ThermoFisher SCIENTIFIC

SOLVED WITH

TECHNOLOGY & TRUST

WHITEPAPER

# Safety first: Controlling occupational exposure in oncology drug development

**Joe Galati, PhD**
*Sr. Director, Global Toxicology Services,*
*Thermo Fisher Scientific*

## Executive summary

Due to the advantages in efficacy and safety compared with traditional chemotherapy drugs, targeted therapeutics that zero in on specific parts of cancer cells while sparing normal cells have become mainstream cancer treatments. Small molecule targeted therapies are an especially attractive option because they can be administered orally, which is associated with improved treatment compliance, cost effectiveness, and ease of large-scale manufacturing. Further, because they are not protein in nature, small molecule targeted compounds are less likely to cause an immune response.

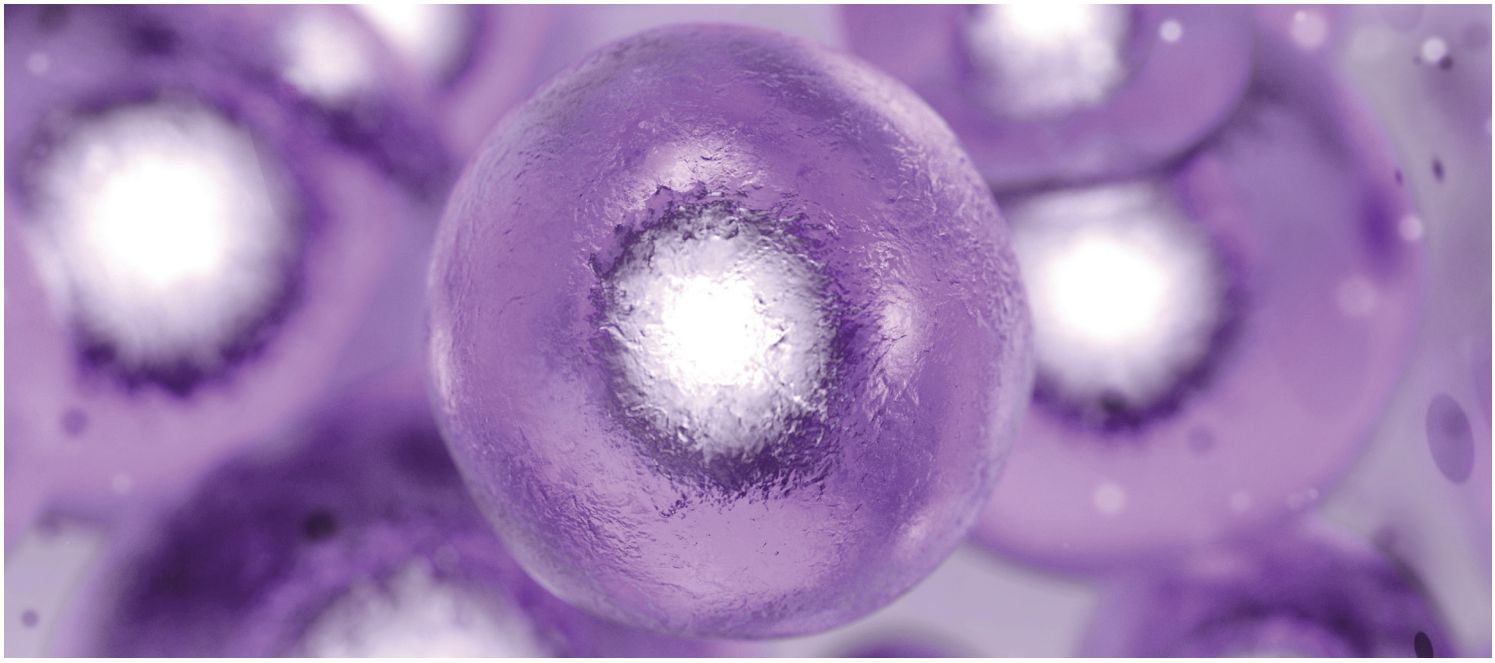
From a manufacturing perspective, small molecule targeted therapies present some challenges. Because they are designed for high selectivity with biological targets, the active pharmaceutical ingredients (APIs) are often highly potent and potentially toxic, even at small doses. This poses occupational exposure risks as well the possibility of cross contamination with other drugs in the manufacturing environment. Underestimating the risks can threaten operator and patient safety, while overestimating them can lead to unnecessary spending on containment, increasing overall project costs.

