September 19, 2023

Dr. Robert McKinnon Califf, FACC, MD
Commissioner
U.S. Food and Drug Administration
Via: commissioner@fda.hhs.gov

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

Dear Commissioner McKinnon:

We are writing to request changes in the FDA's granting of Pediatric Exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act.

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,[1] 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.

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,

[1] 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

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 part D sales of $20.3 billion in 2021.

*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.

Sincerely,

James Love
Manon Anne Ress, PhD.
Claire Cassedy
Knowledge Ecology International (KEI)

## ANNEX: 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<br>Brand name: Bosulif<br>Sponsor: Pfizer<br>September 7, 2023 | Medicare Part D: $148 million<br>Medicaid: $40 million | Minimum of 45 patients |
| Vortioxetine<br>Brand name: Trintellix<br>Sponsor: Takeda Pharmaceuticals<br>August 21, 2023 | Medicare Part D: $338 million<br>Medicaid: $182 million | Unclear from FDA letters and amendments |
| Fluticasone furoate/ vilanterol trifenatate,<br>Brand name: Breo Elipta<br>April 26, 2023<br>GlaxoSmithKlein | Medicare Part D: $1.534 billion<br>Medicaid: $212 million | Minimum of 850 patient |
| Trametinib,<br>Brand name: Mekinist<br>Sponsor: Novartis | Medicare Part D: $137 million<br>Medicaid: $46 million | Study 1: at least 70<br>Study 2: at least 40<br>Study 3: at least 102<br>(same trial as Dabrafenib) |
| Dabrafenib<br>Brand name: Tafinlar<br>Sponsor: Novartis<br>February 9, 2023 | Medicare Part D: $118 million<br>Medicaid: $33 million | Study 1: at least 48<br>Study 2: at least 40<br>Study 3: at least 102<br>(same trial as Trametinib) |
| Nivolumab<br>Brand name: Opdivo<br>Sponsor: BMS<br>February 2, 2023 | Medicare Part B: $1.574 billion<br>Medicare Part D: $34 million<br>Medicaid: $230 million | Study 1: to have 70 patients<br>Study 2: canceled |
| **Selected 2022 PED requests** | | |
| Lanadelumab<br>Brand name: Takhzyro<br>Sponsor: Takeda<br>December 20, 2022 | Medicare Part D: $174 million<br>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<br>Brand name: Jakafi or Opzelura<br>December 1, 2022 | Medicare Part D: $1.492 billion<br>Medicaid: $121 million | Study 1: up to 106 patients<br>Study 2: up to 170 patients |
| Brentuximab vedotin<br>Brand name: Adcetris<br>Sponsor: Seagen (Pfizer)<br>November 18, 2022 | Medicare Part B: $164 million<br>Medicare Part D: $2.4 million<br>Medicaid: $69 million | Study 1: 36 patients<br>Study 2: 46 patients<br>Study 3: 63 patients<br>Study 4: 77 patients<br>Study 5: 600 patients |
| Aflibercept<br>Brand name: Eylea<br>Sponsor: Regeneron<br>October 18, 2022 | Medicare Part B: $3.416 billion<br>Medicare Part D: $31 million<br>Medicaid: $301 million | At least 150 patients |
| Dulaglutide<br>Brand name: Trulicity<br>Sponsor: Eli Lilly<br>October 4, 2022 | Medicare Part D: $4.7 billion<br>Medicaid: $1.186 billion | At least 150 patients |
| Eribulin mesylate<br>Brand name: Halaven<br>Sponsor: Eisai<br>August 9, 2022 | Medicare Part B: $43 million<br>Medicare Part D: $.87 million<br>Medicaid: $10 million | Study 1: minimum 12 patients<br>Study 2: minimum 27 patients<br>Study 3: up to 30 |
