Mismatch between the cost to perform pediatric extension trials and the cost to the public of the six month extension of the drug monopoly

KEI Briefing Note 2023:2
September 20, 2023

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Introduction

When the FDA requests a study under this act, a manufacturer receives a six month extension of its patent and regulatory monopolies. In the FDA Orange Book these extensions are identified as PED extensions.

While the benefits of the US Food and Drug Administration’s pediatric exclusivity program in terms of new safety and efficacy data in pediatric populations cannot be denied, the costs are significant, and in some cases so large as to call into question the appropriateness of using the pediatric extension as an off-budget means to fund the studies.

This issue was explored in a November 2018 article published in JAMA Internal Medicine, which examined 54 drugs receiving pediatric exclusivity under the Best Pharmaceuticals for Children Act from September 27, 2007 to December 31, 2012, and proposed a number of alternatives where there is a significant mismatch between the cost to perform the trials and the cost to the public of the extension of a drug monopoly.

The PED extension is an unusual incentive in that it provides a reward to drug developers regardless of the outcome of the research.

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1 This Briefing Note is based upon and includes the text of a letter submitted to the FDA on September 20, 2023 as a letter to Dr. Robert McKinnon Califf, FACC, MD, Commissioner, U.S. Food and Drug Administration, available at: https://www.keionline.org/39084.

We have reviewed more recent FDA requests for Section 505A studies, and note the following:

1. There are considerable variances in the size of enrollment (and related cost) for the requested studies,
2. There are considerable variances in the associated costs of the monopoly to the public,
3. There are considerable variances in the outlays on the federal Medicare and Medicaid programs for the drugs benefiting from the PED extension,
4. The FDA does not report the actual enrollment of the requested studies,
5. The FDA does not estimate or report on the costs of undertaking the studies,
6. The FDA does not estimate or report on the cost of the monopoly to the public or federal programs.

It is not rocket science to see that the PED extension, while providing benefits to society in terms of new data on the safety and efficacy of products in pediatric populations, is often an extremely expensive way to obtain that data. The costs of this program on the public are also discretionary, in the sense that the FDA needs to request the study from the manufacturer, but also could ask other parties, including the NIH, to undertake the studies.

The government needs to coordinate and manage the PED extension with the objective of getting the data it wants in a cost effective manner. To this end, the FDA needs to:

1. Estimate the cost of the clinical study,
2. Estimate the impact of a 6 month exclusivity extension on the public (as consumers, taxpayers and through insurance reimbursements) in terms of higher prices, and
3. If the cost to the public in terms of higher prices is significantly larger than the costs of the clinical study itself, explore direct public funding of the study.

The FDA should provide ongoing data to evaluate how the program is working, and whenever the FDA does request a 505A pediatric study, the agency should publish on its web page not only the study request letters and amendments, but data on the actual enrollment and costs of the study undertaken, as well as the prices and sales revenue for the drug in the last 12 months of exclusivity, by category of payer, as disclosed by the company doing the requested study.

**Examples of mismatch**

Annex 1 below provides examples of products that have received recent requests for study from the FDA for pediatric studies that extend patent and regulatory monopolies by six months where the costs to the public are excessive relative to the size of the requested trials.

In addition to the product, sponsor and meta data on the requested PED trials, the table provides data on federal outlays of Medicare and Medicaid for the products in 2021, the most recent available data.
Annex 2 includes the 10 drugs that HHS has selected for the drug price negotiations. Of the 10 products, 6 have received a PED extension, and collectively cost Medicaid parts B and D sales of $21 billion in 2021, as well as $3.6 billion in Medicaid spending.

**Significance of Non Medicare/Medicaid costs**

The Medicaid and Medicare outlays, while significant, only describe a portion of the annual costs of the products for the population as a whole, and do not reflect spending by Medicare recipients not enrolled in Medicare Parts B or D, the costs to other federal programs, or persons with or without private insurance. In the spring of 2023, 86.7 million persons were enrolled in Medicaid and 65.7 million Medicare. Among the persons on Medicare, 51.6 million were enrolled in Medicare Part D, while 13 percent had private drug coverage and 9 percent had no drug coverage. Collectively, roughly 126 million persons are covered by the drug benefits in Medicaid or Medicaid Part D, or approximately 37 percent of the US population.

