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Notification commented on:

Draft Commission Regulation amending Annex XIV to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

G/TBT/N/EU/407

Issue Statement:

We urge WTO members to call on the Commission to now do a benefit/risk management assessment on Triton X-100 use in relation to biopharmaceuticals and public health, prior to any decision by the REACH Committee. Triton X-100 is the only substance of the 12 in this proposal which hasn't been the object of a call for socio-economic information by the Commission.

Supporting Rationale:

Eli Lilly and Company (Lilly) welcomes this WTO technical barriers to trade consultation opportunity. We address our comments specifically to 4-(1,1,3,3-Tetramethylbutyl)phenol , ethoxylated (Triton X-100). Pathogen safety is of upmost importance for biopharmaceuticals. Triton X-100 is the 'gold standard' pathogen inactivation method, referenced in WHO and EMA guidance as a viral inactivation agent. For 30+ years it has been robust and effective for viral inactivation, and is widely used in biologics that potentially treat millions of EU and U.S. patients with conditions like Alzheimer's, cancer and diabetes. Its continued use is essential for patient safety and to safeguard against emerging viruses.

In the parallel European Commission process in the EU, their public consultation closed on 14 October, with 38 complete responses (limited to 4,000 characters). **Of the 12 substances consulted on, half of the responses referred solely to Triton X-100**. This focus on Triton X-100 demonstrates a very strong concern over the impact this decision would have on the biopharma industry in the EU, with potential global ramifications for trade, public health and security of supply. **Twelve respondents, including Lilly, called for a detailed impact assessment on Triton X-100 use in biopharmaceuticals to be conducted before any proposal is sent to the REACH Committee**. Seven responses called for an immediate sector exemption, and Sanofi and Bayer called for authorisation periods well beyond the current maximum of 12 years.

The original Commission consultation in 2013 was missed by virtually the whole biopharmaceutical sector, as the paper did not have the CAS numbers on the home page. Therefore, there has never been the opportunity to provide evidence to show the impact specifically on the life-science sector. The life-science sector accounts for less than 10% of all Triton X-100 use. Uniquely, it uses Triton X-100 as a viral inactivation agent that is essential for patient safety.

Analysis of the short Commission consultation that closed on 14 October shows that respondents represented virtually all pharmaceutical companies in Europe and several from the U.S. EFPIA, for

example, represents 33 national associations and 42 leading pharmaceutical companies, and provided a joint response with Medicines for Europe (whose members supply over 56% of all medicines in Europe), Vaccines Europe and IFAH Europe (whose membership covers 90% of the European market for veterinary products). In addition, respondents included EuropaBio (representing 1,800+ SMEs), the European Biopharmaceutical Enterprises (EBE), the Plasma Protein Therapeutics Association (PPTA), Les Entreprises du médicament (LEEM), BioPharmachem Ireland, the Association of the British Pharmaceutical Industry (ABPI) and the UK Bioindustry Association (BIA). Other notable responses included those from the IDA (Ireland's inward investment agency) and Charles River Associates. Company responses were sent by Lilly, Sanofi, Bayer and Biomarin. **We call on members of the WTO to echo the overwhelming view of the life-science sector and urge the Commission to conduct a detailed impact assessment on Triton X-100 use in biopharma before any proposal is sent to the REACH Committee.**

Triton X-100 is the only substance of the 12 in this proposal which hasn't been the object of a call for socio-economic information by the Commission.

The current REACH Authorisation process is uncertain and risks putting patients' health at risk, in the EU, the U.S., and beyond. It is unfortunate that the original Triton X-100 proposal was missed by many stakeholders for technical reasons. The Commission's calls for ECHA's 6th and 7th recommendations indicated that information gathered aims to inform decision-making by the Commission and the REACH Committee. The absence of socio-economic data gathering to feed into an impact assessment at this stage goes against the Commission's Better Regulation guidelines.

Today it is disproportionate to place Triton X-100 on Annex XIV for the life sciences, with the uncertainty it creates for security of supply of life enhancing medicines in human health and veterinary medicines. It also creates regulatory uncertainty for Lilly manufacturing and the patients we seek to supply with medicines worldwide.

As with plasma derived products, viral inactivation is a critical step in the manufacturing process in mammalian culture systems. Alternative viral inactivation processes are unlikely to be validated and approved by regulatory agencies for existing commercialised medicines in time, and the industry could have to seek supply from non-EU countries, like Switzerland, USA and the Far East. This delay would cause major disruption to U.S. manufacturers operating in Europe. Even with Authorisation, the current periods granted (12 years max) does not address the long timelines that are required to bring our medicines to patients. As stated, biopharmaceutical use is <10% of 4-tert-OPnEO use overall, so an early loss of supply could also have an impact on public health.

Global manufacturing location assessments are made today for medicines that are in early development, up to a decade from commercialisation. Lilly's EU manufacturing locations in Ireland, Italy, France and Spain require a stable and predictable regulatory environment in order to make sourcing decisions for its medicines. REACH currently doesn't provide this certainty. If Triton X-100 is banned in the EU, then any potential new viral inactivation methods will have to be assessed and approved by the European Medicines Agency (EMA). If a new viral inactivation manufacturing process is found and implemented at EU manufacturing facilities, a key step in the medicinal approval process could require additional animal testing and clinical trials and would add years of

delay in new medicines reaching patients; with potential supply outages for current medicines. It would also require type II marketing authorisation variations not just to the EMA, but also to the FDA and other national regulators worldwide.

The alternative for multinational manufacturers is to utilise capacity available outside the EU and import the finished medicine. This is not desirable and goes against the Commission's jobs and growth plan. A recent CRA report on Triton X-100 shows c.4,000 EU jobs supporting biopharmaceutical manufacturing are at risk. This could equate to a cost of €3.5 billion. CRA highlights the difficulty changing manufacturing location for marketed products and that revalidating the manufacturing process would add €20m+ cost per product. We believe this place an undue barrier to trade.

The EU is putting €billions in exports – with trade and patient safety implications, many high value jobs and a global life science competitive advantage—at risk. The proposal to place Triton X-100 on the list of Annex XIV banned substances also creates a duplicate regulatory burden on medicines (beyond what is required for EMA approval), and thus an unfair barrier to U.S. companies manufacturing in Europe. These risks cannot be properly considered without an accompanying Commission impact assessment. **We urge WTO members to call on the Commission to now do a benefit/risk management assessment on Triton X-100 use in relation to biopharmaceuticals and public health, prior to any decision by the REACH Committee**. The REACH Committee members can then make an evidence based decision. We support the objectives of REACH and see the current REACH Refit review as a way to make the process fit for purpose for the life sciences sector moving forward.