approval times for DDEP, it seems a simple matter of subtraction to estimate the clinical development time averages. While the arithmetic is simple, using and interpreting the results is not straightforward.

The issue rests with the review and approval times. As noted earlier, a portion of the review and approval time can involve activities unrelated to FDA review, including the reanalysis of data by the sponsor company, the conduct of additional preclinical and clinical trials, and even reformating of data. And there is also the occasional situation where a submission is rejected by the FDA and the project sits on the shelf until a second company picks up the project and addresses the deficiencies. This period of time when the product is back in the hands of the sponsoring company is included in the DDEP review and approval times. It’s not possible to properly estimate when the clock should be stopped and started again in terms of the regulatory review process. Presumably though, the time when the dossier is back in the hands of the filing company should be tacked onto the clinical development, not review and approval, time.

The FDA targets review and approval of all NDAs in a period of ten months or less. Anything longer than this reflects either poor performance on the part of the FDA, a poor or incomplete submission, or the need for an advisory panel. Given that the FDA regularly reviews and approves DDEP in ten months or less, and there is no reason to believe the FDA favors any particular product or company, it seems reasonable to believe differences in review and approval times are largely a function of incomplete submissions or advisory panels. To take into account this last factor, and some FDA tardiness, we will assume the “true” average review and approval time is best estimated by the time taken to approve the fastest third of DDEP,
rather than the mandated ten month review period. Subtracting the time required to review and approve the fastest one-third of DDEP in a defined period from the mean and median clinical development and approval times should provide us with a realistic sense of the actual time it takes companies to conduct all the necessary clinical development stage activities to secure approval for a DDEP. Chart 1-5 summarizes the rolling three-year clinical development and review and approval times for all DDEP from 1996 to 2010.

**Chart 1-5: Clinical Development and Review & Approval Times, Rolling Three-Year Averages (DDEP 1996-2010)**

There is a consistent increase in clinical development times over the fourteen year period from 1996 to 2010. From a base of about 4.5 years in the late 1990s and early 2000’s the clinical development time has increased by about one year to 5.5 years in the latter half of the 2000’s.

In terms of median clinical development times the same one-year increase in clinical development time in the 2003 to 2005 period is sustained through the end of the decade.

**Clinical Development and Approval Times, DDEP Compared with Pharmaceuticals**

We can compare development and review and approval times for DDEP with new drugs as determined by the Tufts CSDD. The Tufts CSDD estimates the overall clinical development and approval times for pharmaceuticals (small molecule and biologicals) ranged from 7.7 years in the period 1996-1998, to 7 years for 1999 to 2001, to 9 years for 2002-2004 and 7 years for 2005 to 2007. These results are tabulated along with the corresponding DDEP clinical development and approval times, Table 1-1.
Table 1-1: Mean Clinical Development and Approval Times (Years)

<table>
<thead>
<tr>
<th>Period</th>
<th>New Drugs (Tufts CSDD)</th>
<th>DDEP (DDEP2011)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996 to 1998</td>
<td>7.7</td>
<td>5.3</td>
<td>2.4</td>
</tr>
<tr>
<td>1999 to 2001</td>
<td>7.0</td>
<td>5.9</td>
<td>1.1</td>
</tr>
<tr>
<td>2002 to 2004</td>
<td>9.0</td>
<td>6.2</td>
<td>2.8</td>
</tr>
<tr>
<td>2005 to 2007</td>
<td>7.0</td>
<td>6.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Whereas DDEP took almost two and a half years less than traditional pharmaceutical products to develop from first clinical to approval in the period 1996 to 1998, this advantage has been reduced to a little less than three quarters of a year by the middle of the ‘00s. The smaller difference is more a result of longer clinical development and approval times for drug delivery enabled/enhanced products than reduced times for pharmaceutical products.
Reflections

The average clinical development time for a drug delivery enabled/enhanced product is five years, adding on another year for regulatory review and approval yields a clinical development and approval time of six to seven years. But this represents an average for the whole group of DDEP. What we will see in Chapters 2 and 3 is that there really is no “average” DDEP. Each drug delivery enabled/enhanced product is the product of a variety of choices made concerning the product configuration and therapeutic target. Does the product require an integrated device? Does the approval package depend on clinical studies demonstrating efficacy and safety, or does it only require bioequivalence studies? There are also multiple parameters to consider related to delivery route, the targeted indication, the delivery route, the pharmaceutical active size/weight, and whether the active has been previously approved in a different dosage form. All of these parameters can influence clinical development and approval times, and are examined further in the two following chapters.

What the figures in this chapter provide us with is a sense of the overall clinical development and approval times for DDEP that have been approved over the past decade and a half. The figures also provide us with a sense of how these clinical development and approval times have evolved over the same period. These figures in the aggregate can provide us with general insights into how long it will take to bring a new drug delivery enabled/enhanced product through clinical development and to approval.

If one were developing the “average” drug delivery enabled/enhanced product one would be advised to plan and budget for a six-year clinical development and regulatory review program. A more conservative developer might add another six to twelve months to account for the apparent lengthening of the development and approval process.

