# An Analysis of Dosing-Related Postmarketing Requirements for Novel Oncology Drugs Approved by the U.S. Food and Drug Administration, 2012–2022

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## ABSTRACT

The FDA's Oncology Center of Excellence's (OCE) launch of Project Optimus signals increased focus on dose optimization approaches in oncology drug development, particularly toward optimization in the premarket setting. Although sponsors continue to adapt premarket study designs and approaches to align with FDA's expectations for dose optimization, including consideration of the optimal dosage(s), there are still instances where questions remain at the time of approval about whether the approved doses or schedules are optimal. In these cases, FDA can exercise regulatory flexibility by issuing postmarketing requirements (PMR) and avoid delaying patient access to promising therapies. This landscape analysis demonstrates that over the past decade (2012–2022), FDA frequently used PMRs to answer additional questions about dosing for novel oncology approvals. We found more than half of drugs (78/132, 59.1%) had a dosing PMR and observed a recent increase in PMRs intended to evaluate whether a lower dose could be more optimal. These results suggest there are opportunities to adapt premarket dose optimization strategies and leverage innovative development tools to ensure timely identification of the optimal dose.

## Introduction

The FDA Oncology Center of Excellence's (OCE) launch of Project Optimus signals a shift in expectations for dose optimization approaches in oncology, particularly towards optimization in the premarket setting (1). Although sponsors continue to adapt premarket study designs and approaches to align with FDA's expectations for dose optimization, including consideration of the optimal dosage(s), there are still instances where questions remain at the time of approval about whether the approved doses or schedules are optimal. In these circumstances, FDA can use its authority to require sponsors to conduct additional dose optimization by issuing postmarketing requirements (PMR). A sponsor may also agree to a postmarketing commitment (PMC) to conduct additional dose optimization, but these are "studies or clinical trials the sponsor has agreed to conduct but are not required by statute or regulation" (2). PMRs are important tools, which allow the FDA to exercise regulatory flexibility and enable timely approval of potentially lifesaving drugs and biologics (collectively referred to herein as drugs) while additional studies are ongoing. This is particularly true in oncology, a disease area in which drugs are often approved on expedited timelines that speed access to innovative treatments for patients with life-threatening cancers who have exhausted all other treatment options.

Given the increased emphasis on the importance of adequate characterization of doses and schedules, we conducted a landscape analysis of dosing PMRs issued to novel oncology drugs approved over the last decade (2012–2022). Previous research has broadly evaluated clinical pharmacology- and immunogenicity-related PMR/Cs and considered how factors such as the use of expedited programs [e.g., accelerated approval (AA)], special designations (e.g., orphan drug designation), and pivotal trial designs influence decisions to assign a PMR or PMC (3–6). These studies briefly acknowledged certain dosing PMR/Cs within the scope of their analyses but did not evaluate trends or characteristics of dosing PMR/Cs for novel oncology drugs. Our analysis provides a comprehensive review of dosing PMRs for oncology drugs to identify the types of dosing information the FDA requires sponsors to collect and how long it takes to complete these activities in the postmarketing setting. We focused our analysis on PMRs because FDA has authority to issue them and ensure they are completed (2). In addition, PMRs better reflect the types of dosing activities and information FDA views as critical to fulfilling statutory requirements that ensure safe and effective use. We also evaluated trends in dosing PMRs over time to assess the impact of the FDA's re-evaluation of the dose optimization and selection paradigm and associated policy related to dose optimization in oncology.

## Materials and Methods

We identified a list of novel drugs approved to treat cancer by the FDA between January 1, 2012, and December 31, 2022. Novel drugs include original applications for drugs that have never been approved before. We focused on this group of drugs because they have no predicates or same in-class drugs, and therefore, no prior knowledge to rely on. Using the publicly available Drugs@FDA database and FDA's web page for products licensed by the Center for Biologics Evaluation and Research's (CBER) Office of Therapeutic Products (OTP), we compiled a list of PMRs included in the original approval letters for these drugs (7). Additional information collected from approval letters included PMR descriptions, statutes under which they were issued, and final report due dates.