The share of Medicare and Medicaid sales depends upon the product. For example, in 2021:

- BMS drug oncology drugs. Opdivo US sales were $4.812 billion. The costs to Medicare and Medicaid combined were $1.838 billion, or 38 percent of US sales. Yervoy reported US sales of $1.265 billion. The combined Medicare and Medicaid spending were $478 million, also 38 percent of US sales. Abraxane reported US sales of $898 million. The combined Medicare and Medicaid costs were $411 million, or 46 percent of US sales.
- The Gilead HIV drug combination Genvoya US sales were $2.267 billion. The combined Medicare and Medicaid sales of $1.363 billion were 60 percent of US sales.
- The Regeneron drug Eylea (Aflibercept) had US sales of $5.792 billion. The combined Medicare and Medicaid sales were $3.748 billion, or 65 percent of US sales.

By extending patent and regulatory monopolies for six months, the FDA imposes large costs on the federal government’s Medicare and Medical programs, as well as for society at large.

For small molecule drugs with large markets, price decreases are enormous once exclusivity expires. For example:

- In 2020, Medicare spent $2 billion on Viagra, the branded version of Sildenafil Citrate, a product that received an FDA PED request letter in 2012. The 2020 Medicare Part D unit price for a tab was $74.65. Generic versions now sell for as low as $.14.
- Latuda, the branded version of Lurasidone HCI, received $3 billion from Medicare Part D and Medicaid in 2021. The unit price was $44.85. Today, the generic version is available for $.26.
- Gleevec, the branded version of the Leukemia drug imatinib that is used daily, was reimbursed by Medicare Part D at $265 per tablet, and had a price as high as $337 per tablet to some patients. Today generic versions are available for $.34 per tablet.
According to the Association of Accessible Medicines (AAM), currently branded drugs represented 88 percent of total outlays on drugs, but only 9 percent of prescriptions, meaning that on average, branded products are 49 times more expensive.

The attached ANNEX 1 is illustrative of common and recent FDA mismatches between the cost to the federal government and the cost of the trials. It is obvious the FDA routinely ignores the impact of its PED requests on the federal budget, let alone the costs imposed on persons outside of the Medicare and Medicaid drug programs. The Administration can fix this, if it chooses, without changes in the 505A statute.
ANNEX 1: Selected recent PED extensions, Medicaid and Medicare outlays, and FDA requested trial enrollments

<table>
<thead>
<tr>
<th>Product, brand name, sponsor and date of initial FDA request</th>
<th>2021 Medicare and Medicaid spending</th>
<th>Study enrollment in FDA request letter or amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bosutinib</strong>&lt;br&gt;Brand name: Bosulif&lt;br&gt;Sponsor: Pfizer&lt;br&gt;September 7, 2023</td>
<td>Medicare Part D: $148 million&lt;br&gt;Medicaid: $40 million</td>
<td>Minimum of 45 patients</td>
</tr>
<tr>
<td><strong>Vortioxetine</strong>&lt;br&gt;Brand name: Trintellix&lt;br&gt;Sponsor: Takeda Pharmaceuticals&lt;br&gt;August 21, 2023</td>
<td>Medicare Part D: $338 million&lt;br&gt;Medicaid: $182 million</td>
<td>Unclear from FDA letters and amendments</td>
</tr>
<tr>
<td><strong>Fluticasone furoate/vilanterol trifenate</strong>&lt;br&gt;Brand name: Breo Elipta&lt;br&gt;April 26, 2023&lt;br&gt;GlaxoSmithKlein</td>
<td>Medicare Part D: $1.534 billion&lt;br&gt;Medicaid: $212 million</td>
<td>Minimum of 850 patients</td>
</tr>
<tr>
<td><strong>Trametinib</strong>,&lt;br&gt;Brand name: Mekinist&lt;br&gt;Sponsor: Novartis</td>
<td>Medicare Part D: $137 million&lt;br&gt;Medicaid: $46 million</td>
<td>Study 1: at least 70&lt;br&gt;Study 2: at least 40&lt;br&gt;Study 3: at least 102 (same trial as Dabrafenib)</td>
</tr>
<tr>
<td><strong>Dabrafenib</strong>&lt;br&gt;Brand name: Tafinlar&lt;br&gt;Sponsor: Novartis&lt;br&gt;February 9, 2023</td>
<td>Medicare Part D: $118 million&lt;br&gt;Medicaid: $33 million</td>
<td>Study 1: at least 48&lt;br&gt;Study 2: at least 40&lt;br&gt;Study 3: at least 102 (same trial as Trametinib)</td>
</tr>
<tr>
<td><strong>Nivolumab</strong>&lt;br&gt;Brand name: Opdivo&lt;br&gt;Sponsor: BMS&lt;br&gt;February 2, 2023</td>
<td>Medicare Part B: $1.574 billion&lt;br&gt;Medicare Part D: $34 million&lt;br&gt;Medicaid: $230 million</td>
<td>Study 1: to have 70 patients&lt;br&gt;Study 2: canceled</td>
</tr>
</tbody>
</table>