For these reasons, the safety risks associated with each substance involved in the drug synthesis must be carefully evaluated ahead of manufacture to identify and reduce health hazards, as well as to optimize manufacturing cost efficiency. Doing so allows manufacturers to tailor techniques, equipment, and containment options to the properties of the molecule at each step of development.

This report provides a roadmap for assessing toxicological and potency risks of small molecule oncology compounds, focusing specifically on the following considerations:

- Criteria for evaluating highly potent small molecules
- Toxicity banding systems
- Potency downgrading
- Safety and handling strategies

Delivering on the potential of small molecule oncology therapies requires understanding and embracing safe handling practices and containment technology. It also requires maintaining, continuously assessing, and aligning infrastructure, technology, and the expertise of stakeholders involved in the development process.



## Introduction

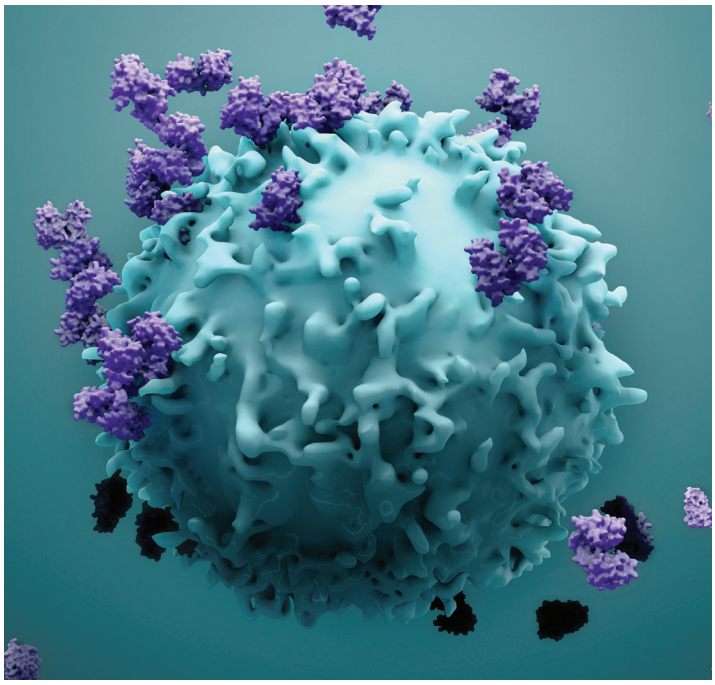
Rising cancer growth rates, driven by environmental factors, lifestyle choices, and an aging population, are putting pressure on pharma companies to develop and manufacture life-saving therapies with both speed and agility. Because small molecule targeted therapies have proven to be more effective at treating cancers with reduced severe adverse effects as compared to traditional chemotherapy drugs, the manufacturing of these molecules is, likewise, increasing. Today, small molecule compounds account for approximately 42% of the oncology market pipeline, and forecasts suggest that percentage will be increasing for many years to come.

However, small molecule oncology APIs are often highly potent and therefore require specialized equipment, expertise, and adherence to strict handling and containment guidelines from development through distribution to ensure operator health and safety and patient safety.

**Today, small molecule compounds account for approximately 42% of the oncology market pipeline, and forecasts suggest that percentage will be increasing for many years to come.**

Even seemingly innocuous compounds can be toxic at a certain dose, so manufacturers' primary focus should be to collect enough information to inform potency classification for every stage of development which is the foundation for a robust handling and containment strategy.