It is not clear what is behind the longer development and approval times and approval times. It may be a result of slower development, more complex development programs, or periods of inactivity while securing financing and resources. It does not seem to be an issue of increased FDA review time. A properly prepared dossier has consistently been reviewed and approved in about a year.

Chapter 2 considers how incorporating a device into a drug delivery enabled/enhanced product impacts clinical development and approval times, and the differences arising from pursuing an approval on the basis of efficacy/safety trials rather than simple bioequivalence studies.

Chapter 3 looks at the impact of a variety of other parameters on clinical development and approval times. These parameters range from the targeted indication to whether the active is a macromolecule, to the validation status of the underlying drug delivery technology.

All of these figures move the analysis from abstract “average” drug delivery enabled/enhanced products to products with unique and perhaps predictable outcomes.
CHAPTER 2 – PARAMETER SPECIFIC DDEP CLINICAL DEVELOPMENT AND APPROVAL TIMES:
DRUG AND DRUG/DEVICE AND DEVELOPMENT STRATEGY

Introduction

Whereas Chapter 1 looked at overall clinical development and approval times, and trends, this chapter looks at the differences between products that incorporate a device (Drug/Device) and those that have no integral device (Drug Only), and separately products that require efficacy and safety endpoint studies (Efficacy/Safety) or only bioequivalence studies (BioEq Only).

Both of these pairs of parameters can have a major impact on the time required to advance DDEP through clinical development and approval, and vary from the overall average clinical development and approval times presented in Chapter 1. Understanding these differences can provide for much better estimates of the time required to develop specific drug delivery enabled/enhanced products.

Methodology

The products included in this analysis are the same as those analyzed in Chapter 1. The full 202 FDA approved Pharmanumbers DDEP database was included in this analysis of clinical development and approval times. For regulatory review and approval times a slightly larger database of 222 products was used. Analysis methodology was similar to that used in Chapter 1; details are available upon request. The analysis includes evaluation of clinical development and approval times, FDA review and approval times, and by extrapolation clinical development times for DDEP approved between 1996 and 2010.

Unless otherwise stated, all development times in this chapter and report refer to clinical stage development times. Preclinical development times are not factored into any of the development times presented in this report.

Regulatory and Approval times are calculated from the date a product NDA was first filed with the FDA until the date it was approved for marketing. No adjustments made for any time that may have been taken by the sponsoring company to provide additional information, perform remedial data analyses or conduct additional studies that may have been requested by the FDA.
Background

Drug Delivery Enabled/Enhanced Products - Segmentation

A simple examination of drug delivery enabled/enhanced products suggests there numerous product configuration differences between any two DDEP chosen at random. These differences can range from targeted therapeutic indication, delivery system, approval status of the pharmaceutical active, and even the choice of clinical trial strategy. Despite these differences it would be wrong to throw up one’s hands and suggest that because all products are different there is little guidance to be found in understanding the clinical development and approval times of previously approved products. As we will see these drug delivery enabled/enhanced products share a number of parameters in common that can provide an understanding of the likely clinical development and approval timeline for any particular DDEP.

This chapter examines two pairs of parameters that are associated with large differences in clinical development and approval times. These parameters depend on:

1) whether or not the DDEP includes an integrated delivery device.
2) whether or not the development program included clinical trials that had efficacy and/or safety endpoints. Those development programs that did not involve these types of studies secured approval solely on the basis of bioequivalence trials.

All drug delivery enabled/enhanced products included in this analysis were approved under the 505(b)(1) or 505(b)(2) regulatory pathways, depending on whether or not the active had been previously approved in another dosage form. None of the products included in this analysis were approved as ANDA (505(j)) products.
Results

Development and Approval Times – Drug Only and Drug/Device DDEP

For the purpose of this analysis a Drug/Device DDEP is a pharmaceutical product incorporating a specific device, typically a mechanical apparatus, integrally included in the product package and/or explicitly specified in the product label. Drug/Device DDEP include inhalation and nasal products as well as active (electrically charged) transdermal products. It does not include DDEP that are administered with a simple syringe, nor does it include passive transdermal products. All products not specifically defined as Drug/Device Products are considered Drug Only DDEP. Drug/Device and Drug Only assignments for the products included in this analysis are available upon request.

As noted in Chapter 1 the mean average development and approval time for all DDEP in the period 1996 through 2010 was 6.2 years.

1. For Drug Only DDEP the mean average clinical development and approval time was 5.8 years (n=155) with a range of 2 to 16 years. The median average for this Drug Only group was 5 years.

2. The mean average clinical development and approval time for the Drug/Device DDEP was 7.5 years (n=46) with a range of 3 to 16 years. The median average clinical development and approval time for this group was 7 years.

The large differences in the mean and median averages for these two groups of DDEP depending on whether or not they incorporated a device can be seen when the distribution of clinical development and approval times is plotted, Chart 2-2. This chart plots the percent of Drug Only and Drug/Device products for each parameter class approved according to the number of years required for clinical development and approval. The development and approval times for Drug/Device DDEP are shifted to the right by about two years relative to Drug Only products.

This is a difference that needs to be understood and accounted for when estimating the development timeline of a pipeline DDEP. Using the average clinical development and approval time for all DDEP is likely to underestimate the time required for a Drug/Device product, and overestimate the clinical development and approval time for a Drug only DDEP.