We then identified PMRs intended to inform dosing by searching PMR descriptions for the keywords "dose," "dosage," and

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Clin Cancer Res 2024;30:937–41

**doi:** 10.1158/1078-0432.CCR-23-2268

**Table 1.** Characteristics of novel oncology drugs approved by the FDA (2012–2022).

| | All drugs | | | | Drugs with a dosing PMR | | | |
|---|---|---|---|---|---|---|---|---|
| | All years | 2012–2015 | 2016–2019 | 2020–2022 | All years | 2012–2015 | 2016–2019 | 2020–2022 |
| Total | 132 | 42 (31.8) | 44 (33.3) | 46 (34.8) | 78 (59.1) | 26 (61.9) | 23 (52.3) | 29 (63) |
| Application type | | | | | | | | |
| NDA | 82 (62.1) | 29 (35.4) | 29 (35.4) | 24 (29.3) | 66 (80.5) | 25 (86.2) | 22 (75.9) | 19 (79.2) |
| BLA | 50 (37.9) | 13 (26) | 15 (30) | 22 (44) | 12 (24) | 1 (7.7) | 1 (6.7) | 10 (45.5) |
| Approval type | | | | | | | | |
| Accelerated approval | 71 (53.8) | 25 (35.2) | 26 (36.6) | 20 (28.2) | 35 (49.3) | 13 (52) | 12 (46.2) | 10 (50) |
| Regular approval | 61 (46.2) | 17 (27.9) | 18 (29.5) | 26 (42.6) | 43 (70.5) | 13 (76.5) | 11 (61.1) | 19 (73.1) |
| Drug class | | | | | | | | |
| Molecular target inhibitors | 68 (51.5) | 23 (33.8) | 27 (39.7) | 18 (26.5) | 56 (82.4) | 20 (87) | 21 (77.8) | 15 (83.3) |
| Monoclonal antibody/ADCs | 38 (28.8) | 11 (28.9) | 11 (28.9) | 16 (42.1) | 11 (28.9) | 1 (9.1) | 1 (9.1) | 9 (56.3) |
| Chemotherapies[a] | 8 (6.1) | 5 (62.5) | — | 3 (37.5) | 7 (87.5) | 4 (80) | — | 3 (100) |
| Cell and gene therapies | 8 (6.1) | 1 (12.5) | 2 (25) | 5 (62.5) | — | — | — | — |
| Endocrine therapies/hormone antagonists and related agents | 4 (3.0) | 1 (25) | 2 (50) | 1 (25) | — | — | — | — |
| Radiopharmaceuticals | 3 (2.3) | 1 (33.3) | 1 (33.3) | 1 (33.3) | 3 (100) | 1 (100) | 1 (100) | 1 (100) |
| Other[b] | 3 (2.3) | — | 1 (33.3) | 2 (66.7) | 1 (33.3) | — | — | 1 (50) |
| Disease setting | | | | | | | | |
| Advanced | 124 (93.9) | 41 (33.1) | 39 (31.5) | 44 (35.5) | 75 (60.5) | 26 (63.4) | 21 (53.8) | 28 (63.6) |
| Both | 4 (3) | 1 (25) | 2 (50) | 1 (25) | 1 (25) | — | — | 1 (100) |
| Early stage | 4 (3) | — | 3 (75) | 1 (25) | 2 (50) | — | 2 (66.7) | — |

[a]Chemotherapies include three alkylating agents, two antimetabolites, one protein biosynthesis inhibitor, and two angiogenesis inhibitors.
[b]*Other* includes two antineoplastic enzymes and one hypoxia-inducible factor (HIF) inhibitor. BLA, biologics license application; NDA, new drug application; ADC, antibody-drug conjugate.

"dosing." Dosing PMR descriptions were reviewed and activities were categorized as: (i) "Extrinsic Factors," which include evaluations of how extrinsic factors affect dosing such as drug interaction, drug-drug interaction, and food effect trials; (ii) "Intrinsic Factors," which include evaluations of how intrinsic factors affect dosing such as dosing in patients with renal and hepatic impairment, pediatric populations, patients with a certain genetic marker not specified in the label, and evaluations of dosing based on body surface area or body weight; (iii) "Dose Variation" PMRs, including evaluations of dosing in a new combination, alternative regimens, levels, schedules, or infusion timelines, studies that informed dose modification and monitoring recommendations, and studies that otherwise compare doses or inform whether the approved dose(s) are optimal; and (iv) "Miscellaneous activities," which include development of new formulation strengths, assessments of the QT interval (QT/QTc studies), long-term safety studies that do not explicitly inform dose modifications and monitoring, animal toxicology studies, and immunogenicity studies.

