Xeljanz, the FDA, and nine years of patient harm

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An example of regulatory delay in the face of pressing safety concerns: Pfizer's Xeljanz

The FDA regulatory history of Pfizer's drug Xeljanz provides an opportunity to examine the mounting toll of harms occurring over the alarmingly long period that it took the agency to resolve important safety questions surrounding the therapy. To review, Xeljanz was approved in November 2012, under a cloud of concerning data suggested the drug caused increased risk of developing cancer, cardiovascular events, and serious infection. Nine years later, in December 2021, the FDA finally narrowed the product's label and added additional warnings regarding the risks that were suspected at approval as well as additional risks that were uncovered while the drug was being sold.

This nearly nine-year span was primarily consumed by the post approval safety study the company was required to conduct when the drug was approved – a study that confirmed that Xeljanz increased a patient's risk of cancer, major cardiovascular events, and death while providing no better efficacy than safer alternative treatments. One key reason why the study took so long to complete is that it included five years of follow-up. That time horizon, however, bore no relation to the time it took to originally observe Xeljanz' safety problems. In the handful of studies that the sponsor submitted for FDA approval, the maximum follow-up time was: six months for four studies (NCT00550446, NCT00413660, NCT00814307, NCT00960440), one year for two studies (NCT00856544, NCT00853385), and two years for one study (NCT00847613). The average weighted follow-up time across these studies was only 11.6 months, less than one-fifth the follow up time of the post approval study.

There were other major delays along the way (Table 1). The FDA allowed Pfizer 16 months to design and launch its safety study. It also endorsed Pfizer's proposed and ultimately underpowered sample size, which led to a delay that further lengthened the study by 7 months. Another six months were consumed by data analysis and release of the study results. Then there was a 7 month lag before the FDA required a updated warnings on the product's label and 2 additional months before the warnings were actually added. Along the way, the FDA lifted the drug's REMS requirement and granted the drug three additional indications (psoriatic arthritis, ulcerative colitis, polyarticular course juvenile idiopathic arthritis). Each of these regulatory actions served to increase the number of patients exposed to Xeljanz even though the drug was suspected to cause harm to patients.

A means of estimating the human consequences of regulatory delays

The agency might have acted more quickly if it were monitoring the harms Xeljanz was likely causing as Pfizer dragged out the safety assessment. The attributable risk calculation is one means that the FDA could do so, as the calculation only requires estimates of: a) the baseline risk of the safety event in the patient population in the absence of the treatment; b) the anticipated relative risk of the safety event in the presence of the treatment; c) the number of patient-years of treatment exposure. In the case of Xeljanz, the risk estimates are available from the sponsor's post-approval safety study posted on ClinicalTrials.gov and cited in both the sponsor's press release and in the FDA's drug safety communication. Estimates of these risks were available to the agency at

the time of approval as well. Person-years of exposure to Xeljanz could be reported by the company to the agency in nearly real time as companies meticulously track prescriptions of high revenue drugs. The aggregate harms from the drug can also be assessed indirectly by dividing reported Xeljanz sales by the average price of Xeljanz – a number available from SSR Health pricing data (Table 2).

Combining this information yields estimated counts of the additional adverse events experienced by patients treated with Xeljanz compared to other popular rheumatoid arthritis treatments for each year following the drug's approval (Table 3), and those data are combined with the timeline of regulatory events in Figure 1. Between November 2012 and December 2021, approximately 897 additional individuals were diagnosed with a malignancy due to receiving Xeljanz rather than another equally effective treatment. Roughly 436 people died unnecessarily, 466 experienced avoidable major adverse cardiovascular events and 429 experienced other types of cardiovascular events. These all occurred during the prolonged evaluation of Xeljanz's safety questions, which took more than nine times as long (108 months) as it did to for them to become apparent in the studies that formed the basis of Xeljanz' initial approval (11.6 months).

In fact, this analysis may underestimate the number of people who were harmed over this time period. The baseline risk of these events in 'real world' Xeljanz patients is likely greater than that for the subjects in the safety study, as clinical trials almost uniformly enroll subjects who are healthier than the population who is ultimately prescribed the product. If the baseline risk is too low, then the absolute number of additional events due to Xeljanz will also be too low. The number of people exposed is also underestimated, as it is based on sales data. Patients who received free Xeljanz through a patient assistance program were not tallied. The calculations do depend on an assumption that risk is constant over time, which is reasonably robust and could be checked by the FDA or Pfizer now that the safety study is completed.

