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Review Times For New Drugs And Submission Delays Among The FDA And 4 International Regulators, 2014–22

Abstract

Factors influencing the timing of regulatory submission across countries are poorly understood. We identified all new drugs approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) from 2014 to 2018 and tracked their regulatory submissions to the US, the European Union, Canada, Australia, and Japan through 2022. We assessed whether disease area, orphan status, therapeutic benefit, market size, and launch price were associated with submission delays. The FDA received the highest proportion of first submissions (70 percent). Median submission delays ranged from zero months (FDA) to 18.5 months (Australia). The range of median regulatory review times was small (9.2–14.1 months) compared with the range of median submission delays (0–18.5 months). Moderate- to high-value drugs were associated with a six-month earlier submission time compared with low-value drugs, on average. Higher-priced drugs were associated with earlier submission, on average. Overall, cross-country differences in drug availability largely reflected differences in submission, not regulatory review, times. Although the US had greater and faster availability of novel therapeutics, the difference was smaller for drugs that offered moderate to high therapeutic benefit.

In recent years, the Food and Drug Administration (FDA) has approved more new drugs each year than any other major regulatory agency, and has reviewed regulatory submissions quicker than either the European Medicines Agency (EMA) or Health Canada.[1–4] Drug companies have generally filed new drug applications with the FDA first.[3] In addition, many other countries have introduced health technology assessment bodies to inform pricing and coverage decisions, which may affect availability of new medicines in these jurisdictions.[5]

Earlier and broader access to drugs in the US may reflect differences in the timing of marketing authorization submissions. Expedited approval pathways, such as the FDA’s accelerated approval pathway, which allows marketing authorization based on surrogate endpoints, may incentivize earlier filing. Other regulators, such as the EMA, have introduced similar pathways more recently, but these vary in design, with some offering only time-limited approval.[6]

In contrast to the US, most other high-income countries have health technology assessment bodies that evaluate the added clinical benefit of new drugs compared with existing therapies. Products offering limited added value may face delayed reimbursement or denied coverage.[7–9] Some payers may also show greater willingness to cover drugs for specific conditions, such as cancers or rare diseases, through targeted funding mechanisms.

Although research suggests that pharmaceutical companies choose to launch later in countries with smaller markets[10] and stricter price controls,[11] few analyses have examined the timing of regulatory submission. An earlier study found that drugs are submitted to the US ahead of other markets, influencing how quickly they become

available in different jurisdictions.[3] Yet the relationship between key product characteristics and regulatory submission timing have not been systematically examined. Understanding whether submission delays are shorter for different types of drugs is important for understanding the potential effect of regulation on delays in availability.

This study examines regulatory submissions across the US, the European Union, Canada, Australia, and Japan from 2014 to 2022 to determine whether there is a relationship between submission delays for regulatory approval and key product characteristics: therapeutic value, orphan status, disease area (cancer versus noncancer), and launch price. We also provide updated estimates of regulatory review times for the FDA, EMA, Australian Therapeutic Goods Administration, Health Canada, and Japanese Pharmaceuticals and Medical Devices Agency.

Study Data And Methods

Sample Identification And Characteristics

Using publicly available data from Drugs@FDA and the European Public Assessment Reports database, we identified all new active substances approved between January 2014 and December 2018 by the FDA or the EMA. For the FDA, we included biologics license applications, type 1 new drug applications (new molecular entity), and type 1/4 new drug applications (new combination with at least one of the active moieties classified as a new molecular entity). Similar to another study,[12] we excluded vaccines, blood products, and cellular and gene therapies. For the EMA, we selected all drugs with a new active substance status.