| Ibrutinib<br>Brand name: Imbruvica<br>Sponsor: Pharmacyclics (AbbVie)<br>August 8, 2022 | Medicare Part D: $3.15 billion<br>Medicaid: $148.2 million | Study 1: a minimum of 35 across Study 1 and 2<br>Study 2: Part A, 12 patients<br>Part B, 10 to 32 patients<br>Study 3: minimum of 65 patients |
| Ticagrelor<br>Brand name: Brilinta<br>Sponsor: AstraZeneca<br>April 8, 2022 | Medicare Part D: $602 million<br>Medicaid: $111 million | Study 1: minimum of 3-5 patients<br>Study 2: terminated<br>Study 3: canceled |
| Afatinib<br>Brand name: Gilotrif<br>Sponsor: Boehringer Ingelheim<br>March 8, 2022 | Medicare Part D: $41 million<br>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<br>Brand name: Xarelto<br>Sponsor: Janssen (J&J)<br>November 23, 2021 | Medicare Part D: $5.2 billion<br>Medicaid: $485 million | Study 1: at least 10 in two age groups<br>Study 2: at least 10 in two age groups<br>Study 3: at least 150 patients<br>Study 4: at least 8 patients<br>Study 5: at least 20 patients<br>Study 6: minimum of 100 patients |
| Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide<br>Brand name: Genvoya<br>Sponsor: Gilead<br>September 13, 2021 | Medicare Part D: $702 million<br>Medicaid: $662 million | Minimum of 20 subjects in each age group (6 to 12 and 2 to 6 years), or 40 in total |
| Lisdexamfetamine<br>Brand name: Vyvanse<br>Sponsor: Takeda/Shire<br>July 27, 2021 | Medicare Part D: $108 million<br>Medicaid: $1.152 billion | Study 1 and 2: sufficient number<br>Study 3: at least 50 |
| Fesoterodine<br>Brand name: Toviaz<br>Sponsor: Pfizer<br>June 3, 2021 | Medicare Part D: $163 million<br>Medicaid: $25 million | Cohort 1: approximately 99 patients<br>Cohort 2: approximately 50 patients |
| Sucroferric Oxyhydroxide<br>Brand name: Velphoro<br>Sponsor: Vifor Fresenius Medical Care<br>June 1, 2021 | Medicare Part D: $381 million<br>Medicaid: $45 million | Minimum of 30 subjects |
| Deutetrabenazine<br>Brand name: Austedo<br>Sponsor: Teva<br>May 5, 2021 | Medicare Part D: 666 $million<br>Medicaid: $132 million | Study 1: at least 116 patients<br>Study 2: at least 150 patients<br>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<br>Brand name: Bydureon<br>Sponsor: AstraZeneca<br>April 1, 2021 | Medicare Part D: $430 million<br>Medicaid: $119 | Study 1: 12 patients<br>Study 2: at least 77 patients<br>Study 3: canceled |
| Teriflunomide<br>Brand name: Aubagio<br>Sponsor: Sanofi<br>March 31, 2021 | Medicare Part D: $778 million<br>Medicaid: $175 million | Study 1: minimum 100 patients |
| Mirabegron<br>Brand name: Myrbetriq<br>Sponsor: Astellas<br>March 1, 2021 | Medicare Part D: $1.989 billion<br>Medicaid: $59.6 million | Study 1: total of 6 evaluable patients<br>Study 2: at least 44 patients |
| **Selected 2020 PED requests** | | |
| Sitagliptin<br>Brand name Januvia<br>Sponsor: Merck<br>October 30, 2023 | Medicare Part D: $5.265 billion<br>Medicaid: $785 | Approximately 350 patients |
| Pomalidomide<br>Brand name: Pomalyst<br>Sponsor: Celgene (BMS)<br>October 16, 2020 | Medicare Part D: $1.595 billion<br>Medicaid: $84 million | Studies 1 and 2: minimum of 50 patients enrolled |
| Atezolizumab<br>Brand name: Tecentriq<br>Sponsor: Genentech/ Hoffmann-La Roche<br>September 22, 2020 | Medicare Part B: $656 million<br>Medicare Part D: $14.5 million<br>Medicare: $151 million | Study 1: between 50 and 100 patients<br><br>Study 2: canceled |
| Vilazodone<br>Brand name: Viibryd<br>Sponsor: Allergan (AbbVie)<br>January 21, 2020 | Medicare Part D: $135 million<br>Medicaid: $89 million | At least 100 patients |
| **Selected 2019 or older PED requests** | | |