Table 1. Timeline from FDA approval to FDA action on Xeljanz safety concerns

Date	Actions
November 6, 2012	• FDA approval for Xeljanz in rheumatoid arthritis • Boxed warning added to FDA label for serious infections and malignancy • Risk evaluation and mitigation strategy (REMS) required to ensure the benefits of the drug outweigh the risks of serious infections, tuberculosis, malignancy, increase in cholesterol, and decrease in blood counts. The REMS consists of a Medication Guide, communication plan, and submission of REMS assessments at 18 months, 3 years, and 7 years from the date of approval. • Post-marketing study required to evaluate the long-term safety of Xeljanz in patients with rheumatoid arthritis. The trial should include two doses of Xeljanz and an active comparator and be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy. Original trial schedule: Final Protocol Submission: March 2013 Trial Completion: December 2019 Final Report Submission: June 2020
March 14, 2014	• Post-marketing study started
May 5, 2014	• Pfizer submitted its 18-month REMS assessment. Pfizer proposed eliminating the Medication Guide requirement as an element of the REMS.
February 11, 2015	• FDA agreed to drop the Medication Guide requirement as an element of the REMS
November 6, 2015	• Pfizer submitted its 3-year REMS assessment and proposed eliminating the REMS requirement because the communication plan had been completed and met its goals
February 8, 2016	• FDA releases Pfizer from REMS requirement
December 14, 2017	• FDA approval for Xeljanz in psoriatic arthritis
May 30, 2018	• FDA approval for Xeljanz in ulcerative colitis
July 25, 2019	• Boxed warning expanded to include mortality and thrombosis
December 2019	• Expected completion date of post-marketing study. Study completion was delayed due to lower-than-expected rates of malignancy and cardiovascular events.
July 22, 2020	• Post-marketing study completed
September 25, 2020	• FDA approval for Xeljanz in polyarticular course juvenile idiopathic arthritis
January 27, 2021	• Pfizer shared co-primary endpoint results from post-marketing study in subjects with rheumatoid arthritis
September 1, 2021	• FDA required revisions to Xeljanz's boxed warning to include new and updated information about the risks of serious heart-related events, cancer, blood clots, and death based on review of post-marketing study.
December 2, 2021	• Boxed warning expanded to include new and updated information about the risks of serious heart-related events, cancer, blood clots, and death in response to FDA requirement

Table 2. Person-years of exposure to Xeljanz

Year	US Revenue for Xeljanz, Millions	SSR Health Net Price Per Tablet (5mg or 10mg) [a]	Yearly cost of Xeljanz (5 mg or 10mg BID)	Person-years of Xeljanz
2012	$6	$31	$22,871	262
2013	$112	$32	$23,097	4,849
2014	$289	$37	$26,747	10,805
2015	$470	$50	$36,653	12,823
2016	$805	$56	$40,938	19,664
2017	$1,133	$59	$43,121	26,275
2018	$1,394	$53	$38,982	35,760
2019	$1,636	$46	$33,230	49,233
2020	$1,706	$47	$34,493	49,460
2021[b]	$1,384	$47	$34,493	40,125