The first step in the potency classification process is identifying the lowest dosage at which harmful effects are observed. Because classification systems vary across companies and regions, there is no universally accepted definition of high-potency substances. However, it is generally recognized that a pharmacologically active ingredient or intermediate that meets any of the following criteria should be considered highly potent:



- Elicits biological activity at or below approximately 150 µg/kg of body weight in humans (therapeutic daily dose at or below 10 mg)
- Has an upper limit of acceptable concentration in workplace air—or occupational exposure limit (OEL)at or below 10 µg/m3 of air as an 8-hour time-weighted average
- Demonstrates high selectivity to bind to specific receptors or inhibit specific enzymes
- May cause cancer, mutations, developmental effects, or reproductive toxicity at low doses
- Is a novel compound with unknown potency or toxicity

Once a compound has been identified as highly potent, it is the responsibility of the manufacturer to implement appropriate handling and safety strategies during the manufacturing process. The top priority of these strategies is to protect the health of workers so that they don't suffer any effects from the drugs that they are handling or exposed to during manufacture. In addition, multi-product manufacturing facilities must ensure that their safety measures provide adequate controls for preventing cross-contamination of the product. Finally, the safety measures must be stringent enough to satisfy the expectations of customers and global regulatory agencies, including the US Food and Drug Administration, Health Canada, and the European Medicines Agency, among others.

## Potency classification: Handle with care

To properly identify the potential risks of exposure, manufacturers must look at how much of the API is needed to achieve therapeutic effect the degree to which the therapeutic dose of the substance may cause harm. APIs are typically categorized using OELs which, as noted above, is the upper limit of API concentration in workplace air that individuals can safely be exposed to for eight hours per day, five days per week for their entire working lives without any ill effects.

Because there is wide variation in how different workers react to similar exposures in the workplace, OELs are not based on fixed standards. A key determinant of an OEL is the level of exposure at which the most sensitive subsection of the target population will experience an adverse effect. This no-observed-adverse-effect level (NOAEL) as the point of departure should typically be obtained for the most relevant critical effect of the API in question, such as from repeated dose toxicity and developmental/reproductive toxicity studies. Together with other variables, including worker body weight, typical breathing rates, bioavailability by the route of administration, and safety related considerations, NOAELs are used to derive OELs, as illustrated in the equation in Figure 1.

## The banding process: Understanding the assignment

In some cases, such as with early-stage compounds, there is not enough data available to define an OEL. In these situations, manufacturers classify APIs into control bands, or occupational exposure bands (OEBs), based on a critical evaluation of all available toxicity data and a rigorous peer review process. Each band is associated with a matching set of engineering controls, handling practices, and requirements for personal protective equipment (PPE).

Each OEB infers a specific level of hazard with a corresponding safe airborne concentration range and has corresponding safety handling requirements, which guide the control measures that should be used in manufacturing.

**Figure 1**

**Occupational Exposure Limits (OELs)**

$$OEL = [(NOAEL)\ (BW)]/[(SF)n\ (BR)]$$

### NOEL

No-Observed-Adverse-Effect-Level for the most sensitive or critical adverse effect

### BW

Body weight of an adult worker, typically assumed to be 70kg by default

### (SF)n

A number of safety factors that consider such uncertainties as animal-to-human variability in response, human-to-human variability in response, duration of the study, severity of effect, quality of the available data, conversion from LOAEL to NOAEL, etc

### BR

Breathing rate of an adult worker, typically assumed by default to be 10m3/8-hour workday

OEB classification is not standardized across the pharma-ceutical industry, however. Rather, each pharma-ceutical company uses its own system, often reflecting differences in manufacturing equipment. The differences across banding classification systems can complicate outsourcing handoffs. For example, an API that is considered an OEB Category 4 in one classification scheme may be a Category 3 or Category 5 in another. Because each band is associated with unique engineering controls, stakeholders must know the OEL range for the molecule in question to determine where it fits in the banding system of the manufacturer responsible for each phase of development.

Despite the variation across banding systems, the distinction between low and high potency is generally in the 10 mcg/m3 range, as can be seen in Thermo Fisher Scientific's banding system, illustrated in Figure 2.