To understand factors influencing the types of PMR issued, we used FDA's public databases to collect information on the approval pathway (AA vs. traditional approval), application type [new drug application (NDA) vs. biologic license application (BLA)], indicated cancer type, and disease setting (advanced vs. early stage) for each drug. We identified drug classes using the National Library of Medicine's (NLM) RxClass database and the Kyoto Encyclopedia of Genes and Genomes (KEGG) Drug database.

## Results

Between January 1, 2012, and December 31, 2022, the FDA approved 132 novel oncology drugs and we identified 376 PMRs for 112 of these novel drugs. Of the 376 PMRs, 43.9% (165/376) collected additional dosing information for 78 of the approved drugs (59.1%, 78/132).

### Characteristics of drugs with a dosing PMR

Between 2012 and 2022, NDAs were more likely than BLAs to have a dosing PMR (80.5%, 66/82, vs. 24%, 12/50). The percentage of BLAs with a dosing PMR increased over time from 7.7% (1/13) of BLAs approved 2012 to 2015 to 45.5% (10/22) of BLAs approved 2020 to 2022. In contrast, the percentage of NDAs with a dosing PMR decreased slightly over time from 86.2% (25/29) of NDAs 2012 to 2015 to 79.2% (19/24) of NDAs 2020 to 2022 (**Table 1**).

Across most drug classes, the percentage of approvals with a dosing PMR increased or remained consistent over the last 10 years (**Table 1**). Although 82.4% (56/68) of molecular target inhibitors had a PMR to inform dosing, there was a slight decrease over time in the percent of drugs in this class with a dosing PMR (87%, 20/23 approved 2012–2015 vs. 83.3%, 15/18 approved 2020–2022). The drug classes with the most approvals assigned a dosing PMR were radiopharmaceuticals (100%, 3/3), chemotherapies (87.5%, 7/8), and molecular target inhibitors (82.4%, 56/68). Drugs classified as other (33.3%, 1/3) and mAbs/antibody–drug conjugates (ADC; 28.9%, 11/38) had the fewest drugs with a dosing PMR. Over time, the percentage of mAbs/ADCs with a dosing PMR increased from 9.1% (1/11) of drugs approved 2012 to 2015 to 56.3% (9/16) of drugs approved 2020 to 2022. Cell and gene therapies and endocrine therapies/hormone antagonists and related agents both had 0 drugs with a PMR to collect additional dosing information in the postmarketing setting (**Table 1**).

### Characteristics of dosing PMRs

Most dosing PMRs (75.6%, 125/165) evaluated the impact of intrinsic factors such as renal/hepatic impairment, body weight, genetic markers, or extrinsic factors such as food effect and drug interactions (**Table 2**). In the past 3 years, there was an increase in the percentage of dosing related PMRs evaluating extrinsic factors (31.3%, 15/48 were issued during 2012–2015 compared with 52.1%, 25/48 issued during 2020–2022). PMRs focused on intrinsic factors had a median of 2.1 years to be completed (years from the approval date to