Restricting the initial basket to the 2014–18 period allowed at least six years of follow-up data at the time of collection (until December 2022) to examine potential submission delays to other national agencies. We selected three additional regulators (the Australian Therapeutic Goods Administration, Health Canada, and the Japanese Pharmaceuticals and Medical Devices Agency) that are often compared with the FDA.[13–15] Three investigators independently determined whether and when each drug was authorized in each country, using the regulatory bodies' publicly available databases (for detailed sources of regulatory data, see exhibit A1 in the online appendix).[16]

Key Outcomes

For each regulator, we estimated four outcomes: number of drugs from the basket that were submitted to the regulatory agency during our study period; median submission delay in months, measured as the time from first submission to any regulator (among the included bodies); median regulatory review times, defined in months between the submission date and the approval date; and median time to marketing authorization (from FDA authorization). To compute these, we extracted the date of application submission and the date of approval (through December 31, 2022) for each product from the public websites of all five regulators, as outlined in appendix exhibit A1.[16]

Key Characteristics

To examine submission times by product type, we collected the following information: disease area (cancer versus noncancer), orphan status, therapeutic value

(moderate to high value versus low value), approval pathway (FDA accelerated approval versus nonaccelerated approval), market size, and launch price.

Information on disease area (cancer versus noncancer) was identified using the anatomical therapeutic chemical classification database. Orphan status was defined according to the FDA designation. In a sensitivity analysis, drugs designated as orphan by either the FDA or the EMA were categorized as such. Accelerated approval status was extracted from the FDA's Novel Drug Approvals annual publications.[17] Therapeutic value was assigned on the basis of therapeutic benefit scores from publicly available reports published by relevant authorities in Canada, France, and Germany. We defined moderate- to high-value drugs as those judged by at least one authority to provide moderate or greater added therapeutic benefit, consistent with previous studies;[18,19] for detailed drug category definitions, see exhibit A2 in the appendix.[16]

We obtained sales data for each drug (2014–22) from IQVIA's MIDAS database, and used these to compute the manufacturer launch price per dose in each setting. We then identified the launch price of the first submission across the regulatory agencies. For the EU, we used the median launch price across France, Germany, and the UK (which was an EU member for most of the study period). Using the IQVIA data, we also computed market size for each region as the total drug revenue during 2014–22. For the EMA, we used total revenue from all EU countries but Denmark (which was not included in the IQVIA data).

Statistical Analysis

Descriptive statistics were used to summarize our four main outcomes. All results were broken down by drug characteristic. We calculated Kaplan-Meier estimates of the

survival functions for each regulator to compare submission delays (time from when a drug was first submitted to any regulator in our sample to when it was submitted to another regulator). Log-rank tests were used to identify statistically significant differences between regulators.

To examine factors associated with submission delay, we used multivariate linear regression analysis. Our dependent variable was the drug-level delay in regulatory submission relative to the earliest submission made to any agency. Our independent variables were disease area (cancer versus noncancer), orphan status, therapeutic value, FDA accelerated approval pathway, market size, and launch price (in the jurisdiction where the first submission was filed). Launch prices were expressed in logarithmic terms (US dollars per standard unit). We reran the analysis for the subset of drugs that were first submitted to the US to better understand the factors related to US submission. For both models, we also included interaction terms between launch price and other characteristics (cancer, orphan, therapeutic value, and accelerated approval), as well an interaction between accelerated approval and cancer drug status.

There were incomplete data on submission dates to several regulators: the Australian Therapeutic Goods Administration had the most missing submissions (71 submission dates missing from the 151 approved drug files; 47 percent), followed by the Japanese Pharmaceuticals and Medical Devices Agency (9 dates from 119 files; 8 percent), Health Canada (7 dates from 171 files; 4 percent), and EMA (6 dates from 206 files; 3 percent). We ran all models with missing values for submission dates and conducted sensitivity analyses with imputed values. We estimated missing submission

dates by combining country-level average review times with each individual drug's standardized delays observed in other countries.

The study was exempt from institutional review board approval. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. All analyses were conducted using R (version 4.4.0) and Python (version 3.11.4).

