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Are high potency active pharmaceutical ingredients (HPAPI) also high risks for cross-contamination?

KEYWORDS: Highly hazardous, high potency, active pharmaceutical ingredient, risk assessment, cross-contamination.

Abstract The terms highly hazardous, highly active and highly potent are often used in mixed or inconsistent contexts regarding good manufacturing practice and worker safety. This article provides an overview of definitions and criteria used for classifying active pharmaceutical ingredients (APIs) and the use of these terms for identification of risks in cleaning validation. While competent toxicological evaluation is required to identify and characterize the health hazards for each drug substance and then calculate a health based exposure limit, further steps in risk assessment for cross-contamination include batch size, maximal daily dose of subsequent products, equipment surface areas, cleaning process parameters and process capability. Risks presented by drug substances cannot be managed by simple classification into highly potent and highly hazardous categories.

INTRODUCTION

Although the terms hazard and potency are thought to be well understood, they are often mixed or used in inconsistent contexts. It is acknowledged that the hazards, as qualitative aspects are much easier to assess, communicate and perceive by the general public, but hazards alone are insufficient to assess the risks for populations and define the risk mitigation strategies that should follow. Scales that include the qualitative and quantitative aspects of hazards and potency that can be used in setting priorities of concern have been proposed for decades. One such example is ranking of possible carcinogenic hazards by an index that relates to potency of each carcinogen in rodents to the exposure in humans (Ames, 1987). In this article we have looked at the common definitions of human health hazards and potency of substances, and the possibility for the consistent use of these terms in risk assessment for cross-contamination of pharmaceuticals in multipurpose manufacturing facilities.

HIGHLY HAZARDOUS, TOXIC, POTENT AND ACTIVE

Human health hazard assessment is defined as "evaluation of the information on the intrinsic properties of a substance to conclude on the hazards to human health" (1). According to the European Chemicals Agency (ECHA) glossary, a human hazard is defined as the "intrinsic properties of a substance that have the potential to cause adverse effects in humans". Hazards are therefore qualitative properties of substances and do not include a quantitative aspect, which involves the dose of that substance that is needed for these hazards to appear. Conversely toxicity is defined as degree to which a substance or mixture of substances can cause adverse effects to humans. The toxicity of a drug depends on its dosage and therefore has a quantitative aspect to it's definition, which is not an intrinsic property.

While hazards are typically grouped into hazard classes, which have been harmonized for chemicals (2), there is no consensus on the term "highly hazardous". European Medicines Agency (EMA) has attempted to give guidance on this term in their Q&A document EMA/CHMP/CVMP/SWP/463311/2016 (3). While there are some qualitative hazard classes mentioned there as the basis for definition (eg. genotoxic, carcinogenic, reprotoxic substances), these terms are combined with the quantitative aspect, their potency. It was pointed out in the publication by Lovsin Barle et al. (4), that additional criteria that require substance specific evaluation of an API may lead to a low health based exposure limit (HBEL), based on the following: potential for bioaccumulation, differences in bioavailability for different routes of exposure, non-daily dosing regime and short treatment periods of patients.

Similarly to EMA, the National Institute for Occupational Safety and Health (NIOSH) provides a definition for hazardous drugs based on qualitative and quantitative criteria (carcinogenicity, teratogenicity or other developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity and structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria). They emphasize the quantitative aspects that include potency in more detail in the footnote which contains the term "level of toxicity". The footnote states "The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less)." (5).

Toxic chemicals are defined as those that can produce injuries or lethal effects on contact with body cells. It is acknowledged that results of the tests that determine toxicity are not absolute due to great variability in the target populations. The term "highly toxic" applies to those substances for which toxic effects are severe and occur in small doses. A problem arises in providing adequate definitions for detailing a list of chemicals of concern, particularly for regulatory purposes. A comparison of the doses used in human therapy with doses that produce lethal doses in animals has been compared by Lovsin Barle et al. (6). Based on their results, toxic classes based on lethal doses in animals are not useful for human estimation of acute toxicity.

Potency is determined qualitatively by the dose of the drug required to produce an effect. An HPAPI(e.g., fentanyl, estrogen, calcitriol) evokes a desired pharmacological response in target population of patients at low doses. On the other hand, these drugs may also evoke unintended, adverse effects at doses lower than the dose for the intended effects. These effects may be acceptable in the patient population; however they are not acceptable in other populations, such as workers, or in patients who might be exposed to such a drug as a contaminant.