**Figure 2**

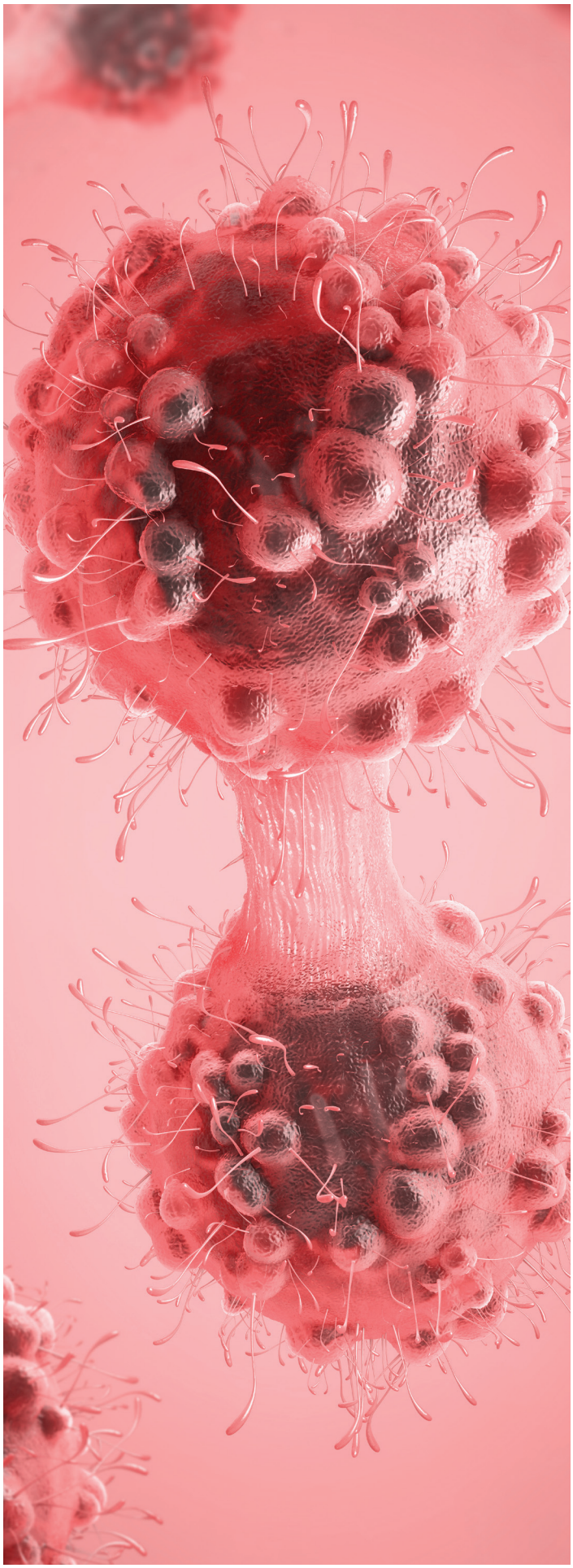
**Toxicity categorization criteria summary table**

| | |
|---|---|
| **Category 1** | Category 1 substances have all or some of the following characteristics:<br>• reversible health effects<br>• low pharmacological potency<br>• therapeutic dose: >1000 mg/day<br>• no carcinogenic effects<br>• no genotoxic effects<br>• no developmental toxicity or teratogenicity<br>• no reproductive toxicity<br>• not a sensitizer<br>• irritant<br>• low acute or chronic systemic effects<br>• good warning properties<br>**OEL > 1 mg/m3** |
| **Category 2** | Category 2 substances have all or some of the following characteristics:<br>• reversible health effects<br>• moderate pharmacological potency<br>• therapeutic dose: 10 – 1000 mg/day<br>• no carcinogenic effects at industrially relevant doses*<br>• equivocal or unclear evidence of genotoxic effects<br>• no developmental toxicity or teratogenicity at industrially relevant doses*<br>• no reproductive toxicity at industrially relevant doses*<br>• weak or rare sensitizers (skin or respiratory)<br>• corrosive<br>• moderate to high acute systemic toxicity such as cardiac or liver toxicity<br>• moderate degree of medical intervention (i.e., not life threatening) may be needed<br>• lacks warning properties<br>**OEL range from 10 µg/m3 to 1 mg/m3**<br>*The design of toxicological studies in animals often involves exposure to doses which are significantly higher than would be present in the industrial environment and therefore produce a nominal risk of effect. |