**Table 2.** PMRs by dosing category and type of information provided to inform dosing over time (2012–2022).

| Dosing category | Type of information | Years of approval | | | |
|---|---|---|---|---|---|
| | | All years | 2012–2015 | 2016–2019 | 2020–2022 |
| Intrinsic factors | Hepatic impairment | 45 (58.4) | 15 (33.3) | 14 (31.1) | 16 (35.6) |
| | Renal impairment | 21 (27.3) | 9 (42.9) | 5 (23.8) | 7 (33.3) |
| | Age (pediatric) | 7 (9.1) | — | — | 7 (100) |
| | Genetic subgroup | 2 (2.6) | 1 (50) | — | 1 (50) |
| | Renal and hepatic impairment | 1 (1.3) | — | 1 (100) | — |
| | Low body weight | 1 (1.3) | — | — | 1 (100) |
| | Subtotal | 77 (46.7) | 25 (32.5) | 20 (26) | 32 (41.6) |
| Extrinsic factors | Drug interaction | 42 (87.5) | 11 (26.2) | 7 (16.7) | 24 (57.1) |
| | Drug–drug interaction | 5 (10.4) | 4 (80) | — | 1 (20) |
| | Food effect | 1 (2.1) | — | 1 (100) | — |
| | Subtotal | 48 (29.1) | 15 (31.3) | 8 (16.7) | 25 (52.1) |
| Dosing variation | Evaluate safety and efficacy of lower dose(s) | 9 (31) | 2 (22.2) | 2 (22.2) | 5 (55.6) |
| | Evaluate alternative dose(s)/dosage(s) | 9 (31) | 6 (66.7) | 1 (11.1) | 2 (22.2) |
| | Inform dose modifications/monitoring | 8 (27.6) | 4 (50) | 4 (50) | — |
| | Inform long-term use/chronic administration | 2 (6.9) | 1 (50) | 1 (50) | — |
| | Determine if additional dosing trial needed | 1 (3.5) | 1 (100) | — | — |
| | Subtotal | 29 (17.6) | 14 (48.3) | 8 (27.6) | 7 (24.1) |
| Miscellaneous | Long-term follow-up | 5 (45.5) | 2 (40) | 2 (40) | 1 (20) |
| | QT/QTc assessment | 4 (36.4) | 3 (75) | — | 1 (25) |
| | Animal toxicology study | 2 (18.2) | 1 (50) | — | 1 (50) |
| | Subtotal | 11 (6.7) | 6 (36.4) | 2 (18.2) | 3 (27.3) |
| Total | | 165 | 60 (36.4) | 38 (23) | 67 (40.6) |

the final report due date indicated in the approval letter) and those focused on extrinsic factors had a median of 1.9 years to be completed (**Fig. 1**).

Dose variation PMRs (17.6%, 29/165) evaluated lower doses (31%, 9/29) or alternative doses/dosages (31%, 9/29), informed dose modifications and monitoring (27.6%, 8/29), dosing for long-term/chronic use (6.9%, 2/29), and helped collect data to determine whether an additional trial would be needed to inform dose optimization (3.5%, 1/29). We also found that several drugs (8/132, 6%) had a PMR to evaluate the safety or efficacy of a lower dose. In the past 3 years, FDA requested five PMRs to evaluate lower doses for 4 of the 46 (8.7%) drugs approved. In contrast, there were only 4 PMRs to evaluate lower doses for 4 of the 86 (4.7%) drugs approved in the prior 8-year period (**Fig. 2**). Dose variation PMRs took a median of 4.5 years to be completed, with PMRs to inform dose modifications and monitoring and investigate lower dosing taking the greatest amount of time at a median of 6.2 years and 5.0 years, respectively (**Fig. 1**).

The remaining 11 miscellaneous dosing PMRs consisted of long-term follow-up studies to characterize safety ($n = 5$), QT/QTc assessments ($n = 4$), and 2 animal toxicology studies (**Table 2**). These took a median of 2.6 years to be completed (**Fig. 1**).

## Discussion

For many oncology drugs, FDA uses PMRs as a tool to further inform safe and effective use of an approved drug, including the optimal dose(s). Traditionally, early-phase oncology clinical trials aimed to identify the maximum tolerated dose (MTD), a dose optimization strategy designed for cytotoxic chemotherapies with which increasing the dose is associated with increasing efficacy. Over the past decade, scientific advancements have led to more approvals of targeted therapies for which efficacy may plateau before reaching the MTD. As has previously been discussed, for these therapies a lower dose can provide the same efficacy with improved safety and tolerability profiles for patients (8).

As our analysis showed, most novel oncology approvals over the past decade have been targeted inhibitors for which FDA continues to emphasize that identification of the MTD is no longer adequate justification for having optimized the dose (9). We also found that more than half of all oncology drugs approved in the last decade had a PMR to further inform dosing (**Table 1**). In addition, we observed an increase in the proportion of approvals for mAbs/ADCs over time and found the percentage of these drugs with a dosing PMR increased six-fold during the 2020 to 2022 period compared with the preceding approval periods (**Table 1**). A prior analysis of small molecules and ADCs for oncologic indications approved 2019 to 2021 showed use of the MTD paradigm persists in the premarket setting (10). This coincided with an increase in PMRs intended to evaluate lower or alternative dosing regimens during the past 3 years (2020–2022), compared with the preceding 8 years combined (2012–2019; **Fig. 2**).

