In My View

BY JAN M. BULT, PPTA PRESIDENT & CEO

I will give you an example how (political) decision-making can have a serious impact on patient access to care; this time I will talk about the European rule for chemical compounds—REACH, which stands for Registration, Evaluation, and Authorization of Chemicals. The goal of REACH is to ensure a high level of safety for humans and the environment at both the production and consumer level. The rule applies for chemicals produced in or imported into the EU and exceeding a volume of 1,000 kg.

Currently, there are 12 chemicals that will be affected by this rule. One of them is 2-[4-(2,4,4-trimethylpentan-2-yl) phenoxy]ethanol (Triton-X 100), in short Triton. Triton is a crucial agent in viral inactivation processes—it's widely available, well-tested, and applicable for a range of different and sensitive proteins, with a very high margin of safety.

The European Commission proposal introduces strict control as of 2018 with a sunset in 2020. It is always mindboggling to me that rules are developed without thinking through what the impact is beyond the goals that are supposed to be accomplished. I will try to explain what is going on here.

Everyone involved in our industry and the users of the therapies that are being manufactured knows that the differentiating factor between the therapies is the manufacturing process. The smallest change can make a difference in efficacy or tolerance of the therapy. For that reason, therapies are different and in many cases non-interchangeable. Though not all manufacturers use Triton, it is too simple to think that it just should be replaced. There are problems with that, as a matter of fact the impact of this ban is enormous.

From 2020 onwards, the affected companies have to file a lot of documentation to seek permission to use Triton under REACH and there is no guarantee that the permission will be granted. If no permission is obtained, the manufacturers have to change each process for each protein affected and each manufacturing step that involves the use of Triton. Each of these steps require again a separate permission. Again, there is no guarantee that the permission will be granted.

If the permission is not granted, then the entire processes need to be re-developed! That includes efficiency of viral inactivation, checking the biological properties of the protein, yield, purity, and effect on patients, and can even include the need for new clinical trials in a rare disease patient population. Because of the small numbers of patients, it is already difficult enough to conduct clinical trials for new plasma protein therapies that are entering the market. All this work on potential alternatives has to be done within very short timelines.

Despite the extensive outreach to various organizations—like the European Medicines Agency, World Health Organization, European Commission, Association of British Pharmaceuticals Industries, UK Office of Life Sciences, Members of the European Parliament, members of the REACH committee and including non-member manufacturers, such as the International Plasma Fractionation Association, as well as patients groups—there was a disappointing outcome.

On March 23, 2017 the European Parliament ratified the REACH vote. This means that Triton needs to be authorized and will be phased out after 2020 unless specific authorization can be obtained. I am extremely puzzled by this for various reasons:

- Nowhere has there been any mention of the impact on the manufacturing of live-saving therapies when (unnecessary) alternatives have to be developed under extreme time-pressure. In fact, PPTA has extensively advocated to conduct impact assessment prior to the REACH vote and the decision in the European Parliament, however, this has not been considered by the European Commission.

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- The ban only affects industry (i.e., not academia) where every drop of used Triton needs to be accounted under robust control mechanisms.
- The main concern of Triton is its effects when degrading and presence in groundwater. It is incomprehensible that no assessment of the current level of Triton in European groundwater and control mechanisms used by the companies have been done or requested by regulators.
- The ban does not affect academia where controls are unlikely to be as robust as in our industry. So, when exemptions are possible, why not for this industry?
- When a suggestion was made to remove Triton from the list of 12, the response was that this may lead to other exemptions. So what, there is also an exemption for use by academia?
- The vote in the European Parliament was following party lines.

I have always thought that members of the European Parliament (MEP) who vote must be able to do that by weighing the arguments and thinking about the ramifications of unintended consequences. The best solution would be to have an exemption for the use of Triton in the manufacture of plasma protein therapies, the second best is to have a sunset date that allows for more time to develop alternatives.

I understand that MEP's need time to study all effects. I know that they have a busy agenda and have to deal with many other issues. I have a suggestion that may result in having more time that can be devoted on important issues.

Why not make a serious effort to stop the monthly traveling between Brussels and Strasbourg? Every month the entire Parliament moves from Brussels to Strasbourg for one week and moves back again. Month after month. This requires all 750 MEP's to travel to and stay in Strasbourg for one week, thousands of boxes with documents have to be packed and unpacked. Separate trains are used as people movers and many trucks are packed and become document movers. All of this is done at the expense taxpayers and costs far more than 100 million euros per year. You may think what this has to do with the main topic? Well, here is an obvious excessive spending that cannot be stopped for political reasons and there is no political will to do something about it. At the same time, there seems to be enough political will to come down on a part of the industry that is very responsible with all the agents they use to manufacture safe lifesaving therapies. This does not seem right to me.

There is something else. The rule to ban Triton only applies to Europe. This means that there is no issue when Triton is used in other parts of the world. If you think that production can just be moved to avoid the problem, this is not true because of multiple reasons:

- Not all manufacturers have plants outside of Europe. There is a risk that some manufacturers may be forced to stop production.
- Several licenses are linked to one manufacturing site; therapies produced in another site (even with the same technology) then cannot be used.
- This ban moves us further away from regulatory harmonization.

I urge the policymakers to reconsider this ban. •

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