Limitations

This study had limitations. First, the drug basket was restricted to drugs approved by the FDA or EMA. We did not include drugs that were only authorized in other countries. Other work has shown that the majority of drugs are submitted to the FDA and EMA, so it is unlikely that we had a large number of omissions.[1,18] Second, submission dates were missing for some regulators. We imputed values for these missing estimates based on the observed data to conduct sensitivity analyses, but this may have introduced bias if the missing data were systematically different. Third, our categorization of drugs by therapeutic value was based on value scores from Canadian, French, and German authorities, as outlined in the appendix.[16] We could not measure value for drugs that were not reviewed by one of these three agencies. Fourth, we used manufacturer launch list prices from IQVIA as a proxy for differences in price levels across countries. Although list prices are not the actual prices paid (after discounts and rebates), they signal the relative revenue potential of a drug, which may influence submission decisions. Fifth, the data reflect a basket of drugs that were approved between 2014 and 2018 with a follow-up through 2022. The results are not necessarily generalizable to more recent approvals, given changes to drug regulations in each

jurisdiction since 2019. Finally, given the study design, we cannot make any causal claims about the associations we observe.

Study Results

Sample Characteristics

From 2014 to 2018, 241 drugs were approved by the EMA or FDA. Of these, 237 (98 percent) were approved by the FDA and 206 (85 percent) by the EMA by the end of 2022. Fewer products were submitted to Health Canada (171, 71 percent), Australia's Therapeutic Goods Administration (151, 63 percent), and Japan's Pharmaceuticals and Medical Devices Agency (119, 49 percent) for review. Most new drugs were first submitted to the FDA (70 percent), followed by the EMA (27 percent), the Japanese Pharmaceuticals and Medical Devices Agency (7 percent), and Health Canada (1 percent). No drugs were submitted first to the Australian Therapeutic Goods Administration. Across regulators, few drugs were reviewed but not approved, ranging from 0 percent by the FDA to 2 percent by Japan's Pharmaceuticals and Medical Devices Agency (exhibit 1).

Although the majority of drugs in our study were submitted to the FDA before other regulators, the relative proportion submitted to the FDA first was greater for noncancer drugs compared with cancer drugs, nonorphan drugs compared with orphan drugs, low-value drugs compared with moderate- to high-value drugs, and accelerated approval drugs compared with nonaccelerated approval drugs (exhibit 1).

Time To Submission And Approval

Median submission delays ranged from zero months at the FDA to 18.5 months at Australia's Therapeutic Goods Administration. From 2014 to 2022, cancer drugs were

submitted for review more often than noncancer drugs at the EMA (93 percent versus 83 percent), Health Canada (90 percent versus 65 percent), Japan's Pharmaceuticals and Medical Devices Agency (61 percent versus 46 percent), and Australia's Therapeutic Goods Administration (83 percent versus 56 percent), whereas at the FDA, submission rates were the same (98 percent). Drugs with moderate to high therapeutic value had higher submission rates than those with low value at the EMA (98 percent versus 81 percent), Health Canada (94 percent versus 63 percent), the Japanese Pharmaceuticals and Medical Devices Agency (73 percent versus 41 percent), and the Australian Therapeutic Goods Administration (87 percent versus 54 percent). Submission rates for orphan versus nonorphan drugs, as well as for drugs with FDA accelerated approval versus nonaccelerated approval, were similar across agencies (exhibits 1 and 2).

Kaplan-Meier estimates of cumulative submissions, which account for censoring, show slightly different proportions than raw counts (see exhibit A3 in the appendix).[16] Our sensitivity analysis with imputed data for missing submission dates showed consistent results, with a slight improvement for Australia's Therapeutic Goods Administration in terms of the speed and number of submissions (see appendix exhibit A4).[16]

Median regulatory review times varied across agencies, ranging from 9.2 months at Japan's Pharmaceuticals and Medical Devices Agency to 14.1 months at the EMA, with the FDA's median at 9.6 months. All regulators had shorter review times for cancer drugs, moderate- to high-value drugs, and those receiving FDA accelerated approval, and all except the EMA had shorter times for orphan drugs. Median time to marketing

authorization by foreign regulators after FDA approval ranged from 5.2 months at the EMA to 11.9 months at Australia's Therapeutic Goods Administration. Across regulators, review and authorization times were generally shorter for drugs with higher therapeutic value and exhibited variation by other characteristics (exhibit 2).

Association Between Drug Characteristics And Submission Delays

Exhibit 3 indicates the characteristics associated with submission delays across countries. Relative to the FDA, there was a 1.5-month difference in submission delays for the EMA, on average. The average delay, relative to FDA submission, was approximately six months for submission to Health Canada, ten months for the Japanese Pharmaceuticals and Medical Devices Agency, and sixteen months for the Australian Therapeutic Goods Administration.