**Figure 2 (continued)**

## Toxicity categorization criteria summary table

| | |
|---|---|
| **Category 3** | Category 3 (3A and 3B) substances have all or some of the following characteristics:<br>• irreversible health effects<br>• high pharmacological potency<br>• therapeutic dose<br>• 3A: 1 - 10 mg/day<br>• 3B: 10 µg/day - 1 mg/day<br>• carcinogenic<br>• genotoxic<br>• developmental toxicity or teratogenicity<br>• reproductive toxicity<br>• severe or frequent sensitization<br>• severe acute or chronic systemic effects<br>• potential need for immediate medical intervention<br>**Category 3A substances** typically have OELs in the range of**: 1 µg/m3 to 10 µg/m3**<br>**Category 3B substances** typically have OELs in the range of: **10 ng/m3 to 1 µg/m3** |
| **Category 4** | Category 4 substances have all or some of the following characteristics:<br>• irreversible health effects<br>• very high pharmacological potency<br>• therapeutic dose: < 10 µg/day<br>• highly carcinogenic<br>• genotoxic<br>• severe developmental toxicity and/or teratogenicity<br>• severe reproductive toxicity<br>• severe acute or chronic systemic effects<br>• severe or frequent sensitization<br>• immediate medical intervention required<br>• toxic effects with increased degree or severity in sensitive sub-populations* at very low doses (i.e., producing OELs of <10 ng/m3)<br>**OEL < 10 ng/m3**<br>*Sub-populations are those which may experience increased risk of toxicity due to exposure, when compared to the general population. These may include individuals with a pre-existing medical condition, those with an occupational illness, and hyper susceptible individuals. Hypersensitivity can develop because of genetic factors, age, personal habits (e.g., smoking, alcohol, or other drugs), medication or previous exposures. |



Another similarity across banding systems is that bands are assigned based on toxicity data derived from methodical research. Typically, the Category 1 band includes compounds or APIs that have low pharmacological potency with a therapeutic dose of greater than 1g per day and an OEL of greater than 1mg/cm3 . Essentially, these are non-carcinogenic and non-genotoxic and are not expected to cause developmental or reproductive toxicities. An example of a compound in this Category would be a non-steroidal anti-inflammatory drug such as aspirin or ibuprofen. Category 2 compounds can be more potent as compared to Category 1, and have a therapeutic dose from 10 mg per day to up to 1 g per day. Examples of Category 2 compounds would be cardiac drugs or well-known and well-documented neurology drugs that don't cause irreversible effects.

Some banding systems use subcategories reflecting more nuanced distinctions. In Thermo Fisher's banding system, for example, all Category 3 molecules are considered potent and have a therapeutic dose of less than10 mg per day, but compounds with an OEL range of 1 to 10 µg/$m^3$ are classified as Category 3A. These are typically oncology drugs that target receptors overexpressed in a tumor but don't necessarily cause toxicity to all cells in the body. They may, however, cause certain teratogenic effects if administered to a pregnant woman. Molecules classified as Category 3B are differentiated by their potency and OEL. These compounds typically have a dosage of less than 1 mg per day, down to as low as 10 mcg per day, and an OEL range of 10 ng/$m^3$ to 1 mcg/$m^3$ and they can cause carcinogenic, genotoxic, teratogenic, or other irreversible effects. Classic cytotoxic drugs including alkylating agents, nitrogen mustard-type compounds, certain steroids, sex hormones, and oral contraceptive-type drugs fall into this Category.

Category 4 compounds are considered to be of the highest potency in Thermo Fisher's banding system and are rare. These are therapeutic drugs that can cause severe adverse effects and typically have a dosage of less than 10 mcg per day and an OEL of less than 10 ng/$m^3$. In general, Category 1 and 2 compounds typically cause reversible adverse effects, while Category 3A, 3B, and 4 compounds can cause irreversible adverse effects.

## What goes up can come down

Banding categorization is not static. When there is limited toxicity data on a molecule or drug, conservative banding is a necessary precaution. For this reason, novel compounds with unknown potency or toxicity are considered highly potent until science says otherwise. As molecules move from early to later stages of development and additional animal and human data are accumulated as illustrated in the progression shown in Figure 3, it may be possible to downgrade the Category if the new data support the change.

In all cases, determining whether an API or compound can be downgraded requires the same considerations that are assessed during initial classification, including a thorough review of all toxicity data available to date. For example, when considering a small molecule oncology drug such as a kinase inhibitor, this is a mechanism of action with known potential to cause developmental toxicity. It is possible that developmental toxicity studies were not completed at the time of the initial categorization, and therefore a default to a conservative band (Category 3A) was used.