**Selected 2022 PED requests**

<table>
<thead>
<tr>
<th>Product, brand name, sponsor and date of initial FDA request</th>
<th>2021 Medicare and Medicaid spending</th>
<th>Study enrollment in FDA request letter or amendment</th>
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</thead>
<tbody>
<tr>
<td><strong>Lanadelumab</strong>&lt;br&gt;Brand name: Takhzyro&lt;br&gt;Sponsor: Takeda&lt;br&gt;December 20, 2022</td>
<td>Medicare Part D: $174 million&lt;br&gt;Medicaid: $87 million</td>
<td>At least 20 subjects will be enrolled to ensure 15 complete study</td>
</tr>
<tr>
<td>Product, brand name, sponsor and date of initial FDA request</td>
<td>2021 Medicare and Medicaid spending</td>
<td>Study enrollment in FDA request letter or amendment</td>
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<tr>
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</tr>
<tr>
<td>Ruxolitinib Brand name: Jakafi or Opzelura December 1, 2022</td>
<td>Medicare Part D: $1.492 billion Medicaid: $121 million</td>
<td>Study 1: up to 106 patients Study 2: up to 170 patients</td>
</tr>
<tr>
<td>Brentuximab vedotin Brand name: Adcetris Sponsor: Seagen (Pfizer) November 18, 2022</td>
<td>Medicare Part B: $164 million Medicare Part D: $2.4 million Medicaid: $69 million</td>
<td>Study 1: 36 patients Study 2: 46 patients Study 3: 63 patients Study 4: 77 patients Study 5: 600 patients</td>
</tr>
<tr>
<td>Aflibercept Brand name: Eylea Sponsor: Regeneron October 18, 2022</td>
<td>Medicare Part B: $3.416 billion Medicare Part D: $31 million Medicaid: $301 million</td>
<td>At least 150 patients</td>
</tr>
<tr>
<td>Dulaglutide Brand name: Trulicity Sponsor: Eli Lilly October 4, 2022</td>
<td>Medicare Part D: $4.7 billion Medicaid: $1.186 billion</td>
<td>At least 150 patients</td>
</tr>
<tr>
<td>Eribulin mesylate Brand name: Halaven Sponsor: Eisai August 9, 2022</td>
<td>Medicare Part B: $43 million Medicare Part D: $.87 million Medicaid: $10 million</td>
<td>Study 1: minimum 12 patients Study 2: minimum 27 patients Study 3: up to 30</td>
</tr>
<tr>
<td>Ibrutinib Brand name: Imbruvica Sponsor: Pharmacyclics (AbbVie) August 8, 2022</td>
<td>Medicare Part D: $3.15 billion Medicaid: $148.2 million</td>
<td>Study 1: a minimum of 35 across Study 1 and 2 Study 2: Part A, 12 patients Part B, 10 to 32 patients Study 3: minimum of 65 patients</td>
</tr>
<tr>
<td>Afatinib Brand name: Gilotrif Sponsor: Boehringer Ingelheim March 8, 2022</td>
<td>Medicare Part D: $41 million Medicaid: $5 million</td>
<td>50 patients over 4 cohorts</td>
</tr>
<tr>
<td>Product, brand name, sponsor and date of initial FDA request</td>
<td>2021 Medicare and Medicaid spending</td>
<td>Study enrollment in FDA request letter or amendment</td>
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</tr>
<tr>
<td><strong>Selected 2021 PED requests</strong></td>
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</tr>
</tbody>
</table>
| Rivaroxaban  
Brand name: Xarelto  
Sponsor: Janssen (J&J)  
November 23, 2021 | Medicare Part D: $5.2 billion  
Medicaid: $485 million | Study 1: at least 10 in two age groups  
Study 2: at least 10 in two age groups  
Study 3: at least 150 patients  
Study 4: at least 8 patients  
Study 5: at least 20 patients  
Study 6: minimum of 100 patients |
| Elvitegravir/Cobicistat/Etricitabine/Tenofovir Alafenamide  
Brand name: Genvoya  
Sponsor: Gilead  
September 13, 2021 | Medicare Part D: $702 million  
Medicaid: $662 million | Minimum of 20 subjects in each age group (6 to 12 and 2 to 6 years), or 40 in total |
| Lisdexamfetamine  
Brand name: Vyvanse  
Sponsor: Takeda/Shire  
July 27, 2021 | Medicare Part D: $108 million  
Medicaid: $1.152 billion | Study 1 and 2: sufficient number  
Study 3: at least 50 |
| Fesoterodine  
Brand name: Toviaz  
Sponsor: Pfizer  
June 3, 2021 | Medicare Part D: $163 million  
Medicaid: $25 million | Cohort 1: approximately 99 patients  
Cohort 2: approximately 50 patients |
| Sucroferric Oxyhydroxide  
Brand name: Velphoro  
Sponsor: Vifor Fresenius Medical Care  
June 1, 2021 | Medicare Part D: $381 million  
Medicaid: $45 million | Minimum of 30 subjects |
| Deutetrabenazine  
Brand name: Austedo  
Sponsor: Teva  
May 5, 2021 | Medicare Part D: 666 $million  
Medicaid: $132 million | Study 1: at least 116 patients  
Study 2: at least 150 patients  
Study 3: at least 100 patients |
<table>
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<th>2021 Medicare and Medicaid spending</th>
<th>Study enrollment in FDA request letter or amendment</th>
</tr>
</thead>
</table>
| Exenatide  
Brand name: Bydureon  
Sponsor: AstraZeneca  
April 1, 2021 | Medicare Part D: $430 million  
Medicaid: $119 | Study 1: 12 patients  
Study 2: at least 77 patients  
Study 3: canceled |
| Teriflunomide  
Brand name: Aubagio  
Sponsor: Sanofi  
March 31, 2021 | Medicare Part D: $778 million  
Medicaid: $175 million | Study 1: minimum 100 patients |
| Mirabegron  
Brand name: Myrbetriq  
Sponsor: Astellas  
March 1, 2021 | Medicare Part D: $1.989 billion  
Medicaid: $59.6 million | Study 1: total of 6 evaluable patients  
Study 2: at least 44 patients |