It’s interesting to speculate as to why there is such a large difference in clinical development and approval times for these two segments. The incorporation of an integral device generally involves additional manufacturing, supply and drug/device performance issues that can translate into longer timelines. In addition as we’ll see later in this chapter the more substantial clinical trial requirements for Drug/Device DDEP probably contributes to the longer average clinical development and approval times for these products.

**Chart 2-2: Development and Approval Times (Drug Only & Drug/Device, 1996-2010)**
Evolution of DDEP Clinical Development and Approval Times, Drug Only and Drug/Device DDEP

The analysis in the previous section covered DDEP for the full 1996 to 2010 period. It is worth looking at how clinical development and approval times for Drug/Device and Drug Only DDEP have evolved over the last decade and a half. Charts 2-3 and 2-4 present the evolution of clinical development and approval times for both product groups over the period 1996-2010 as a series of rolling three-year averages.

What we see are opposing trends in terms of evolving clinical development and approval times. While clinical development and approval times for Drug Only products has increased by a little less than two years over the period of 1996 to 2010, the times for Drug/Device products have remained largely constant and may optimistically be thought of as shortening.
It’s reasonable to ask whether the difference between Drug Only and Drug/Device clinical development and approval times may be related to longer FDA review and approval times for Drug/Device DDEP. This suspicion is supported in part by the data in Chart 2-5. Drug/Device DDEP have consistently taken one to one and half years longer than Drug Only DDEP to move through FDA review and approval. This difference seems to have largely disappeared since about 2008 and may account in part for the decrease in overall Drug/Device clinical development and approval times. The greater part of the shrinking difference between Drug Only and Drug/Device clinical development and approval times seems related to a considerable increase in FDA review and approval times for Drug Only products rather than a drop in the Drug/Device review and approval times.
The overall increase in clinical development and approval times for Drug Only DDEP deserves some discussion. This increase is contrary to recent review and approval times for pharmaceutical products as a whole. The Tufts Center for the Study of Drug Development has noted when referring to pharmaceutical development in their report *Outlook 2010* that “total average clinical time dropped 10% from 1992 through 2007, even as trials became more complex, while average approval time declined nearly 60%”.

The increase in review time for Drug Only DDEP seems to be particular to this class of pharmaceutical products. Assuming there is no FDA bias against these products (unlikely) it is possible that the general quality of Drug Only DDEP regulatory filings has dropped over the past decade. This is confirmed in one sense by the increase in FDA review and approval times for this group, which would include time required for remedial clinical and regulatory work by the filing company, Chart 2-5. But this accounts for only half of the almost two year increase in clinical development and approval time for this Drug Only group.

It is possible that the increasing sophistication of recently developed DDEP contributes to the increase in clinical development and approval time. Newer DDEP often go beyond the simple improvement of dosing interval seen with many of the solid oral dosage DDEP of the 1990s. These newer drug delivery enabled/enhanced products often focus on securing improved efficacy, safety and tolerability claims. In some cases these DDEP are pursuing novel indications, and in other cases they are incorporating new molecular entities. In some ways the clinical development and approval times for these DDEP are more comparable to new chemical entity pharmaceutical products than drug delivery enabled/enhanced products approved in the 1990s.

The requirement of a Risk Evaluation and Mitigation Strategy (REMS) for certain products may also be a contributor. But this is a requirement that applies to only a small number of DDEP, and has not been in effect long enough to account for the increase in regulatory review and approval times prior to 2007/8. Perhaps the relative lack of funding for emerging drug delivery focused companies has led to development stops and starts that have lengthened development timelines.

Regardless, the increase in clinical development and approval times for Drug Only DDEP seems to be real. The estimate of 6.4 years for Drug Only DDEP may provide a reasonable benchmark for the clinical development and approval time of drug delivery enabled/enhanced products now in development. But as we’ll see in the next section and in Chapter 3, this can figure can vary considerably depending on the particular regulatory strategy chosen and the type of technology incorporated into the product.
Development and Approval Times – Bioequivalence Only and Efficacy/Safety DDEP

Clinical development strategy has a powerful impact on clinical development and approval times for DDEP. All pharmaceutical products are required to provide evidence of efficacy and safety as part of the FDA approval process. In most cases, and certainly always for new chemical entity pharmaceutical products, this is accomplished by the successful completion of human clinical trials with efficacy and safety endpoints.

In the case of Abbreviated New Drug Approvals (ANDA) and some 505(b)(2) New Drug Approvals the demonstration of efficacy and safety can be accomplished by cross referencing a previously approved product and demonstrating bioequivalence to this reference product. This development ‘shortcut’ is available to DDEP that: pursue the 505(b)(2) approval process; are administered by the same general dosing route as the reference product; and demonstrate bioequivalent serum levels of active. This approach eliminates the need to conduct efficacy and safety studies, and can lead to a smaller, less costly, and much shorter clinical development program. These bioequivalent DDEP are not able to make claims of improved efficacy, safety or tolerability versus the reference product but they can claim benefits related to a more convenient dosing form or schedule. Examples include a quick dissolve tablet that doesn’t require administration with water, and once-a-day products that eliminate the need for more frequent dosing. While these Bioequivalence Only DDEP are less common than DDEP involving efficacy and safety studies (Efficacy/Safety DDEP) they represent an important subset of these products.

