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Internal Deadlines, Drug Approvals, and Safety Problems

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Our research documents a global surge in drug approvals preceding informal deadlines. These include spikes in December, at the end of each calendar month, and just before important national holidays in respective countries. The magnitude of these effects is striking: for instance, across a data set recording drug approvals in the United States, European Union (EU), Japan, China, and South Korea, 18.64 percent of all approved drugs are approved in December—more than double the average in any other month. Moreover, we examine the safety ramifications of these approval surges. When we hold disease type, year, and various other controls as constant, drugs approved just before informal deadlines are associated with significantly more adverse effects, including more hospitalizations, life-threatening incidents, and deaths.

The approval patterns we observe exist at periodicities consistent with regulators rushing to meet internally imposed benchmarks associated with calendar events such as year-ends, month-ends, and holidays. In particular, while evidence has shown that drug regulators rush to meet formal deadlines in the United States, we identify a distinct behavioral phenomenon that persists across different formal regulatory regimes in many countries. For example, drug regulators are not formally evaluated on their year-end output in any country that we are aware of; rather, they are typically given target times for processing applicants and evaluated in part based on the percentage of applications that receive a timely review. These specific targets differ across regulators in different countries (within 300 days in the United States versus 210 days in the EU, for instance). Rushing to comply with these formal policies would not generate the pattern of year-end, month-end, and holiday surges that we document.

We argue, instead, that these patterns indicate that regulators use salient calendar periods to clear their workloads so that they can start with a "clean desk" in the next period. We show that, consistent with this interpretation, regulators approve an especially large number of drugs in December in years when they have approved relatively few drugs in the first part of the year. Moreover, December drugs approved during these especially busy months are associated with even more adverse effects. This suggests that regulators engage in hastier desk clearing either when their workload is high (e.g., when there are more drug candidates left to be decided upon in December) or when they feel greater informal pressure to increase output (e.g., when their approval numbers look low leading into December).

There are a number of alternative explanations; however, we provide evidence that our findings are not driven by any of them. First, it is possible that regulatory bodies may evaluate different types of drugs in December or at the end of each month. Regulators may, for instance, collect their most complex cases throughout the year or month to be considered at the end of that period. In this case, the higher adverse

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effects that we see for drugs approved during these periods would reflect the nature of the drugs themselves rather than the quality of the decisionmaking process that led to their approval. To explore this possibility, we examine whether there are ex ante divergences among drugs approved during output surges that may explain their ex post differences in adverse effects. We show that controlling for a battery of drug characteristics—the disease a drug is meant to treat, its market size, and its priority review status—does not alter our findings, suggesting that our results are not driven by differences on these dimensions. We further show that drugs approved in December do not appear to be more complicated or difficult to review, as explicitly measured by their chemical or functional novelty.

It is also possible that firms time application submissions in the hopes of receiving a lax December review. Using information on application dates available for a subset of U.S. drugs, we find no evidence that the December effect is generated by strategic timing, which would generate a surge of applications in February (for regular review) or a surge in June (for priority review).

If regulators make rushed decisions to meet internal deadlines, a natural question is why they seem to err on the side of approval rather than rejection. We believe that this may be the result of informal performance benchmarks that focus on the quantity of drugs that are approved rather than the quality of those decisions. The number of drugs that are approved is immediately visible and is likely to be much more salient than an approved drug's adverse effects, which may take years to be realized. Indeed, in the public discourse, drug regulators around the world are evaluated and compared on the basis of their drug output. This, combined with the fact that industry and patient groups typically advocate for the approval rather than rejection of new drugs, may bias regulators toward approval.

Finally, we consider the policy implications of our findings. First, we note that the welfare implications of our findings are unclear. One possibility, of course, is that a rushed review process decreases public welfare by increasing the likelihood that dangerous drugs enter the market. However, if regulators were generally too conservative in new drug approvals, then rushed review could actually improve welfare—even given an increase in adverse effects—because it would move the review standard closer to first best. Because we cannot observe the benefits that accrue to patients who are administered these drugs, our analysis cannot distinguish between these two possibilities. That said, we do perform a back-of-the-envelope estimation to get a sense of the magnitude of the costs associated with this pattern of rushed review. Our calculation suggests that between 1,400 and 9,000 lives are lost per year to rushed review; given a low-end estimate of the value of a statistical life ($885,000 per life), this works out to between roughly $1.2 and $8 billion of implied loss per year over our sample period. That said, even if a drug-approval agency were broadly too conservative in its approval decisions across all drugs, an optimal policy response would not be to apply more-lax screening only to those drugs nearing approval at the end of the year or month. We outline two potential policy responses, one based on a mandated smoothing of approvals over time, and another based on using a "holding tank" mechanism in which some drugs approved during high-volume periods are slated for re-review prior to receiving a final go-ahead. These behavioral responses to informal deadlines—precisely because they are not generated by any specific administrative policy—are a robust worldwide phenomenon. Such patterns highlight the importance of developing policy responses to address non-policy-induced inefficiencies in behavior.

NOTE:

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