The definition of an HPAPI varies significantly in the literature and is not harmonized. The following descriptions may be found:

1. Based on therapeutic dose (quantitative criteria): A substance with biological activity at approximately 150 μg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg) (7)
2. Based on Occupational Exposure Limit (OEL) (quantitative criteria): Substance with an OEL at or below 10 $\mu g/m^3$ of air as an 8-h time-weighted average (7) or OEL below 1$\mu g/m^3$ (8)
3. Based on hazards (qualitative and quantitative criteria): Substance with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects, target organ effects or reproductive toxicity at low doses
4. Based on risks (quantitative criteria): extreme acute and chronic toxicity, irreversible effects, strong sensitizer, poor or no warning properties, quick absorption rate, known "genic" effects, higher degree of medical intervention required, affecting sensitive subpopulations (9)
5. Or, by default, a novel compound of unknown potency and toxicity (7)

The term highly potent is most frequently used as a synonym to highly active. Due to the perceived risk, certain classes of medicinal product have previously been required to be manufactured in dedicated or segregated self-contained facilities including, "certain antibiotics, certain hormones, certain cytotoxics and certain highly active drugs" (10). No definitions for these criteria, including highly actives were available at that time. This has been since revised; the EU Guidelines for Good Manufacturing Practice (GMP) for Medicinal Products for Human and Veterinary Use Chapter 5 now states that a Quality Risk Management process which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Where the toxicological evaluation supports a threshold value, this should be used as an input parameter in risk assessment (11). Potential absence of thresholds is connected to certain genotoxic mechanisms and indicates an absence of a dose under which there would be no effects. Examples of threshold mechanisms and setting limits for genotoxic substances have been published by Lovsin Barle et al. (12).

The problem is that, despite their ease of communication and understanding, quantitative hazard classes alone cannot be used in the risk assessment and risk mitigation measures cannot be based on qualitative criteria alone. The interchangeable usage of these qualitative and quantitative criteria for describing hazards and potency as we have seen in this section demonstrates this. For example, for occupational health purposes processes require specialized containment to ensure that employees and their environment are protected from exposure. These processes can limit the exposure to a certain level, e.g. OEL, which is a quantitative measure. But designing containment for a qualitative hazard class is not possible.

HIGH RISKS FOR CROSS-CONTAMINATION

Risk is the probability that some adverse effect (e.g. skin irritation or cancer) will result from a given exposure to a chemical. The risk posed by a substance depends both on the intrinsic properties of the substance (hazard) and of exposure (1). The intrinsic hazards and the potency of substances are substance specific. These characteristics are normally assessed by qualified toxicologists (for definition see Olson et al., (13)). The outcome of such a toxicological assessment is a Permitted Daily Exposure (PDE) value, as is now required by the EU GMP chapter 5. The PDE has been defined by the 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" (14) as "a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime". The PDE and its definition are synonymous with the Acceptable Daily Exposure (ADE).

For PDE calculations based on toxicological criteria a critical effect needs to be identified; in this context any effect is an adverse effect. Identification of the critical effect dose termed the Point of Departure (POD) which is used for the PDE calculation (15). Depending on the POD, several adjustment factors (AF) are used to account for uncertainties when extrapolating the hazard information to the target population of human patients and differences in routes of administration (16).

OELs (Occupational Exposure Limits) are calculated in a very similar way; the critical difference is in the determination of the critical effect for the target population of healthy workers vs. patients, followed by modification of AFs to adjust for this criterion. Also the OEL is expressed in $\mu g/m^3$ to extrapolate to the volume of air inhaled in 8h working time (10 m^3).

Similarly to the OEL, PDE values fall into a range that spans several orders of magnitude. In a study done with over 200 substances in a typical pharma portfolio, there were about 63% of drugs with a PDE ≥100 μg/day, while there were only 2% of substances with PDE < 1 μg/day (figure 1).