Review of the clinical development and approval times for DDEP approved on the basis of Bioequivalence Only or Efficacy/Safety trials reveals significant differences, Chart 2-6. This is reflected in their mean and median development and approval times. The mean and median average clinical development and approval times for Bioequivalence Only products in the 1996 to 2010 period were 3.5 and 3 years (n=37). For Efficacy/Safety DDEP the mean and median averages were 6.8 and 6 years (n=163).

Chart 2-6: Clinical Development and Approval Times, Development Strategy (1996-2010)
The distribution of clinical development and approval times are presented graphically in Chart 2-7. The differences between Bioequivalence Only and Efficacy/Safety DDEP is obvious on first glance. There is no question that taking a Bioequivalence Only product through clinical development and approval is on average a much quicker route to approval than pursuing efficacy and safety trials. The downside of course is that Bioequivalence Only DDEP usually have approved claims that are quite limited and restricted at most to an enhanced dosing convenience.

**Chart 2-7: Chart 2-2: Development & Approval Times (BioEq Only & Efficacy Safety, 1996-2010)**

### Evolution of Clinical Development and Approval Times, Bioequivalence Only Versus Efficacy/Safety DDEP

An analysis of the trend in clinical development and approval times for Bioequivalence Only and Efficacy/Safety DDEP over the past decade reveals remarkable differences, Charts 2-8 and 2-9. While the time taken to develop Bioequivalence Only products has held steady, or even dropped slightly over the last decade, the time required for DDEP developed on the basis of efficacy and safety studies has increased sharply. It should be recalled that Bioequivalence Only DDEP are approved as NDA, not ANDA, products.

This difference is much greater than what was seen when comparing Drug Only and Drug/Device DDEP. The reasons for the difference may be similar to those discussed earlier. While Bioequivalence Only product development endpoints and requirements have for the most part
changed little over the last decade, Efficacy/Safety DDEP seem to have taken on a greater level of complexity, at least as evidenced by the change in mean clinical development and approval times over the past decade.

**Chart 2-8: Development & Approval Times, BioEq Only DDEP, Rolling Three-Year Average**

**Chart 2-9: Development & Approval Times, Efficacy/Safety DDEP, Rolling Three Year Average**
Some insight into how much of the increase in clinical development and approval time for Efficacy/Safety DDEP is related to longer FDA review and approval times can be found in Chart 2-10. Whereas the FDA review and approval times for Bioequivalence Only DDEP have remained steady over the period 1996 to 2010, the times for DDEP requiring efficacy and safety trials have increased by about one year. As noted earlier it is our opinion that this increase in review and approval time is not a function of slower FDA review, note the constant times for Bioequivalence Only DDEP. Rather it seems the companies developing Efficacy/Safety based DDEP are having more trouble meeting the FDA requirements with their submissions which results not only in longer reviews but also remedial, post-submission work by the companies.

**Chart 2-10: FDA Review and Approval Times, Rolling Three Year Average (1998-2010)**

![Chart 2-10: FDA Review and Approval Times, Rolling Three Year Average (1998-2010)](image-url)

Development and Approval Times – Drug Only, Drug/Device, Bioequivalence Only and Efficacy/Safety DDEP Matrix

An obvious question to ask is how these four DDEP parameters interact, and how they impact clinical development and approval times. For example, what is the average clinical development and approval time for a Drug Only DDEP that is developed using clinical and efficacy trials as opposed to a Drug/Device product developed using the same strategy. This numbers are presented in a simple 2x2 matrix, Table 2-1. This table covers the full cohort of DDEP in the Pharmanumbers 1996-2010 database approved between 1996 and 2010. There are few surprises.

The mean average clinical development and approval time was 6.4 years for Drug Only DDEP, the largest subpopulation, developed and approved on the basis of efficacy and safety trials. Drug/Device products took an additional 1.5 years on average, or 7.9 years. As noted earlier, Bioequivalence Only – Drug Only DDEP took by far the shortest time at 3.4 years.

Table 2-1: Clinical Development and Review Approval Time Matrix (DDEP, 1996 – 2009)

<table>
<thead>
<tr>
<th></th>
<th>Bioequivalence Only Studies</th>
<th>Efficacy/Safety Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=</td>
<td>Mean Clinical Development and Approval Time (years)</td>
</tr>
<tr>
<td>Drug Only DDEP</td>
<td>34</td>
<td>3.4</td>
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<tr>
<td>Drug/Device DDEP</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td>All DDEP</td>
<td>37</td>
<td>3.5</td>
</tr>
</tbody>
</table>

N/A – insufficient numbers of products (<5)

These figures hide the substantial increase in clinical development and approval time for Drug Only – Efficacy/Safety DDEP over the 1996 to 2010 period, Chart 2-11. The rise in clinical development and approval time for this group is steady over this whole period and amounts to an overall three-year increase. The increase seems to primarily be an issue of extended development times as the review and approval time increased by about a year over that same period. And even much of that increased review and approval time may well be associated with an increase in post-filing remedial work by the sponsoring company.

