What is driving the increase in HPAPI products?

There are numerous societal and technological reasons why there has been an increased percentage in the number of HPAPIs products. These reasons include, but not limited, to the following:

- **A greater focus on oncology and increased-life expectancy products.** As the world's average life expectancy continues to lengthen beyond 72 years, the need for therapeutics associated with age-related diseases increases. As is well known, increased age results in an increased risk of cancer. For example, of the 53 novel drug approvals by the FDA in 2020, 19 of the new novel drug approvals were related to the treatment of cancer (35.8%) and for the year to date 2021, 12 of the 28 novel drug approvals were related to the treatment of cancer (42.9%). Often, while oncology products have fairly large therapeutic doses, these products may have reproductive and developmental effects at low doses. Thus, meeting the definition of a highly potent compound. In addition, renewed interest in the development of antibody drug conjugate (ADC) compounds requires the handling of highly potent warhead compounds, such as mertansine or ravtansine.

- **Improvements in drug targeting and candidate selection.** Improvements in drug discovery technologies have progressed such that only the best drug candidates are selected, which are often the most targeted and potent drugs.

- **Improvements in preclinical safety studies.** Potential adverse effects are being evaluated more thoroughly during the preclinical safety studies. For example, almost every new drug needs to be evaluated for cardiac toxicity prior to being marketed. Advances in *in silico*, *in vitro*, and clinical study protocols have made it possible to detect significant adverse drug effects prior to the drug being approved for market release.

- **Better data collection, review, and analysis of drug safety.** Periodic drug safety update reports (PSUR) required by the various regulatory agencies throughout the world provide an evaluation of the risk-benefit balance of a drug product at defined time points after its authorization. The generation of PSURs is a proactive means of identifying potential safety issues of a pharmacological product. Signal detection is information that arises from one or multiple sources which suggest a new potentially causal association, or a new aspect of a known association with a drug product. Increased awareness of adverse effects may cause drugs that were previously non-HPAPIs to be reclassified as HPAPIs.

- **Advances in database and search technologies.** While it may not be readily apparent, advances in database and search technologies have improved the "discoverability" of hazard information associated with drug products. For example, in May of 2017, PubMed announced that it had updated its algorithm for search. The PubMed database now uses a search algorithm that uses machine learning and to re-rank the top articles returned for improved relevance. In addition, even commonly used search engines such as Google change their search algorithms frequently to improve relevance and eliminate poor quality information from appearing in the search results. Improved search relevance and quality increases the likelihood that important safety and adverse effect information related to the setting of OELs and HBELs is discovered. Here at Affygility Solutions, we use proprietary artificial intelligence tools that use machine

learning and "grey literature" deep-learning techniques to “discover” data that would otherwise be extremely difficult to locate by traditional search techniques.

- **Improvements in ensuring a thorough evaluation of compounds by competent occupational toxicologists.** Prior to the release of the European Medicines Agency’s (EMA)’s Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, there was no regulatory requirement that the setting of HBELs be performed by expert toxicologists. Since 2015 this has changed, and currently, the European Medicines Agency (EMA), the Pharmaceutical Inspection Co-operation Scheme (PICs), Brazilian Health Regulatory Agency (Portuguese: Agência Nacional de Vigilância Sanitária) (ANVISA), and the World Health Organization (WHO) required all HBELs to be established by expert toxicologists. This has greatly improved the thoroughness and quality of both OELs and HBELs.

What is the impact on the pharmaceutical industry?

The impact that increasingly more highly potent compounds have on the pharmaceutical industry is significant. These impacts include, but are not limited to the following:

- Limited manufacturing space and capacity. Better facility design, engineering controls, and HVAC systems are costly to build out and validate. Therefore, HPAPI manufacturing space and capacity is limited. Limited capacity can result in longer lead times.
- Greater demand for high-containment pharmaceutical manufacturing equipment such as hard-wall and flexible isolators, high-containment valves and connections. This can also create longer lead times and scheduling challenges. In addition, due to the COVID-19 pandemic and disruptions in supply chains, replenishment of disposable items necessary for the production of HPAPIs is taking longer.
- Retrofitting of existing pharmaceutical manufacturing equipment to add containment or engineering controls.
- The need for more sensitive analytical methods to be used for performing occupational hygiene air monitoring (otherwise known as OEL testing), and containment validation, and cleaning validation.
- The need for more stringent cleaning methods and accessibility to clean-in-place equipment.
- Due to the high potency of the compound, when cleaning verification cannot be performed - dedicated equipment, manufacturing suites, or a thorough risk-management plan may be required.
- Increased training needs for operators, increased demands for industrial hygiene analysis, and more complex standard operating procedures (SOPs).

Reference: 2021 data: What percentage of drug compounds are highly potent? (affygility.com)