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.

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**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.
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.
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.

Chart 2-3: Development and Approval Times, Drug Only Rolling Three-Year Average
Chart 2-4: Development and Approval Times, Drug/Device Rolling Three-Year Average

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.

Chart 2-5: FDA Review and Approval Times, Rolling Three-Year Average
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: Development & Approval Times (BioEq Only & Efficacy Safety, 1996-2010)**

![Chart 2-7](image)

**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)
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)

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<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>
</tr>
<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>
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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.
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.