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Reflections

It seems inappropriate to use the full 1996 through 2010 average clinical development and approval times for all DDEP as a benchmark for estimating times for any particular new drug delivery enabled/enhanced pipeline product. That’s because no product is truly average, product configuration (drug or drug/device), development strategy (bioequivalence only or safety/efficacy) all impact to development and approval times. The figures in this chapter help provide guidance of how development and approval times can be estimated with information on the product configuration and development strategy. Using the average times for a DDEP that is Drug Only and requires only Bioavailability trials will overestimate the time required, while underestimating the time required to develop and gain approval for a Drug/Device DDEP that requires extensive Efficacy and Safety trials.

If 6.5 years, the 2010 rolling average clinical development and approval time for all DDEP, represents a first-order benchmark, then the Bio Only, Efficacy/Safety, Drug Only and Drug/Device 2010 figures represent second-order benchmarks. These benchmarks are 2.8, 7.8, 6.4 and 7.0 years respectively. Any company developing a new drug delivery enabled/enhanced product would be advised to compare their program clinical development and approval program timelines with these figures and identify why their estimates differ from these timelines. There may be very good reasons for significant differences but they need to be understood to provide comfort to management and investors.

Means and medians also need to be understood for what they are. Although the mean average clinical development and approval time for a Drug Only DDEP requiring Efficacy/Safety trials was 7.5 years, and the median seven years, there are a number of products that were approved in as little as four and five years. And there were others that took more than eight years. Understanding why certain products varied from these averages can provide important insight to estimating the clinical development and approval time for any new DDEP.

Additional parameter related benchmarks are provided in Chapter 3. In general these product parameters have less impact on clinical development and approval times. Nonetheless in certain cases they can provide critical guidance on how product and technology parameters might impact clinical development and approval times.
CHAPTER 3 – CLINICAL DEVELOPMENT AND APPROVAL TIMES, EXTENDED PARAMETERS

Introduction

Chapter 3 extends the analyses presented in Chapters 1 and 2 to look at the correlation between clinical development and approval times for drug delivery enabled/enhanced products (DDEP) and additional product specific parameters. A number of these parameters can be correlated with clinical development and approval times, but whether they are causally related is harder to confirm. Nonetheless, these are parameters companies developing drug delivery enabled/enhanced products need to consider as they estimate clinical development and approval times for their own pipeline products.

Defining DDEP

This report uses the acronym DDEP for drug delivery enabled/enhanced product. We define a DDEP as a pharmaceutical product used for the treatment of humans that incorporates a drug delivery technology to alter the absorption, distribution, metabolism and/or excretion of a pharmaceutical active with the intention of enabling and/or enhancing its therapeutic benefits. DDEP are restricted to products that utilize non-toolbox formulation technologies. By non-toolbox we refer to drug delivery and formulation technologies that are proprietary, if not patented, and are not generally accessible to all companies. Examples of these non-toolbox technologies are PEGylation, Oral Dissolution Technologies (ODT) and Transdermal Patches, all of which in the period covered by this report are available from multiple sources but generally require certain proprietary materials or know-how. One technology not included in our definition of DDEP is enteric coating as used to avoid gastric degradation. Accordingly, products such as proton pump inhibitors are excluded from this analysis. The purpose of defining a DDEP in this manner is to provide a reasonable break between drug delivery and simple formulation impacted pharmaceutical products. This is a sliding definition. What was considered a breakthrough drug delivery technology when first introduced is often considered a toolbox or formulation technology a decade or two later.
Methodology

The analysis process is similar to that used for Chapters 1 and 2. Because of the larger number of parameters being studied, DDEP clinical development and approval times are analyzed as a function of the full 1996-2010 period, and the more recent 2006-2010 time period. Looking at three-year rolling averages often resulted in too few products, less than five in many subsets, to permit reliable results. Even expanding analysis to the larger 2006-2010 period resulted in too small a sample for certain parameter subsets. These instances are noted in the tables, charts and text.

Additional description of methodology and included products is available upon request.

Analysis Parameters

The product parameters analyzed in this chapter are:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Platform Status</td>
<td>Validated or Unvalidated platform technology</td>
</tr>
<tr>
<td>2. Active Approval Status</td>
<td>Approved Active (AA) or New Molecular Entity (NME)</td>
</tr>
<tr>
<td>3. Molecule Size</td>
<td>Small Molecule (SM) or Macromolecule (MM) pharmaceutical active</td>
</tr>
<tr>
<td>4. Product Benefit</td>
<td>Therapeutic or Convenience</td>
</tr>
<tr>
<td>5. Delivery Route</td>
<td>Oral SR, Injectable SR, Topical, Inhalation, etc.</td>
</tr>
<tr>
<td>6. Approved Indication</td>
<td>Primary targeted indication: CNS, Infectious Disease, Urology, etc.</td>
</tr>
</tbody>
</table>

Additional explanation of these parameters is provided in the corresponding sections in this chapter. For each parameter a limited subset of analyses are provided in this chapter. The key analyses provided in this chapter are:

1. Mean and median averages 1996 to 2010 period.
2. Mean and median averages 2006 to 2010 period.
Results

Platform Status

The Platform Status analysis looks at the clinical development and approval time for DDEP developed using a platform technology that had, or had not, been validated by virtue of incorporation into a DDEP previously approved by the FDA. It is reasonable to expect that a DDEP based on a drug delivery platform validated by a previously approved product might have a shorter development and review time. Presumably technology performance, scale-up, and regulatory issues would have been largely ‘worked out’ for a product based on a platform incorporated into a previously approved product.