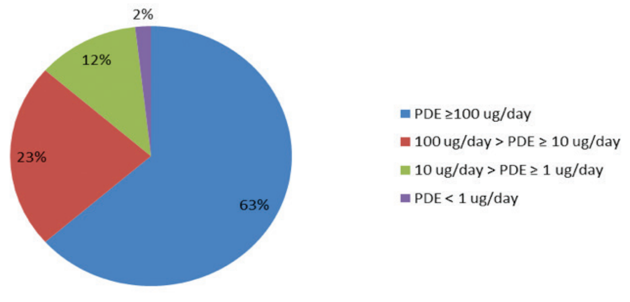

Figure 1. Percentage of substances' PDEs, grouped by order of magnitude in a study of over 200 drug substances in a typical pharma portfolio.

However, the calculation of the PDE is only the first step in assessing the risks for cross-contamination in multipurpose manufacturing facility. The use of the PDE as a tool for determining risks in cross-contamination has been published recently (17). In this article, the PDE is converted into a value on a "Toxicity Scale" which ranges from 1 - 10, with 1 being the least hazardous and 10 being the most hazardous which makes it potentially useful as a scale for Severity in FMEAs (Failure Modes and Effects Analyses). For example, using this scale a PDE of 10 µg/day results in a toxicity score of 5, which lies in the middle of the scale (Note: the Scale is a logarithmic scale).

In general there are several groups of substances that can be considered HPAPI based on the previously mentioned criteria, such as low therapeutic dose (eg., the peptide hormone oxytocin, guanylate cyclase stimulant for irritable bowel syndrome, dopamine agonists for Parkinson's disease), drugs that have adverse effects in low doses (eg. certain genotoxic antineoplastics, toxins used in antibody-drug conjugates (ADCs)) or both of these criteria (eg. sex steroids and sex hormone modulators). However there are some substances that might have relatively high therapeutic doses, which are not dosed daily (eg. bisphosphonates) that could be considered HPAPI. For the purposes of PDE and OEL calculations these doses must be extrapolated to daily doses, showing that the therapeutic dose alone is not necessarily a good indicator of HPAPI (4). In total, there are only about 14% of substances in the above study that would fall into the highly hazardous substances group based on their PDE. Out of these 14%, there are four drugs which would have not been identified as "highly hazardous" based on the EMA's definitions (3), which is also 14% of substances with a PDE < 10 µg/day. (see table 1 for details):

Therapeutic uses	MOA	Highly Hazardous (EMA)	EMA criteria number
Antiarrhythmic	Cardiac Glycoside	yes	4 , 3
Antiarrhythmic	Cardiac Glycoside	yes	4
Antiasthmatics	Beta-2 adrenergic Receptor Agonists	yes	4
Antineoplastic	Pyrimidine DNA Polymerase Inhibitor	yes	2
Antineoplastic	Proteasome Inhibitor	yes	2
Antineoplastic	Pyrimidine Hypomethyling Agent	yes	1
Antineoplastic	Intercalating Agent	yes	1
Antineoplastic	Folic Acid Metabolism Inhibitor	yes	1
Antineoplastic	Histone Deacetylase Inhibitor (HDAC)	yes	1
Antineoplastic	Hedgehog Signaling Pathway Inhibitor	no	Not identified
Biphosphonate		yes	3
Cholinergic Antagonist	Muscarinic Antagonist	no	Not identified
Corticosteroid	Glucocorticoid Receptor Agonist	yes	2
Corticosteroid	Corticosteroid	yes	3
Corticosteroid	Glucocorticoid Receptor Agonist	yes	4
Corticosteroid	Glucocorticoid Receptor Agonists	yes	4
Hormone	Nonapeptide	yes	4
Irritable Bowel Syndrome	Guanylate Cyclase Stimulants	yes	4
OpthalmicOphthalmic	Prostaglandin F2α Analog	yes	2
OpthalmicOphthalmic	Mast cell inflammatory mediators	yes	4
OpthalmicOphthalmic	Prostaglandin F2α Receptor Agonist	yes	2
Organ transplantation	mTOR protein Inhibitor	yes	3
Parkinson's Disease	Dopamine Agonist Of The Non-Ergoline Class	no	Not identified
Sex Hormone Modulator	Estrogen Receptor Antagonist	yes	2
Sex Hormone Modulator	Estrogen Receptor Antagonists	yes	2
Sex Steroid	Progestin	no	Not identified
Sex Steroid	Estrogen Receptor Agonist	yes	2
Vitamine	Vitamin D3 Analog	yes	4

Table 1. A table of drugs with PDE <10 µg/day with their therapeutic indication and MoA and their concordance with EMA's definition of highly hazardous (3).