Several characteristics were associated with submission delays: market size, launch price, orphan drug status, and therapeutic value. Orphan drugs had average submission delays of four months compared with nonorphan drugs. Moderate- to high-value drugs were submitted for review approximately six months earlier, on average, compared with those with low therapeutic value. Every unit increase in the log manufacturer list price corresponded to an average reduction of approximately one month in submission delay, whereas every unit increase in log market size corresponded to an average reduction in submission delay of approximately two months.

We observed no meaningful differences in submission times between cancer and noncancer drugs or between drugs that received accelerated approval versus those that did not. When interaction terms were included, cancer drugs with accelerated approval

were associated with submission times that were, on average, about fourteen months later. Cancer drugs with higher launch prices and accelerated approval drugs with higher launch prices were associated with submission times that were, on average, about three months and five months longer, respectively (see appendix exhibit A5).[16]

Exhibit 4 presents results for drugs first submitted to the FDA, showing factors associated with submission delays to other regulators. For these drugs, average delays ranged from six months at the EMA to about fifteen months at the Australian Therapeutic Goods Administration. Greater market size was associated with shorter delays, and therapeutic value was meaningfully linked to submission time: moderate- to high-value drugs were submitted to other regulators, on average, about five months earlier than low-value drugs. In contrast, drugs with accelerated approval were submitted, on average, about seven months later, increasing to fourteen months for products also classified as cancer drugs. Launch price alone was not associated with delay, but in models that accounted for interaction effects, moderate- to high-value drugs with higher prices were submitted about two months earlier, whereas accelerated approval and orphan drugs with higher prices were submitted about two and six months later, respectively (see appendix exhibit A7).[16]

We ran sensitivity analyses for both models, using the imputed data to account for some of the missingness in submission dates, and our results were robust (see appendix exhibits A6 and A8).[16]

Discussion

On the basis of data for 241 products approved by the FDA and EMA between 2014 and 2018, we found that the FDA received more and earlier regulatory

submissions than four other regulators. Our analysis indicates that this pattern was most pronounced for drugs with low therapeutic value. For products with moderate to high therapeutic value or for cancer drugs, submission patterns across regulators were more similar.

These findings have important implications for policy makers in the US and elsewhere who are interested in understanding the factors that may influence the availability of novel therapeutics for their populations. In the US, brand-name drug manufacturers are allowed to set prices for products at launch. In all of the study countries outside the US, there is a health technology assessment body that evaluates the effectiveness or cost-effectiveness of new drugs compared with existing treatment options, and this information is used to inform price negotiations.[19,20] It is possible that these mechanisms may influence the decision of companies regarding whether and when to submit drugs with low therapeutic value to other regulators.

We also observed associations between launch price and submission delay, suggesting that revenue potential could be a factor companies weigh when determining submission timing and may potentially prioritize drugs with a higher initial launch price. Conversely, drugs for rare diseases were more likely to experience larger average delays, with the FDA and EMA being more likely to receive submissions for these products first. More research on this finding is needed to understand why delays occur for rare disease drugs and whether such delays are less prevalent in countries with specialized regulatory or health technology assessment processes for such drugs.[21]

We also examined the association between the FDA's accelerated approval pathway and submission delays. Given that the accelerated approval pathway allows

the FDA to approve certain drugs based on early evidence, it could encourage manufacturers to submit certain products to the US ahead of other countries. Although we did not find a significant relationship for all drugs, we did see longer average submission delays for cancer drugs with accelerated approval submitted to non-US countries. Other research has shown that accelerated approval has resulted in quicker review times since its introduction in 1992, particularly for cancer drugs in the US.[22] More recently, other countries have adopted similar pathways for cancer drugs,[6] possibly mitigating this delay in the future. Other efforts are also underway to ensure greater consistency in regulatory submission across, such as Project Orbis, in which participating regulators conduct independent assessments of new cancer drugs while sharing information.[23] Current partners include several agencies from our study countries, such as Australia and Canada.