| Product, brand name, sponsor and date of initial FDA request | 2021 Medicare and Medicaid spending | Study enrollment in FDA request letter or amendment |
|---|---|---|
| Fidaxomicin<br>Brand name Dificid<br>Sponsor: Cubist (Merck)<br>December 13, 2019 | Medicare Part D: $68 million<br>Medicaid: $11 million | At least 135 patients (approximately 90 to fidaxomicin and 45 to vancomycin) |
| nab-Paclitaxel<br>Brand name: Abraxane<br>Sponsor: Abraxis<br>November 8, 2019 | Medicare Part B: $334 million<br>Medicare Part D: $10 million<br>Medicaid: $67 million | Minimum of 14 patients in each of the three age groups |
| Sacubitril / Valsartan<br>Brand name: Entresto<br>Sponsor: Novartis<br>September 26, 2019 | Medicare Part D: $1.723 billion<br>Medicaid: $281 million | Part 1: minimum 16 patients<br>Part 2: at least 100 patients |
| Teduglutide<br>Brand name: Gattex<br>Sponsor: Shire-NPS<br>March 7, 2019 | Medicare Part D: $165 million<br>Medicaid: $121 million | Study 1: at least 24 patients<br>Study 2: at least 28 patients |
| Varenicline<br>Brand name: Chantix<br>Sponsor: Pfizer<br>Pfizer paused distribution in 2021<br>November 15, 2018 | Medicaid Part D: $314.7 million in 2020<br>Medicaid: $269 million in 2020 | Study 1: minimum of 12 patients per treatment group<br>Study 2: sufficient number to detect 20 percent quit rate. |
| Tocilizumab<br>Brand name: Actemra<br>Sponsor: Genentech/ Hoffmann-La Roche<br>July 18, 2018 | Medicare Part B: $289 million<br>Medicare Part D: $217 million<br>Medicaid: $88 million | Study 1: at least 10 patients<br>Study 2: at least 160 patient<br>Studies 3 and 4: “sufficient number” to determine dosing |
| Nilotinib<br>Brand name: Tasigna<br>Sponsor: Novartis<br>March 20, 2018 | Medicare Part D: $352.2 million<br>Medicaid: $93.7 million | Study 1: At least 14 patients<br><br>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<br>Brand name: Latuda<br>Sponsor: Sunovion (Sumitomo)<br>December 20, 2016 | Medicare Part D: $1.367 billion<br>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,<br>Brand name Spiriva<br>Sponsor: Boehringer Ingelheim<br>December 14, 2016 | Medicare Part D: $2.238 billion<br>Medicaid: $652 million | Minimum of 125 patients per treatment group (2 or more groups). |
| Fluticasone furoate/vilanterol trifenatate<br>Brand name: Breo Ellipta,<br>Sponsor: GlaxoSmithKline<br>March 35, 2015 | Medicare Part D; $1.534 billion<br>Medicaid $212 million | Minimum of 850 patients |
| Dasatinib<br>Brand name: Sprycel<br>Sponsor: BMS<br>Data missing on main FDA page on PED requests. Amendment 5 request was apparently June 21, 2018 | Medicare Part D: $450 million<br>Medicare: $228 million | Data missing on main. FDA web page. Appears to be 2 trials. |

## ANNEX 1: 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: $3.737 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 D: $2.5 billion |