For the full 1996-2010 period, DDEP using a Validated platform had a mean average clinical development and approval time of 5.9 years. This compared with 6.7 years for Unvalidated platform DDEP. The medians were 5 and 6 years respectively. For the more recent 2006 to 2010 period the difference in mean averages narrowed to an arguably negligible 6.6 (Validated) and 6.9 (Unvalidated) years, with a median of 6 years for both groups. These results are summarized in Table 3-1, and Chart 3-1 at the end of this chapter.

Table 3-1: Platform Status, Clinical Development and Approval Times (1996-2010)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Validated Platform DDEP</td>
<td>5.9 Years</td>
<td>5 Years</td>
<td>6.6 Years</td>
<td>6 Years</td>
</tr>
<tr>
<td>Unvalidated Platform DDEP</td>
<td>6.7 Years</td>
<td>6 Years</td>
<td>6.0 Years</td>
<td>6 Years</td>
</tr>
</tbody>
</table>
Active Approval Status

This analysis considers how the approval status of the active incorporated into the drug delivery enabled/enhanced product correlates with clinical development and approval times. One might expect a previously approved active (AA) would be quicker to develop and approve as it would not require as extensive a preclinical and clinical package to support efficacy, and particularly safety, claims. This assumption is borne out by the data even though the differences are not as great as might have been expected. The fact that many of these new molecular entity (NME) DDEP are conjugates of previously approved actives, for example, PegIntron, Pegasys, Neulasta and Vyvanse, probably reduces the burden of demonstrating efficacy and safety, and accordingly the development and review time.

For the full 1996-2010 period NME DDEP took a mean average of 7.9 years versus 6.0 years for DDEP incorporating a previously approved active (medians of 7 and 5 years). If we restrict the study groups to only those DDEP that required efficacy and safety studies, eliminating Bioequivalence Only DDEP, we see the difference narrows to 7.9 and 6.6 years; still an appreciable difference. For the more recent 2006 to 2010 period the mean averages were 7.4 and 6.6 years for NME versus AA DDEP. This is one of the very few instances where we see shorter clinical development and approval times for DDEP approved in the 2006-2010 period versus the full 1996-2010 period. Figures are summarized in Table 3-2 and Chart 3-1.

Table 3-2: Active Approval Status, Clinical Development and Approval Times (1996-2010)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>New Molecular Entity DDEP</td>
<td>7.9 Years</td>
<td>7 Years</td>
<td>7.4 Years</td>
<td>7 Years</td>
</tr>
<tr>
<td>Approved Active DDEP</td>
<td>6.0 Years</td>
<td>5 Years</td>
<td>6.6 Years</td>
<td>6 Years</td>
</tr>
</tbody>
</table>
Molecular Size

This analysis considers how clinical development and approval times for DDEP differ based on whether they incorporate small molecule or macromolecule actives. For the purpose of this analysis a macromolecule is an active with a molecule weight above 900 Daltons. While this is not an industry-standard figure, it reasonably defines a molecular weight above which the challenge of drug delivery increases substantially. In general we find macromolecule drug delivery does not use the same types of well known, and validated, drug delivery technologies used with small molecule therapeutics.

For the full 1996-2010 period the mean average clinical development and approval time for small molecule DDEP was 6.1 years (median 5 years) versus 7.2 years (median 6 years) for macromolecule DDEP. This one-year difference was maintained for DDEP approved in the 2006-2010 period, with mean averages of 6.7 and 7.6 years for small molecule and macromolecule DDEP respectively.

Looking only at DDEP that required clinical and efficacy studies (eliminating the Bioequivalence Only DDEP population, defined in Chapter 2) the difference drops to around 3 months. The relatively small difference in the clinical development and approval time for those macromolecule and small molecule DDEP requiring efficacy and safety trials may simply reflect the fact that many of the macromolecule products are developed as injectable sustained release formulations. As will be noted later in this chapter the clinical development and approval time for Injectable SR DDEP comes in at, or below, the average for all delivery approaches. The injectable delivery route, whether sustained or immediate release, avoids issues related to bioavailability, a significant challenge for many other delivery approaches targeting macromolecules.

Table 3-3: Molecular Size, Clinical Development and Approval Times (1996-2010)

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecule DDEP</td>
<td>6.1 Years</td>
<td>5 Years</td>
<td>6.7 Years</td>
<td>6 Years</td>
</tr>
<tr>
<td>Macromolecule DDEP</td>
<td>7.2 Years</td>
<td>6 Years</td>
<td>7.6 Years</td>
<td>7 Years</td>
</tr>
</tbody>
</table>
**Product Benefit**

Drug delivery enabled/enhanced products are capable of providing a variety of therapeutic benefits. These benefits can range from simple enhancements of convenience without any improvement in efficacy, safety or tolerability, to improved efficacy and safety. Some DDEP address new therapeutic indications.