We found that differences in the availability of new products were driven more by submission delays than by differences in review times. Regulatory review times were comparable across countries, with the US and Japan faster by about two to four months than other regulatory bodies, whereas the delay to submission to regulators outside the FDA and EMA was notably longer, averaging one to two years for Canada, Japan, and Australia.

Other factors that were not considered in this analysis could also be important in shaping submission decisions to national regulators, such as international reference pricing. Research suggests that international reference pricing can incentivize manufacturers to delay submissions in lower-priced markets to avoid triggering price erosion in referencing countries.[24] Strategic launch sequencing could help explain some

of the cross-country patterns we observe and is consistent with our findings on launch price.

This work builds on prior studies that have compared regulatory review times across countries,[1,3,15,25,26] which have found that FDA and EMA review times were comparable, but that new drugs were typically submitted to the FDA ahead of the EMA and other regulators, with updated data and new comparators.

Our study is the first to look at what factors are associated with timing of regulatory submissions. We found that delays are longer for low-value drugs, which may reflect deliberate policy choices to prioritize high-value products in settings outside the US. Greater and faster approval of low-value drugs in the US may help explain why a large share of Medicare drug expenditure is directed toward low-value drugs.[19]

Conclusion

In this study of new drug approvals by regulators in five high-income settings, variation in the availability of new medicines was more closely associated with differences in submission timing than in review durations. The US generally received submissions earlier than other regulators, particularly for drugs with low therapeutic value. For drugs with moderate to high therapeutic value, cancer drugs, and products with FDA accelerated approval, submission and review timelines across regulators were comparable. Across all settings, higher launch prices and larger markets were associated with shorter submission delays, whereas orphan drugs had longer delays outside the US.

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Exhibit List:

Exhibit 1 (table):

Exhibit 2 (table):

Exhibit 3 (figure):

Caption: Average drug regulatory submission delay in months, by drug characteristic, 2014–22

Sources/Notes: SOURCES Data compiled from FDA, European Medicines Agency (EMA), Health Canada (HC), Australian Therapeutic Goods Administration (TGA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) websites and databases. Price information obtained from IQVIA MIDAS. NOTES The reference groups for each variable are the FDA, noncancer drugs, nonorphan rugs, low-value drugs, and non-accelerated approval pathway, respectively. Launch price is a continuous variable, and the coefficient indicates the number of months' submission delay associated with a unit increase in log launch price. Market size is a continuous variable, and the coefficient indicates the number of months' submission delay associated with a unit increase in total drug revenue for each region.

Exhibit 4 (figure):

Caption: Average drug regulatory submission delay in months by drug characteristic, for drugs submitted to the Food and Drug Administration (FDA) first, 2014–22

Sources/Notes: SOURCES Data compiled from FDA, European Medicines Agency (EMA), Health Canada (HC), Australian Therapeutic Goods Administration (TGA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) websites and databases. Price information obtained from IQVIA MIDAS. NOTES The reference

groups for each variable are the FDA, noncancer drugs, nonorphan drugs, low-value drugs, and non-accelerated approval pathway, respectively. Launch price is a continuous variable, and the coefficient indicates the number of months' submission delay associated with a unit increase in log launch price. Market size is a continuous variable, and the coefficient indicates the number of months' submission delay associated with a unit increase in total drug revenue for each region.

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Exhibits

Exhibit 1: Drug regulatory submission by country and drug characteristic, 2014–22

