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From Alex To – LLY/INCY: FDA Briefing Document Hints Lilly Has Upset the Agency

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- Briefing documents for next Monday's advisory committee meeting on baricitinib were out this morning. In an unusual move, the FDA included much of the internal communication throughout the review process in the briefing doc. Therefore, we could glean much more color on the interaction between the sponsor and the agency than what we usually get. It almost reads like the latest expose tomes, the fashionable genre of late. It is not as amusing a read as the Wolff book; but it was definitely more readable than the Comey book. It was a treat to those of us accustomed to speed-read mind bogglingly boring AdComm briefing docs month after month.

- In a nut shell: Lilly pissed off the FDA reviewers. Lilly really, we mean really, pissed them off. Here is a chronicle from what we can glean. The initial review was not favorable, with some nitpicking on the safety issues, on which we will comment later. It may have stemmed from some friction between the two parties from get-go. Towards the end of the original review cycle, the review team recommendation to the division chief was to approve the baricitinib 2 mg dose with a box warning, and not to approve the 4 mg dose. Lilly pushed back hard, because it needed the 4 mg dose to market the drug as superior to Humira. The reviewers were unhappy with Lilly's pushback, and wrote another memo to the division chief, saying "Oops, we changed our mind. Let's not approve the drug at all." Hence, the complete response letter. Lilly resubmitted the application. Now the review team is saying Lilly didn't really address their concerns. So, now they go in front of the advisory panel.

- Lilly had originally wanted the 4 mg to be the recommended dose. Again, this is so they can claim superiority to Humira. The FDA thinks there are more side effects in the 4 mg than the 2 mg dose. This is true. However, in the absolute terms, most of the adverse event issues the agency raised are not exactly reasonable; so, this implied some underlying rancor. For example, in the original submission, the malignancy rate for baricitinib 4 mg was 0.66% per patient year. The rate for placebo was 0.49% per patient year. To put this into proper perspective, if one picks 151 adults at random from the street, the chance that 1 of them will be diagnosed with cancer within a year is perfectly reasonable. This is not even taking into account the fact that people with rheumatoid arthritis have a higher incidence of cancer. There were no signs of cumulative malignancy risk as there were in Xeljanz's initial review. There was no cluster of specific cancer types, which further argues that there is no drug-related malignancy risk. And, in the resubmission, there was only 1 arguably new case of malignancy. In this case, a patient randomized to placebo group was switched to baricitinib on Day 168. 120 days after the switch

the patient was diagnosed with lung cancer. But, we would wager that no drug could cause lung cancer in merely 120 days, not even the most carcinogenic ones.

- One legitimate concern is the thrombotic events. That could potentially be related to JAK inhibition, as the mechanism does affect platelets.

- The outcome of the AdComm meeting next Monday will depend on if the FDA reviewers will go all out to influence the panel members against approval. Usually in a public forum, the agency workers will be more restrained, especially against a large pharmaceutical company. There will be concerns for potential litigation, considering some of the objections may not stand up to cross examination in court.

- For Lilly, however, the question is whether the bad blood will affect its future interactions with the arthritis reviewers. Not only will these people be reviewing related future baricitinib label expansions, assuming the drug gets approved this time; they could also be involved with reviews of Lilly's other rheumatology drugs, such as Taltz and IL-23.