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

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James Love, Manon Ress and Claire Cassedy

Introduction[1]

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,[2] 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.

[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.
[2] Sinha MS, Najafzadeh M, Rajasingh EK, Love J, Kesselheim AS. Labeling Changes and Costs for Clinical Trials Performed Under the US Food and Drug Administration Pediatric Exclusivity Extension, 2007 to 2012. JAMA Intern Med. 2018;178(11):1458–1466. doi:10.1001/jamainternmed.2018.3933

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

Product, brand name, sponsor and date of initial FDA request	2021 Medicare and Medicaid spending	Study enrollment in FDA request letter or amendment
Selected 2023 PED requests		
Bosutinib Brand name: Bosulif Sponsor: Pfizer September 7, 2023	Medicare Part D: $148 million Medicaid: $40 million	Minimum of 45 patients
Vortioxetine Brand name: Trintellix Sponsor: Takeda Pharmaceuticals August 21, 2023	Medicare Part D: $338 million Medicaid: $182 million	Unclear from FDA letters and amendments
Fluticasone furoate/ vilanterol trifenatate, Brand name: Breo Elipta April 26, 2023 GlaxoSmithKlein	Medicare Part D: $1.534 billion Medicaid: $212 million	Minimum of 850 patient
Trametinib, Brand name: Mekinist Sponsor: Novartis	Medicare Part D: $137 million Medicaid: $46 million	Study 1: at least 70 Study 2: at least 40 Study 3: at least 102 (same trial as Dabrafenib)
Dabrafenib Brand name: Tafinlar Sponsor: Novartis February 9, 2023	Medicare Part D: $118 million Medicaid: $33 million	Study 1: at least 48 Study 2: at least 40 Study 3: at least 102 (same trial as Trametinib)
Nivolumab Brand name: Opdivo Sponsor: BMS February 2, 2023	Medicare Part B: $1.574 billion Medicare Part D: $34 million Medicaid: $230 million	Study 1: to have 70 patients Study 2: canceled
Selected 2022 PED requests		
Lanadelumab Brand name: Takhzyro Sponsor: Takeda December 20, 2022	Medicare Part D: $174 million Medicaid: $87 million	At least 20 subjects will be enrolled to ensure 15 complete study

Product, brand name, sponsor and date of initial FDA request	2021 Medicare and Medicaid spending	Study enrollment in FDA request letter or amendment
Ruxolitinib Brand name: Jakafi or Opzelura December 1, 2022	Medicare Part D: $1.492 billion Medicaid: $121 million	Study 1: up to 106 patients Study 2: up to 170 patients
Brentuximab vedotin Brand name: Adcetris Sponsor: Seagen (Pfizer) November 18, 2022	Medicare Part B: $164 million Medicare Part D: $2.4 million Medicaid: $69 million	Study 1: 36 patients Study 2: 46 patients Study 3: 63 patients Study 4: 77 patients Study 5: 600 patients
Aflibercept Brand name: Eylea Sponsor: Regeneron October 18, 2022	Medicare Part B: $3.416 billion Medicare Part D: $31 million Medicaid: $301 million	At least 150 patients
Dulaglutide Brand name: Trulicity Sponsor: Eli Lilly October 4, 2022	Medicare Part D: $4.7 billion Medicaid: $1.186 billion	At least 150 patients
Eribulin mesylate Brand name: Halaven Sponsor: Eisai August 9, 2022	Medicare Part B: $43 million Medicare Part D: $.87 million Medicaid: $10 million	Study 1: minimum 12 patients Study 2: minimum 27 patients Study 3: up to 30
Ibrutinib Brand name: Imbruvica Sponsor: Pharmacyclics (AbbVie) August 8, 2022	Medicare Part D: $3.15 billion Medicaid: $148.2 million	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
Ticagrelor Brand name: Brilinta Sponsor: AstraZeneca April 8, 2022	Medicare Part D: $602 million Medicaid: $111 million	Study 1: minimum of 3-5 patients Study 2: terminated Study 3: canceled
Afatinib Brand name: Gilotrif Sponsor: Boehringer Ingelheim March 8, 2022	Medicare Part D: $41 million Medicaid: $5 million	50 patients over 4 cohorts

Product, brand name, sponsor and date of initial FDA request	2021 Medicare and Medicaid spending	Study enrollment in FDA request letter or amendment
Selected 2021 PED requests		
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/Emtricitabine/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

Product, brand name, sponsor and date of initial FDA request	2021 Medicare and Medicaid spending	Study enrollment in FDA request letter or amendment
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		
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

Product, brand name, sponsor and date of initial FDA request	2021 Medicare and Medicaid spending	Study enrollment in FDA request letter or amendment
Selected 2019 or older PED requests		
Fidaxomicin Brand name Dificid Sponsor: Cubist (Merck) December 13, 2019	Medicare Part D: $68 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

Product, brand name, sponsor and date of initial FDA request	2021 Medicare and Medicaid spending	Study enrollment in FDA request letter or amendment
Lurasidone Brand name: Latuda Sponsor: Sunovion (Sumitomo) December 20, 2016	Medicare Part D: $1.367 billion Medicaid: $1.64 billion	Sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and Pharmacokinetics. At least 100 combined from studies for long-term safety.
Tiotropium, Brand name Spiriva Sponsor: Boehringer Ingelheim December 14, 2016	Medicare Part D: $2.238 billion Medicaid: $652 million	Minimum of 125 patients per treatment group (2 or more groups).
Fluticasone furoate/vilanterol trifenatate Brand name: Breo Ellipta, Sponsor: GlaxoSmithKline March 35, 2015	Medicare Part D; $1.534 billion Medicaid $212 million	Minimum of 850 patients
Dasatinib Brand name: Sprycel Sponsor: BMS Data missing on main FDA page on PED requests. Amendment 5 request was apparently June 21, 2018	Medicare Part D: $450 million Medicare: $228 million	Data missing on main. FDA web page. Appears to be 2 trials.

ANNEX 2: Medicare price negotiation drugs

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