Regulatory Submissions	FDA (%)	EMA (%)	HC (%)	PMDA (%)	TGA (%)
All drugs (241, 100%)[a]					
Drugs reviewed	98	85	71	49	63
First submission	70	27	1	7	0
Drugs reviewed but not approved	0	2	1	0	1
Disease area					
Cancer (59, 24%)[a]					
Drugs reviewed	98	93	90	61	83
First submission	16	7	0	2	0
Drugs reviewed but not approved	0	0	2	0	0
Noncancer (182, 76%)[a]					
Drugs reviewed	98	83	65	46	56
First submission	54	20	0	5	0
Drugs reviewed but not approved	0	3	1	0	1
Orphan status					
Orphan (111, 46%)[a]					
Drugs reviewed	100	86	72	50	64
First submission	30	15	0	3	0
Drugs reviewed but not approved	0	2	1	0	0
Nonorphan (130, 54%)[a]					
Drugs reviewed	97	85	70	48	62
First submission	39	12	0	4	0
Drugs reviewed but not approved	0	2	1	0	1
Therapeutic value					
High to moderate (62, 26%)[a]					
Drugs reviewed	98	98	94	73	87
First submission	16	9	1	2	0
Drugs reviewed but not approved	0	0	0	0	0
Low (179, 74%)					
Drugs reviewed	98	81	63	41	54
First submission	54	18	0	5	0
Drugs reviewed but not approved	0	3	2	0	1
Approval pathway					
Accelerated (33, 14%)[a]					
Drugs reviewed	100	88	79	58	76
First submission	11	2	0	1	0
Drugs reviewed but not approved	0	3	4	0	0
Non-accelerated (208, 86%)[a]					
Drugs reviewed	98	85	70	48	61
First submission	59	25	1	6	0
Drugs reviewed but not approved	0	2	1	0	1

SOURCE Data compiled from Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada (HC), Australian Therapeutic Goods Administration (TGA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) websites and databases. NOTES [a]Numbers in parentheses are the total

number of regulatory submissions for the named category and the percentage of the total for all drugs (*N*=241).

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Exhibit 2: Time to regulatory submission and market authorization by regulatory agency and drug characteristic, 2014–22

Time to submission, review, and approval by cohort	Media time (months)				
	FDA	EMA	HC	PMDA	TGA
All drugs					
Delay from the first submission	0.0	0.6	7.9	9.6	18.5
Regulatory review time	9.6	14.1	11.4	9.2	11.6
Time to market authorization from FDA approval	—[a]	5.2	9.6	8.4	11.9
Disease area					
Cancer					
Delay from the first submission	0.0	0.9	8.0	10.5	17.1
Regulatory review time	6.9	13.9	10.8	9.0	11.3
Time to market authorization from FDA approval	—[a]	7.7	11.3	12.5	15.0
Noncancer					
Delay from the first submission	0.0	0.5	7.8	8.4	21.6
Regulatory review time	10.9	14.5	11.5	9.8	11.6
Time to market authorization from FDA approval	—[a]	3.0	8.5	7.3	8.0
Orphan status					
Orphan					
Delay from the first submission	0.0	0.6	11.3	9.7	19.2
Regulatory review time	8.0	14.1	10.3	8.7	11.0
Time to market authorization from FDA approval	—[a]	5.5	9.9	6.8	12.7
Nonorphan					
Delay from the first submission	0.0	0.6	5.6	9.1	16.0
Regulatory review time	11.3	14.1	11.7	10.9	11.7
Time to market authorization from FDA approval	—[a]	4.6	9.1	9.0	7.8
Therapeutic value					
High to moderate					
Delay from the first submission	0.0	0.6	5.8	9.8	8.1
Regulatory review time	8.0	12.7	10.2	9.0	11.5
Time to market authorization from FDA approval	—[a]	4.2	6.9	9.0	9.4
Low					
Delay from the first submission	0.0	0.6	14.8	8.8	24.3
Regulatory review time	10.4	14.8	11.5	9.6	11.6
Time to market authorization from FDA approval	—[a]	5.5	12.7	7.3	13.3
Approval pathway					
Accelerated					
Delay from the first submission	0.0	3.2	6.0	15.3	14.6
Regulatory review time	6.6	13.1	9.5	9.0	11.3
Time to market authorization from FDA approval	—[a]	10.1	9.6	20.1	15.1
Non-accelerated					
Delay from the first submission	0.0	0.5	8.0	8.3	21.6
Regulatory review time	10.6	14.3	11.5	9.3	11.6
Time to market authorization from FDA approval	—[a]	4.4	9.6	7.4	9.9

SOURCE Data compiled from Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada (HC), Australian Therapeutic Goods Administration (TGA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) websites and databases. NOTES [a]Not applicable.

Acknowledgment

The authors acknowledge receiving funding from the Commonwealth Fund. To access the authors’ disclosures, click on the Details tab of the article online.BIOS for 2025-00595 (Papanicolas)

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