**Selected 2020 PED requests**

<table>
<thead>
<tr>
<th>Product, brand name, sponsor and date of initial FDA request</th>
<th>2021 Medicare and Medicaid spending</th>
<th>Study enrollment in FDA request letter or amendment</th>
</tr>
</thead>
</table>
| Sitagliptin  
Brand name Januvia  
Sponsor: Merck  
October 30, 2023 | Medicare Part D: $5.265 billion  
Medicaid: $785 | Approximately 350 patients |
| Pomalidomide  
Brand name: Pomalyst  
Sponsor: Celgene (BMS)  
October 16, 2020 | Medicare Part D: $1.595 billion  
Medicaid: $84 million | Studies 1 and 2: minimum of 50 patients enrolled |
| Atezolizumab  
Brand name: Tecentriq  
Sponsor: Genentech/  
Hoffmann-La Roche  
September 22, 2020 | Medicare Part B: $656 million  
Medicare Part D: $14.5 million  
Medicare: $151 million | Study 1: between 50 and 100 patients  
Study 2: canceled |
| Vilazodone  
Brand name: Viibryd  
Sponsor: Allergan  
(AbbVie)  
January 21, 2020 | Medicare Part D: $135 million  
Medicaid: $89 million | At least 100 patients |
<table>
<thead>
<tr>
<th>Product, brand name, sponsor and date of initial FDA request</th>
<th>2021 Medicare and Medicaid spending</th>
<th>Study enrollment in FDA request letter or amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selected 2019 or older PED requests</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Fidaxomicin  
Brand name: Dificid  
Sponsor: Cubist (Merck)  
December 13, 2019 | Medicare Part D: $68 million  
Medicaid: $11 million  
Medicaid: $11 million | At least 135 patients  
(approximately 90 to fidaxomicin and 45 to vancomycin) |
| nab-Paclitaxel  
Brand name: Abraxane  
Sponsor: Abraxis  
November 8, 2019 | Medicare Part B: $334 million  
Medicare Part D: $10 million  
Medicaid: $67 million | Minimum of 14 patients in each of the three age groups |
| Sacubitril / Valsartan  
Brand name: Entresto  
Sponsor: Novartis  
September 26, 2019 | Medicare Part D: $1.723 billion  
Medicaid: $281 million | Part 1: minimum 16 patients  
Part 2: at least 100 patients |
| Teduglutide  
Brand name: Gattex  
Sponsor: Shire-NPS  
March 7, 2019 | Medicare Part D: $165 million  
Medicaid: $121 million | Study 1: at least 24 patients  
Study 2: at least 28 patients |
| Varenicline  
Brand name: Chantix  
Sponsor: Pfizer  
Pfizer paused distribution in 2021  
November 15, 2018 | Medicaid Part D: $314.7 million in 2020  
Medicaid: $269 million in 2020 | Study 1: minimum of 12 patients per treatment group  
Study 2: sufficient number to detect 20 percent quit rate. |
| Tocilizumab  
Brand name: Actemra  
Sponsor: Genentech/Hoffmann-La Roche  
July 18, 2018 | Medicare Part B: $289 million  
Medicare Part D: $217 million  
Medicaid: $88 million | Study 1: at least 10 patients  
