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Universal PFAS Restriction and Sorafenib

Possible Consequences of a PFAS REACH restriction on medicinal products – Sorafenib as one example out of many potentially impacted active pharmaceutical ingredients (API)

Background

Five national competent authorities (Germany, the Netherlands, Norway, Sweden and Denmark) have submitted an annex XV dossier under EU REACH on the restriction of per- and polyfluoroalkyl substances (PFAS) in January 2023 to ECHA. Restrictions are normally used to limit or ban the manufacture, placing on the market (including imports) or use of a substance, but can impose any relevant condition, such as requiring technical measures or specific labels. The definition of PFAS is very broad with including molecules with the smallest possible PFAS chain length of 1 (one $-CF_2-$ or $-CF_3$ moiety is sufficient). Under restriction option 2 the dossier submitters have proposed a time unlimited derogation for active substances in human medicinal products which is the favored restriction option by the dossier submitters. Under restriction option 1, a full ban of all uses and manufacturing of PFAS chemicals after 18 months transition period is analyzed. Under restriction option 1 **active pharmaceutical ingredients (APIs) falling under the broad definition of PFAS would be banned from the EU market**. Therefore, approved medicinal products under pharmaceutical legislation might be banned in Europe due to chemical law. APIs are not registered under REACH, however, restrictions under REACH also apply to APIs.

In this paper we would like to describe the consequences of ban of APIs falling under the PFAS definition for one example API – Sorafenib. One should bear in mind that this is only one example of an API potentially falling in scope of a REACH PFAS restriction and there are many more APIs on the market potentially affected, too[1].

Chemistry

The Chemical Structure of Sorafenib is displayed in Figure 1. Due to the CF_3-moiety (highlighted in yellow) Sorafenib is in scope of the current proposed definition of PFAS.

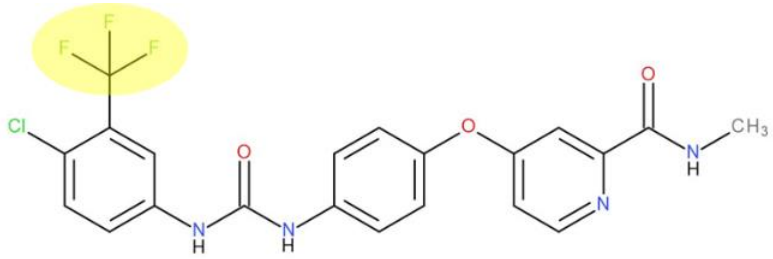

Figure 1 Chemical structure of Sorafenib - fluorinated moiety is highlighted in yellow

[1] Njardarson, et al, J. Chem. Ed. 2010, 87, 1348, 200 most important small molecule drugs (by retail sales 2018)

During drug discovery it became evident that the CF_3-group is important for inhibition of the Raf-1 kinase and therefore for the efficacy of the compound. Efficacy of structurally related compounds without the CF3 group in meta position relative to the amine was 10fold lower. Effectiveness of the active pharmaceutical ingredient was extensively studied and shown prior to clinical development. *In vivo* studies have shown that the activity is driven by the presence of a substituent at the meta position relative to the amine. Most noteworthy was the effect of non-polar substituents trifluoromethyl, which led to a significant improvement in activity in comparison to other groups studied, such as, e.g., methyl, ethyl, isopropyl, or tert.-butyl.[2]

Environmental Profile

For Sorafenib an Environmental Risk Assessment (ERA) has been prepared in accordance with the EMA ERA guidance. It was concluded that sorafenib is persistent, bioaccumulative and toxic (PBT) as well as very persistent and very bioaccumulative (vPvB).

Medical Importance

Sorafenib is a targeted treatment, a multikinase inhibitor, approved in renal cell carcinoma, differentiated thyroid carcinoma and hepatocellular carcinoma (HCC) or liver cancer. It is part of the only validated sequence option followed at progression by regorafenib. The liver cancer patient journey can be very different from one patient to the other. Some patients have a very early diagnosis which allow them to be treated by a liver transplantation or surgical resection. Due to their immune-suppressive treatment to tolerate the external graft, the only drug these patients can receive safely is sorafenib (the other drugs have not been proven as safe). For the patients who are diagnosed with an advanced deterioration of their liver function due to e.g. cirrhosis and hepatitis the only therapeutic option which can be proposed by the physician is sorafenib again. All these data in these special populations have been based on the biggest real-world evidence generated by treating physicians all around the world.
With extensive clinical and real-world experience sorafenib is part of the standard of care in treatment guidelines and has a lasting impact on the therapeutic landscape in HCC but also in various cancer types and remains an important treatment option in improving patient management.

Socioeconomic Impact

Sorafenib, with the medical importance specified above, is a lifesaving drug in HCC patients. Approximately 2.5 – 5 million doses of Sorafenib are applied per year in Europe. If APIs in medicinal products such as Sorafenib, falling under the definition of PFAS, would be restricted (i.e. banned) in the European Union via REACH, these patients would be cut off their life saving drug. As described previously, sorafenib is one of the standard of care in HCC patients and the first step for the only

[2] Lowinger *et al.*, „Design and Discovery of Small Molecules Targeting Raf-1 Kinase", Current Pharmaceutical Design, 2002, 8, 2269-2278

approved systemic treatment sequence. All the trials allowing treatment options in Europe after first line systemic treatment failure require a prior treatment with sorafenib based on their label (regorafenib, cabozantinib and ramucirumab). The impact would be on the whole outcome of HCC patients, reducing the median life expectancy of these patients of at least 26 months[3].

At present there is no alternative to Sorafenib without the chemical moiety in discussion (fluorinated alkyl chain). Moreover, it is totally unknown if such alternatives may be developed providing the same medical service and efficacy as Sorafenib. Finally, search for alternatives lasts long and approval processes take at least 15 years, which would leave open a large non-acceptable supply gap for patients.

Summary

A REACH restriction of PFAS which would ban APIs falling under the PFAS definition would have an immense impact on availability and the development for the European market of efficient and safe drugs for European patients. These medicinal products may provide lifesaving treatment to many patients in the EU. Medicinal products under PFAS definition should therefore not be in the focus of REACH and clearly be exempted from an upcoming PFAS restriction.

[3] Finn R *et al*, Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial, J Hepatol 2018, 69, 353–35