Ideally, APIs should be reviewed on a periodic basis of approximately every 3 years (or earlier, if new relevant toxicity data becomes available sooner) to check for any new toxicity data, especially for APIs in an early stage. Now, considering the same kinase inhibitor, it is possible that animal developmental toxicity studies would be completed a few years after the initial classification. Perhaps there is new toxicity data or NOAEL values to show that developmental toxicity is only observed at high doses or not at all, suggesting that a downgrade to Category 2 may be warranted. One should consider a downgrade if the new toxicity data available is for the most critical effect, such as for developmental toxicity in this example.

If the science dictates, a downgrade in Category may allow for more flexibility in terms of choosing a manufacturing site, less stringency in the required containment, and less cost to manufacture. However, it should also be noted that there could be challenges when downgrading, such as with tech transfer, logistics, and worker/client communication, and therefore the toxicologist must be sure that the initial classification is as accurate as possible the first time, and that a downgrade in the Category, when warranted, is fully supported by the science.

**Figure 3**

**Downgrading a molecule from high potent to low potent**

Consider the lifecycle of drug development. The OEL/OEB can change as more toxicity data become available.

| Early development stage (before animal studies) | Preclinical stage (animal studies) | Clinical studies |
|---|---|---|
| • Mainly in vitro studies, such as in vitro receptor binding assays<br>• May have in silico toxicity data, such as genotoxicity, sensitization, etc., based on structural alerts<br>  • A selection of candidate molecules<br>  • Evaluate mechanism of action<br>  • No in vivo toxicity data available | • Single-dose or sub-chronic animal studies (7-day, 28-day)<br>• Genotoxicity studies (Ames test)<br>• Years later: reproductive toxicity studies (fertility, embryonic development), carcinogenicity studies | • **Phase 1:** Start with a few healthy volunteers in the study<br>• **Phase 2:** An increase in number of participants, now considering the intended patient population<br>• **Phase 3:** A further increase in number of participants; additional toxicity data becomes available |

## Cytotoxic vs. non-cytotoxic oncology drugs and cGMP

Anti-cancer drugs are often collectively referred to as cytotoxic agents. In fact, although many of the oncology drugs in the development pipeline are highly potent substances with cytotoxic or genotoxic effects, many others are not. This distinction is essential for compliance with current good manufacturing practice (cGMP) regulations, however there currently is no universally accepted definition of “cytotoxic drug” to guide the assessment.

Following are some of the key questions that must be addressed:

- Does the drug directly disrupt DNA?
- Is it genotoxic?
- Does it have an effect on healthy cells, or is there data to show that the effect on cancerous cells is at a much lower dose when compared to the effect on healthy cells?
- Is the drug toxic regardless of any threshold or is there a NOAEL?
- Does it have adverse effects on white blood cells or on the gastrointestinal tract lining?

In the absence of a technical definition for cytotoxic drugs, a functional definition developed by myself and fellow toxicologist colleagues and cited by the US Department of Health can help differentiate between cytotoxic cancer drugs and non-cytotoxic targeted cancer therapeutics.

**Although many of the oncology drugs in the development pipeline are highly potent substances with cytotoxic or genotoxic effects, many others are not.**

Based on this guidance, targeted oncology drugs that are toxic to a tumor but not healthy cells can be considered non-cytotoxic/selectively cytotoxic, while those that have a direct mechanism of action on DNA and are not selective to tumor cells should be considered cytotoxic. With respect to cGMP requirements, non-cytotoxic/selectively cytotoxic drugs can be manufactured in multiproduct facilities, while cytotoxic drugs may require dedicated area/equipment.

## Establishing Safety Protocols

Once an OEB or OEL has been determined for a given molecule or compound, the manufacturer must institute the proper handling and manufacturing safety guidelines. It is important to note that a strong focus should be placed on containing the product at the source of emission of airborne material through engineering controls. Personal protective equipment (PPE) or worker protective clothing should only be used as a redundant control measure.

While many of the guidelines will be driven by the OEB or OEL, there are additional considerations that influence safety protocols, such as the percentage of API being handled, the volume of material, and the level of interaction required to manufacture it. The physical properties of the material also come into play. For example, in the case of a powder, if it disperses into dust easily, the inhalation potential is likely high, necessitating the use of more stringent protective measures.