This Product Benefit analysis looks at how clinical development and approval times are impacted by whether a DDEP incorporates efficacy and/or safety benefits in its approved product label, or whether it simply offers some sort of convenience benefit. FDA approved product labels were reviewed for each DDEP to determine if they provided for new indications, claims of superior efficacy, safety and tolerability, and/or more convenient dosing. If the only label benefit(s) was related to enhanced convenience the product was labeled as Convenience Only. If the product label provided for a new indication or an efficacy or safety enhancement the DDEP was labeled as Efficacy Enhanced. These Efficacy Enhanced products might also have convenience benefits, but were assigned to the Efficacy Enhanced group.

It is reasonable to expect that Convenience Only products would require shorter development times, as they do not necessarily need to show superiority in terms of efficacy or safety, claims that are associated with increased clinical trial demands. This is the case with many oral once-daily and ODT products that are approved solely on the basis of bioequivalence trials.

Overall, for the 1996-2010 period Convenience Only DDEP took an average 5.9 years for clinical development and approval. The corresponding figure for Efficacy Enhanced DDEP was 7.6 years, a difference of 1.7 years. For the 2006-2010 period the difference shrinks to a little less than a year.

**Table 3-4: Product Benefit, Clinical Development and Approval Times (1996-2010)**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Efficacy Enhanced DDEP</td>
<td>7.6 Years</td>
<td>7 Years</td>
<td>8.1 Years</td>
<td>7 Years</td>
</tr>
<tr>
<td>Convenience Only DDEP</td>
<td>5.9 Years</td>
<td>5 Years</td>
<td>7.2 Years</td>
<td>6 Years</td>
</tr>
</tbody>
</table>
Parameters of Development - Drug Delivery Enabled/Enhanced Products (DDEP 1996-2010) – A

Delivery Route

This analysis looks at the clinical development and approval times for DDEP as a function of the drug delivery technology/route. The number of delivery route categories was limited to those that included at least five products.

Not surprisingly, given the limited demands of a Bioequivalence Only strategy, Oral ODT DDEP recorded the shortest clinical development and approval times, 3.3 and 4.3 years for the 1996-2010 and 2006-2010 periods respectively. And, as might be expected, Inhalation DDEP took a longer than average 7.9 years (1996-2010) and 8.2 years (2006-2010) to progress through clinical development and approval. One surprise though was the longer than average clinical development and approval time for Passive Transdermal DDEP. These products required a mean average of 8.0 (1996-2010) and 10.2 (2006-2010) years. Clinical development and approval times are summarized in Tables 3-5 and Chart 3-1.

Table 3-5: Delivery Route, Clinical Development and Approval Times (1996-2010)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>7.9</td>
<td>7</td>
<td>8.2</td>
<td>8</td>
</tr>
<tr>
<td>Injectable SR</td>
<td>6.4</td>
<td>6</td>
<td>7.7</td>
<td>7</td>
</tr>
<tr>
<td>Nasal</td>
<td>7.1</td>
<td>6</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>Oral Buccal/Sublingual</td>
<td>6.4</td>
<td>6</td>
<td>7.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Oral ODT</td>
<td>3.3</td>
<td>3</td>
<td>4.3</td>
<td>3</td>
</tr>
<tr>
<td>Oral SR</td>
<td>5.7</td>
<td>6</td>
<td>6.2</td>
<td>6</td>
</tr>
<tr>
<td>Topical</td>
<td>6.6</td>
<td>6</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>Transdermal (Passive)</td>
<td>8.0</td>
<td>7.5</td>
<td>10.2</td>
<td>10</td>
</tr>
</tbody>
</table>
Indication Analysis

It is possible to calculate mean and median clinical development and approval times for DDEP as a function of their approved indications. The significance of these results needs to be carefully considered by the reader. There can be a large variation in the product design (Regulatory Strategy, Delivery Route, Drug Only, Drug/Device etc.) that might have a larger impact on overall clinical development and approval time than the particular therapeutic indication. Because of the relatively large number of indications there are too few DDEP in each therapeutic group to permit a separate analysis of the 2006-2010 period.

Only a few indication classes showed a notable deviation from the overall average in terms of clinical development and approval time. Most notable were DDEP targeted to the treatment of Neurology indications, taking a longer than average 8.4 years. This may be a result of the inherently more difficult endpoints for these conditions, i.e., multiple sclerosis, seizure disorders, migraine, or it may reflect the requirement for more efficacy and safety trials. Alternatively it could be a simple statistical outlier.

DDEP approved for Pain indications also took a longer than average 8.1 years. The longer clinical development and approval time for Respiratory DDEP, 7.6 years, is probably related to the common use of Drug/Device product configurations.

DDEP developed for Infectious Disease indications were notable for having a shorter than average 4.6 year clinical development and approval time. The remaining products had clinical development and approval times clustered around the overall mean average time of 6.2 years. Results are summarized in Table 3-6, and Chart 3-1.