- Criteria 1: Genotoxic (specifically mutagenic) compounds that are known to be, or highly likely to be, carcinogenic to humans
- Criteria 2: Compounds that can produce reproductive and/or developmental effects at low dosages in animal studies of ≤1 mg/kg/day
- Criteria 3: Compounds that can produce serious target organ toxicity or other significant adverse effects at low doses in animal studies of ≤1 mg/kg/day
- Criteria 4: Compounds with a high pharmacological potency i.e. recommended daily dose of <1 mg
- Criteria 5: Compounds with a high sensitizing potential

But it's important to understand that the PDE is not the sole parameter that determines the risk of cross-contamination. As noted in ICH Q9, the level of risk is a function of a hazard and the level of exposure to that hazard. While the degree of hazard can be measured or visualized using the Toxicity Scale mentioned above, this only shows the relative toxicity of drugs to one another and not the level of risk they pose. It is the level of exposure to those hazards that reveals the level of risk to a patient or worker from cross contamination. For a patient, this may be measured by the amount of residue that remains after cleaning manufacturing equipment that might contaminate the next drug product. For a worker, this may be measured by the amount of drug substance in the air in the manufacturing area that they might inhale.

For cleaning of manufacturing equipment, the PDE is only the starting point for determining what levels of drug residues are safe. A recent article demonstrated how batch size, the maximal daily dose of the next product, as well as the equipment surface influence the calculation of safe residue levels and consequently the level of risks for cross contamination (18). While these parameters influence the calculation of limits they provide no input into the level of Exposure. Other criteria may directly influence the cleaning capability of a substance such as manufacturing equipment Materials of Construction (MOC), the cleaning process parameters (e.g., cleaning agent, temperature, etc.) and most importantly the physico-chemical properties of the substances and their product matrices that affect their cleanability. These factors directly impact the level of residues and therefore the level of exposure. The PDE only reveals what the safe levels of these residues are. The actual level of residues found after cleaning reveals the level of exposure and this can be used to measure the level of risk.

In the world of cleaning validation, drug residue levels have been collected for many years. These drug residue levels have typically been compared to one or more limits that are not health-based or arbitrary (19). The drug residue levels either passed or failed these limits. What has been missing, in almost all cases, has been an evaluation of the level of risk that these drug residues actually show. Another recent article has shown how these residues can be compared to true health-based limits to determine the "margin of safety" the removal of these residues provides which also offers an indication of the level of risk. This "margin of safety", or level of risk, can be quantified using the statistical technique of Process Capability (20).

As with the Toxicity Scale derived from the PDE, it would be convenient and informative to have a similar scale for Process Capability. Another Scale has been developed that is converts the Process Capability value into a value on a "Process Capability Scale" which ranges from 0 - 10, with 0 being the lowest exposure level and 10 being the highest exposure level. This scale is also potentially useful as a scale for Occurrence or Likelihood FMEAs (20). While these scales have several potential applications, at the most basic level they can be used to clearly visualize the level of risk, and for the purposes of this article, why HPAPI does not necessarily translate to "high risk".

Table 2 below shows two drugs that have very different Toxicity Scores and Process Capability Scores and would clearly present different levels of risk - even though in a typical FMEA their Risk Priority Numbers (RPNs) would be the same (10). Drug 1 has a Toxicity Score of 10 (very high hazard) and would most likely be classified as an HPAPI. But it has a corresponding Process Capability Score of 1.0 (excellent cleaning) which would constitute a low risk situation. On the other hand, Drug 2 has a Toxicity Score of 1 (very low hazard) so it would not be classified as an HPAPI. But Drug 2 has a corresponding Process Capability Score of 10.0 (very poor cleaning), which indicates that patients would be exposed to residues exceeding the PDE and therefore represents a potentially high-risk situation.

Compound	Toxicity Score	Process Capability Score	Level of Risk
Drug 1 (HPAPI)	10	1.0	Low
Drug 2 (not-HPAPI)	1	10.0	High

Table 2. Risk based on Toxicity Scores and Process Capability Scores.

In summary, the risks presented by drug substances cannot be managed by simple classification into highly hazardous and highly potent categories of drugs. The hazard level (toxicity) of the compound and the level of exposure (Process Capability) must be considered together to arrive at a true measure of the level of risk and categories such as HPAPI are not helpful.

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