The differences between safety and handling strategies for the manufacture of low- and high-potency molecules are significant. For example, some engineering primary controls for a Category 1 powder compound based on Thermo Fisher's OEB classification system are local exhaust ventilation (LEV) for high dust-generating procedures and contained handling where practical. Some secondary controls are mechanical ventilation, good housekeeping processes, and high-efficiency particulate air (HEPA) filters. In terms of PPE, the use of gloves, safety shoes, safety glasses, and a standard work uniform is typical.

In contrast, for a Category 3B powder or molecule, open handling is not recommended. Instead, contained handling should be implemented, using tools such as a powder weighing hood, a laminar flow hood, an isolator, mechanical airflow, clean or wash in place systems, and glove box isolators. Secondary controls include no air recirculation in production suites, frequent air changes, high potency safe-change HEPA filters, negative air pressure cascade from process room to outer areas, buffer zones, and other strategies. With respect to PPE, the higher potency of molecules in this Category warrant respiratory fit testing, medical clearances, double-bib powered air-purifying respirator (PAPR) with HEPA cartridges, sleeve covers, double gloves, and booties.

Additional controls that come into play for high potency molecules and compounds are air monitoring and alarm systems, highly trained personnel, medical surveillance, and restrictions for pregnant women.

## Conclusion

Chemical process development of targeted oncology APIs involves handling often highly potent substances for which little or no hazard or dose-response information is available. Because OELs cannot be set in the absence of this toxicity data, manufacturers develop in-house exposure limit ranges to guide protection strategies. These ranges, reflected in OEBs, map to engineering and administrative controls to prevent worker exposure to airborne substances above the exposure limit and to eliminate the risk of cross contamination with other drugs in the manufacturing environment. As control levels increase, so does the intensity of the processes and equipment needed to ensure optimal protection, as well as the associated costs.

Classifying exposure limits for a given substance is a dynamic process. As more information becomes available through pre-clinical animal toxicity studies and human clinical trials, novel compounds that were originally classified as highly potent because of the absence of toxicity data may be downgraded if the science supports the change. Fully understanding the risks through ongoing data collection and analysis is essential. This knowledge enables manufacturers to identify and implement the best control strategy to protect operators and drug products to reliably and consistently ensure worker and patient safety), while also preventing unnecessary spending on containment efforts that are misaligned to the actual risks.

### References


1 IQVIA (2021) Global MIDAS Edition. Includes antineoplastic agents (L01) and endocrine therapy (L02)- 248 molecules, OSD includes: tablets, ODT, capsules/

2 Winkler GC, Barle EL, Galati G, Kluwe W<. (2014)Functional differentiation of cytotoxic cancer drugs and targeted cancer therapeutics, Regulatory Toxicology and Pharmacology, Volume 70, Issue 1, 2014, Pages 46-53, ISSN 0273-2300, https://doi.org/10.1016/j.yrtph.2014.06.012.

## About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics, and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services, and commercial manufacturing and packaging. Built on a reputation for scientific and technical excellence, we provide pharma and biotech companies of all sizes instant access to a global network of facilities and experts across the Americas, Europe, Asia, and Australia. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. Our Quick to Clinic™ programs for large and small molecules help you balance speed and risk during early development so that you can file your IND quickly and successfully. Digital innovations such as our mysupply Platform and Pharma 4.0 enablement offer real-time data and a streamlined experience. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

### Dr. Joe Galati

*Senior Director of Global Toxicology Services*

Dr. Joe Galati is the Senior Director of Global Toxicology Services. He has more than 20 years of pharmaceutical industry experience in the fields of occupational toxicology and patient/product safety. A full member of the U.S. Society of Toxicology, as well as the Society of Toxicology of Canada, Dr. Galati earned his Ph.D. in Pharmacology and Molecular Toxicology from the University of Toronto. He has authored several peer-reviewed publications, and has presented at various international scientific meetings, conferences, and universities, in North America and Europe.

+1 919 226 3200 • thermofisher.com/patheon • pharmaservices@thermofisher.com

Published 07/22

ThermoFisher SCIENTIFIC