Table 3-6: Delivery Route, Clinical Development and Approval Times (1996-2010)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>6.7</td>
<td>5</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>CNS – Neurology</td>
<td>8.4</td>
<td>6</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>CNS – Psychiatry</td>
<td>6.1</td>
<td>5</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>CNS – Pain</td>
<td>8.1</td>
<td>8</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular (All)</td>
<td>6.5</td>
<td>5</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>Endocrinology (All)</td>
<td>6.1</td>
<td>6</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>Infectious Disease (All)</td>
<td>4.6</td>
<td>4.5</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory (All)</td>
<td>7.6</td>
<td>7</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
<tr>
<td>Urology (All)</td>
<td>6.2</td>
<td>6.5</td>
<td>Insufficient Data</td>
<td>-</td>
</tr>
</tbody>
</table>
Compiled Clinical Development and Approval Times

Chart 3-1 summarizes in color matched graphical form mean average clinical development and approval times as a function of parameter relative to the overall average for all DDEP. This chart covers the full period of 1996 through 2010 and includes parameters reviewed in Chapter 2.

Chart 3-1: Variations from Mean Average Clinical Development and Approval Time, by Parameter
Additional Analysis

Additional, more detailed, analysis of the correlation between particular parameters incorporated in a drug delivery enabled/enhanced product and its clinical development and approval time is available upon request. The supplemental information includes two- and three-parameter analysis of these products. These analyses examine, for example, the clinical development and approval times for DDEP that are Drug Only using a Validated Platforms versus DDEP that are Drug Only using an Unvalidated Platform. This allows the impact of particular parameters to be isolated and the impact of dependant parameters more clearly understood. This analysis is carried to a depth of three parameters whenever there are subgroups sufficiently populated to allow for reasonable conclusions (five or more).

Reflections

The significance of the analyses presented in this chapter, and how they apply to real world drug delivery enabled/enhanced products, needs to be carefully considered by the reader.

Even a cursory look at Chart 3-1 reveals some rather obvious conclusions.

1. Bioequivalence Only DDEP progress through clinical development and approval in a much shorter time than the average drug delivery enabled/enhanced product.
2. Drug/Device products seem to take longer than the average DDEP to move through clinical development and approval.
3. Oral ODT DDEP, perhaps because they are typically developed as Bioequivalence Only products also progress through development in a much shorter period of time than the average DDEP.
4. Inhalation and Transdermal DDEP seem to take longer than average. The reason for longer times for Inhalation products seems intuitive, they involve a drug and a device, and the safety standards are generally set higher because of the target organ. The reason for longer times for transdermals is less obvious.
5. There is no surprise that Macromolecules and New Molecular Entity DDEP take longer. The difference of one- to two-years relative to the overall averages for DDEP seems to be a reasonable adjustment to make to any forecast of approval times for these products.

It is reasonable to expect that any DDEP developed for a new label indication, or with specific claims in terms of efficacy and safety should be forecast to take longer than average, and longer than a DDEP developed with none of these claims, i.e., a Convenience Only DDEP. The reason for
the longer development time probably relates to more demanding trials in support of the efficacy, safety and/or expanded indication claims.

The differences seen with Molecular Size, Molecule Type, and Product Benefit, like Product Configuration (Drug Only and Drug/Device) and Regulatory Strategy are probably real and need to be accounted for when estimating clinical development and approval times for pipeline DDEP. It seems less likely that differences in Indication and Platform Status impact clinical development and approval times, even though some differences are seen. Rather, these differences may be the result of choices related to particular Product Configurations, Regulatory Strategy or Product Benefit. The subset analyses presented in the appendix to Chapter 3 (available upon request) provides some insights in this regard. The intention of the subset analysis is to strip away as many of the interplaying parameters as possible to reveal the naked impact of each parameter.

The analyses in Chapter 3 reinforce the observation of Chapters 1 and 2 that the overall clinical development and approval time for DDEP is increasing. While a portion of the longer times can be ascribed to an increased regulatory review and approval period, this is secondary to a longer period of time being spent at the clinical development stage. The reasons for this are not clear and may include, more complex development programs, slowdowns mandated by funding challenges, or an increase in the number of relatively inexperienced development teams. While these teams are ultimately successful in gaining approval they may not be as efficient as their predecessors. Many of the companies responsible for DDEP approved in the 1980s and 1990s have been acquired or changed their focus to sales and marketing, leaving a younger group of companies to pursue the development and approval of drug delivery enabled/enhanced products.

Perhaps the most valuable insight provided by these analyses is the help they can offer in establishing realistic estimates of approval and development times. This is particularly important when estimating resource requirements for product development. A program that takes five years rather than four will require more resources, both human and financial. Similarly a program that is reasonably forecast to take five and a half years for clinical development and approval, and takes five and a half years, will come in on schedule and hopefully on budget. That same project unrealistically forecast to take four years will certainly be late, and probably over budget. It may also be considered a failure by investors and partners despite being efficiently developed. It’s all about expectations and too often product development timelines are the victim of over promise based on best estimates and plans rather than real world experience.