Dosing PMRs designed to evaluate a lower dose had a median of 5 years to be completed after approval and evaluations of alternative doses/dosages had a median of 4.2 years (**Fig. 1**). During this time, there is a risk of patients being exposed to suboptimal doses. Trial design and analytical methods to support timely identification of the optimal dose other than the MTD approach, is paramount given the length of time it takes to evaluate lower and alternative dose(s). Recent Oncologic Drugs Advisory Committee (ODAC) meetings focusing on a certain class of targeted therapies, Phosphoinositide 3-kinase (Pi3K) inhibitors, provide another example of challenges arising when pre-market dosing strategies fail to adequately optimize the dose and postmarketing trials designed to further inform dosing raise additional questions about safety and efficacy leading to withdrawal from the market (11).

Increased focus on dosages aligns with the OCE's recent efforts to reform approaches to dose optimization in oncology. In 2021, OCE launched Project Optimus, "an initiative to reform the dose

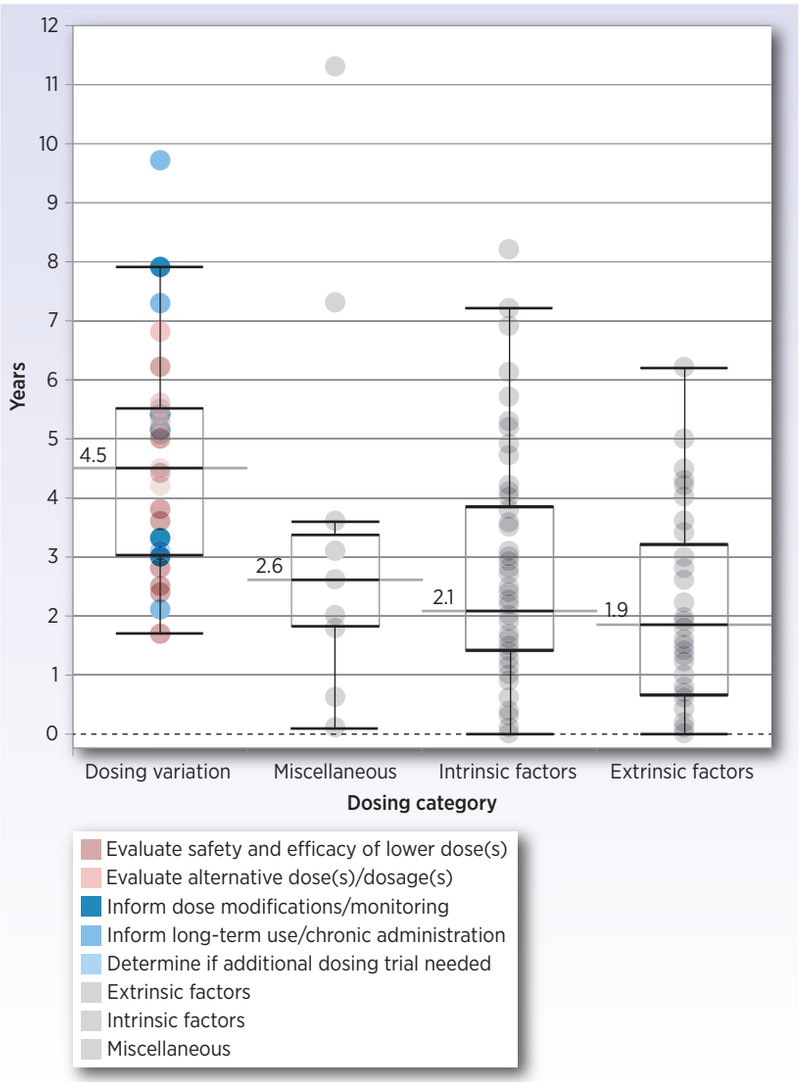


**Figure 1.**
Median time from approval to final report due date for dosing PMRs. Dosing variation PMRs have the longest median time to be completed (4.5 years from date of approval to final report due date).

optimization and dose selection paradigm in oncology drug development" (1, 8). As more of these targeted therapies are introduced, there will be a need to develop tailored dose optimization strategies that account for the nuances that exist between drugs and drug classes. As such, opportunities to adapt dosing strategies and identify appropriate flexibilities that enable timely identification of the optimal dose will be important.