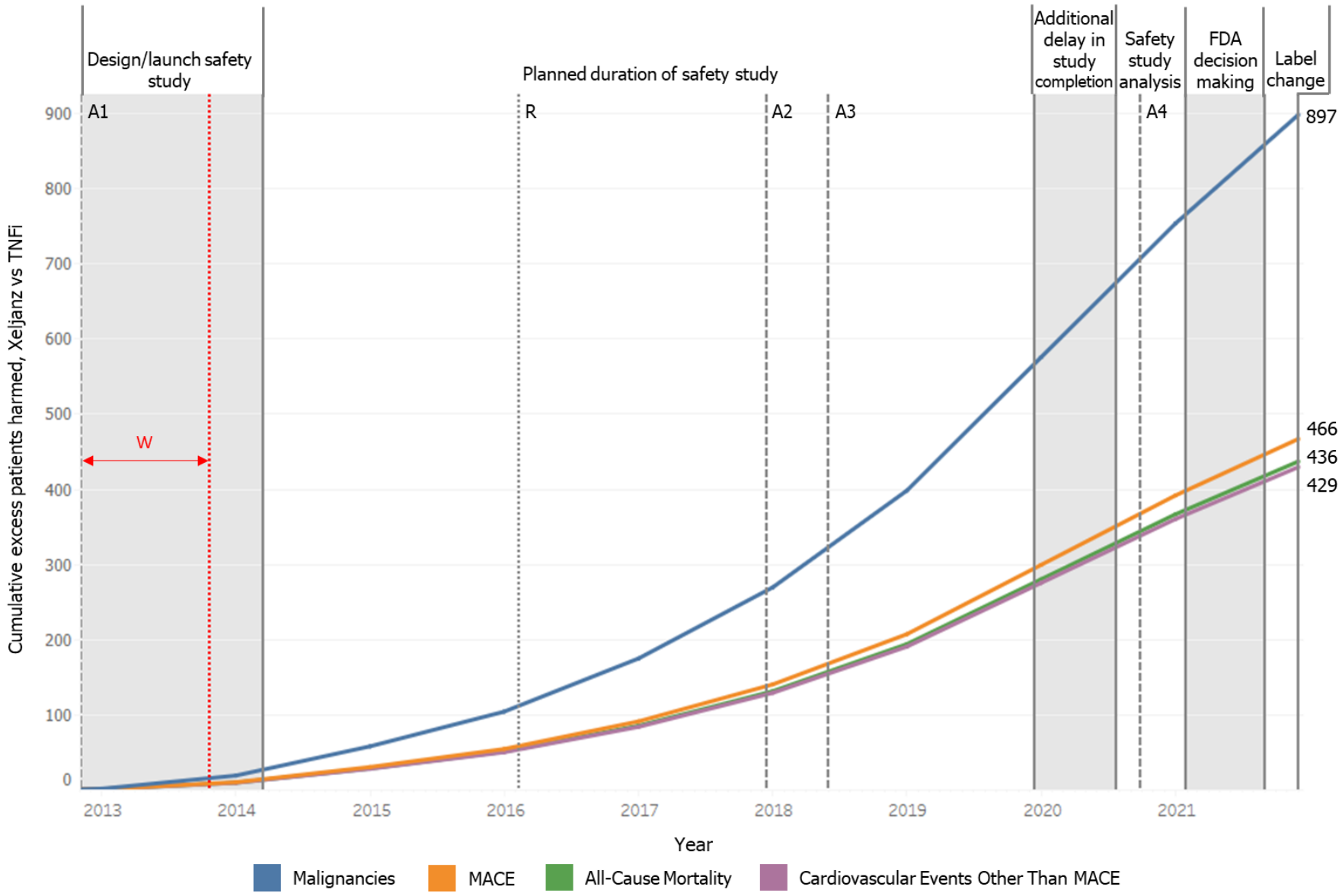
[a] SSR *Health net price extracted for Q4 of each year*
[b] *Estimates were extrapolated through December 2nd assuming a constant rate of revenue in 2021 based on Pfizer's quarter 3 earnings report. Net prices based on 2020 Q4.*

Table 3. Person-years of exposure to Xeljanz

	All-Cause Mortality	Malignancies[a]	Major Adverse Cardiovascular Events (MACE)[b]	Cardiovascular Events Other Than MACE
Risk[c]				
Baseline risk per 100 person-years	0.34	0.77	0.73	1.05
Relative risk	1.51	1.47	1.26	1.16
Year				
2012	0.5	0.9	0.5	0.5
2013	8.5	17.5	9.1	8.3
2014	18.9	38.9	20.2	18.6
2015	22.4	46.2	24.0	22.1
2016	34.4	70.8	36.8	33.8
2017	46.0	94.6	49.1	45.2
2018	62.6	128.7	66.9	61.5
2019	86.2	177.2	92.1	84.7
2020	86.6	178.1	92.5	85.1
2021[d]	70.2	144.4	75.0	69.0
Total Excess Events	436.2	897.3	466.1	428.7

[a] *Excludes non-melanoma skin cancers*
[b] *Includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke of any classification*
[c] *Incidence rate of adverse events, defined as the number of events per 100 person-years, were pulled from Xeljanz's post-marketing study results (NCT02092467). We assumed 95% percent of the Xeljanz population received 5mg BID and 5% received 10mg BID at a constant rate, based on Pfizer estimates.*
[d] *U.S. revenues used to calculate person-years was extrapolated through December 2nd assuming a constant rate of revenue in 2021 based on Pfizer's quarter 3 earnings report. Net prices based on 2020 Q4.*

Figure 1. Cumulative excess patient harms, Xeljanz vs TNFi, November 6, 2012 – December 2, 2021



Too slow on safety: Xeljanz, the FDA, and nine years of patient harm

Key events:

FDA approvals for Xeljanz:

A1: rheumatoid arthritis, November 2012
A2: psoriatic arthritis, December 2017
A3: ulcerative colitis, May 2018
A4: juvenile idiopathic arthritis, September 2020

R: REMS requirement dropped, February 2016
W: Weighted average time for safety signals to emerge from pre-approval studies, 11.6 months

Note: The malignancies category excludes non-melanoma skin cancers. The major adverse cardiovascular events (MACE) category includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke of any classification.