Study 2: at least 160 patient  
Studies 3 and 4: “sufficient number” to determine dosing |
| Nilotinib  
Brand name: Tasigna  
Sponsor: Novartis  
March 20, 2018 | Medicare Part D: $352.2 million  
Medicaid: $93.7 million | Study 1: At least 14 patients  
Study 2: At least 50 evaluable patients |
<table>
<thead>
<tr>
<th>Product, brand name, sponsor and date of initial FDA request</th>
<th>2021 Medicare and Medicaid spending</th>
<th>Study enrollment in FDA request letter or amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone Brand name: Latuda Sponsor: Sunovion (Sumitomo) December 20, 2016</td>
<td>Medicare Part D: $1.367 billion Medicaid: $1.64 billion</td>
<td>Sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and Pharmacokinetics. At least 100 combined from studies for long-term safety.</td>
</tr>
<tr>
<td>Tiotropium, Brand name Spiriva Sponsor: Boehringer Ingelheim December 14, 2016</td>
<td>Medicare Part D: $2.238 billion Medicaid: $652 million</td>
<td>Minimum of 125 patients per treatment group (2 or more groups).</td>
</tr>
<tr>
<td>Dasatinib Brand name: Sprycel Sponsor: BMS Data missing on main FDA page on PED requests. Amendment 5 request was apparently June 21, 2018</td>
<td>Medicare Part D: $450 million Medicare: $228 million</td>
<td>Data missing on main. FDA web page. Appears to be 2 trials.</td>
</tr>
</tbody>
</table>
## ANNEX 2: Medicare price negotiation drugs

<table>
<thead>
<tr>
<th>Brand</th>
<th>INN (generic name)</th>
<th>BLA/ NDA</th>
<th>PED extension</th>
<th>2021 Medicare outlays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliquis</td>
<td>Apixaban</td>
<td>NDA</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Jardiance</td>
<td>Empagliflozin</td>
<td>NDA</td>
<td>PED</td>
<td>Part D: $4.064 billion</td>
</tr>
<tr>
<td>Xarelto</td>
<td>Rivaroxaban</td>
<td>NDA</td>
<td>PED</td>
<td>Part D: $5.226 billion</td>
</tr>
<tr>
<td>Januvia</td>
<td>Sitagliptin Phosphate</td>
<td>NDA</td>
<td>PED</td>
<td>Part D: $5.265 billion</td>
</tr>
<tr>
<td>Farxiga</td>
<td>Dapagliflozin</td>
<td>NDA</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Entresto</td>
<td>sacubitril/ valsartan</td>
<td>NDA</td>
<td>PED</td>
<td>Part D: $1.723 billion</td>
</tr>
<tr>
<td>Enbrel</td>
<td>etanercept</td>
<td>BLA</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Imbruvica</td>
<td>Ibrutinib</td>
<td>NDA</td>
<td>PED</td>
<td>Part D: $3.15 billion</td>
</tr>
<tr>
<td>Stelara</td>
<td>Ustekinumab</td>
<td>BLA</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>NovoLog and Fiasp</td>
<td>Insulin Aspart Recombinant And Insulin Aspart</td>
<td>BLA</td>
<td>PED</td>
<td>Part B and D: $3.068 billion</td>
</tr>
</tbody>
</table>