## Moving Forward

PMRs are important tools that enable FDA to exercise regulatory flexibility and facilitate timely access to promising therapies, particularly for patients living with cancer. For oncology drugs approved over the past decade, FDA has frequently used PMRs to gain additional information about the optimal dose. The push for dose optimization of oncology drugs in the premarket setting is not a new concept; however, this analysis provides timely insights on the types of dosing activities FDA has requested in the postmarketing setting over the last decade which could identify areas where additional dosing information could be collected in the premarket setting. In addition, the analysis demonstrated certain dosing activities take longer to complete in the postmarketing setting than others. While PMRs remain an important tool for exercising regulatory flexibility, they may be more appropriate for dosing questions that can be efficiently answered. The dosing evaluations that take longer, such as the exploration of a range of lower doses, could be prioritized earlier in development to avoid exposing patients to potentially suboptimal doses. Leveraging scientific advances and innovative trial designs can help enhance dose optimization strategies and enable more efficient dosing studies in the premarket setting. For instance, the use of novel biomarkers, such as circulating tumor DNA (ctDNA), also holds promise by providing less invasive and real-time insights into tumor dynamics and treatment responses associated with different dosages. The 3+3 trial design is frequently used in early phase dose escalation studies for oncology drugs; however, other, more flexible trial designs could enable more dynamic adjustments to dosing regimens based on accumulating trial data and allow for quicker identification of the most effective doses (12). As we continue to advance our approaches for optimizing

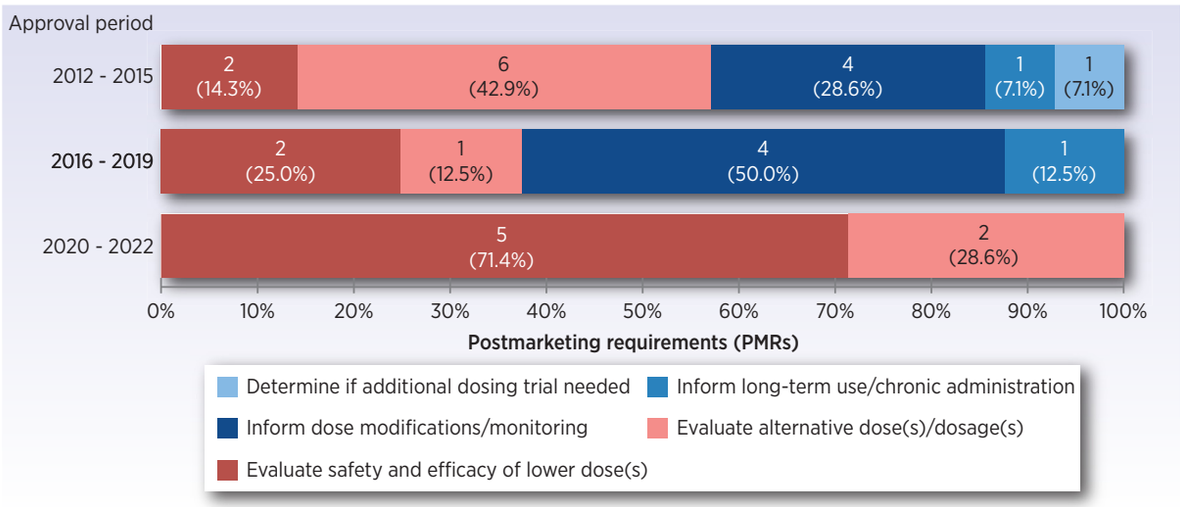


**Figure 2.**
Dosing variation PMRs by type of information over time. FDA issued more PMRs directing sponsors to evaluate a dose lower than the one approved in the last 3 years ($n = 5$, 2020–2022) compared with the preceding 8-year period ($n = 4$, 2012–2019).

dosage selection in oncology drug development, we should do so with the goal of bringing safer and more tolerable drugs to patients.

## Authors' Disclosures

No disclosures were reported.

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Received August 2, 2023; revised September 20, 2023; accepted October 19, 2023; published first December 12, 2023.

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