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Occupational Exposure Limits for Active Pharmaceutical Ingredients: A Comparative Review of ICH Q3C, OSHA, NIOSH, and European Medicines Agency Regulatory Frameworks and their Implications for Worker Health Surveillance

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Abstract

Active Pharmaceutical Ingredients (APIs) pose a significant occupational health challenge in pharmaceutical manufacturing and healthcare settings, where workers involved in synthesis, formulation, packaging, dispensing, and administration may be exposed to pharmacologically potent substances. Occupational Exposure Limits (OELs) are essential for protecting workers from unintended biological effects. This review critically evaluates four regulatory frameworks relevant to pharmaceutical occupational exposure: ICH Q3C on residual solvents, Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limits (RELs), and the European Medicines Agency (EMA) guideline for health-based exposure limits (HBELs). Their scientific foundations, derivation methodologies, applicability, legal status, and implications for occupational health surveillance were compared. A literature search was conducted using PubMed, Scopus, Web of Science, and regulatory databases, including OSHA, NIOSH, EMA, ICH, and ISPE, covering publications from 1990 to 2024. Studies addressing OEL derivation, occupational exposure assessment, worker health outcomes, and regulatory compliance were narratively synthesised. Considerable heterogeneity was identified among frameworks regarding scientific basis, methodology, update frequency, and enforceability. ICH Q3C provides classifications and permitted daily exposure limits for residual solvents but is not specifically designed for API dust. OSHA PELs is legally enforceable but include numerous limits that have not been comprehensively updated. NIOSH RELs incorporate scientific evidence but are generally advisory. EMA HBEL methodology offers an API-specific approach based on pharmacological and toxicological evaluation, although its primary regulatory purpose is prevention of cross-contamination. Occupational Exposure Banding (OEB) approaches, including ISPE systems, provide practical support where substance-specific OELs are unavailable. Overall, no single framework fully addresses pharmaceutical occupational health needs. Greater international harmonisation, periodic review, exposure monitoring, and health surveillance are needed to strengthen worker protection.

Major Findings: Regulatory frameworks differ substantially in scope, legal status, and scientific basis for API occupational exposure. EMA HBEL/PDE, NIOSH, and ISPE OEB approaches provide complementary tools, but no single framework fully addresses worker protection. An integrated OEL/OEB-based exposure assessment, biological monitoring, and proportional health surveillance framework is proposed.

Keywords: Active Pharmaceutical Ingredients, EMA Health-Based Exposure Limits, NIOSH Recommended Exposure Limits, Occupational Exposure Banding, Occupational Exposure Limits, OSHA Permissible Exposure Limits
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List of Abbreviations

Abbreviation	Full Term	Abbreviation	Full Term
API	Active Pharmaceutical Ingredient	NIOSH	National Institute for Occupational Safety and Health
OEL	Occupational Exposure Limit	OSHA	Occupational Safety and Health Administration
OEB	Occupational Exposure Band	PEL	Permissible Exposure Limit
HBEL	Health-Based Exposure Limit	REL	Recommended Exposure Limit
PDE	Permitted Daily Exposure	TWA	Time-Weighted Average
ICH	International Council for Harmonisation	TLV	Threshold Limit Value
EMA	European Medicines Agency	BEI	Biological Exposure Index
ISPE	International Society for Pharmaceutical Engineering	PBPK	Physiologically Based Pharmacokinetic (Model)
NOAEL	No Observed Adverse Effect Level	HD	Hazardous Drug
LOAEL	Lowest Observed Adverse Effect Level	QSAR	Quantitative Structure-Activity Relationship
ACGIH	American Conference of Governmental Industrial Hygienists	STEL	Short-Term Exposure Limit
IARC	International Agency for Research on Cancer	GHS	Globally Harmonised System of Classification
USP	United States Pharmacopeia	CSTD	Closed System Transfer Device
HPAPI	Highly Potent Active Pharmaceutical Ingredient	ATMP	Advanced Therapy Medicinal Product

1. Introduction

The pharmaceutical industry constitutes one of the most chemically diverse and pharmacologically complex occupational environments in the global workforce. Workers across the drug discovery, development, manufacturing, quality control, dispensing, and clinical administration continuum encounter exposure to hundreds of Active Pharmaceutical Ingredients (APIs) — biologically potent molecules designed to elicit specific physiological and pharmacological responses in human subjects at precisely defined therapeutic doses.

By definition, APIs are substances intended to produce pharmacological effects, and this very characteristic confers their occupational hazard potential. Unlike conventional industrial chemicals, where toxicity is largely a function of non-specific physicochemical interactions with biological macromolecules, APIs act through specific molecular targets — receptors, enzymes, ion channels, and transporters — often at extraordinarily low concentrations. Workers chronically exposed to even sub-therapeutic doses of pharmacologically active substances may experience unintended systemic effects: occupational sensitisation from beta-lactam antibiotics, hormonal disruption from corticosteroids and oral contraceptives, cardiovascular effects from antiarrhythmic agents, or haematological suppression from antineoplastic drugs[1-3].

The concept of an Occupational Exposure Limit (OEL) — the concentration of a chemical substance in workplace air below which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects — is the fundamental regulatory and scientific instrument for worker protection in chemical industries. For APIs, however, the derivation of OELs carries particular complexity: therapeutic dose-response relationships, species-specific pharmacokinetics, target organ toxicity profiles, sensitisation potential, reproductive and developmental toxicity, and genotoxic/carcinogenic classifications must all be considered within a regulatory framework that was originally designed for conventional industrial chemicals and solvents, not pharmacologically active molecules.

The global pharmaceutical manufacturing workforce is substantial and growing. The pharmaceutical market was valued at approximately USD 1.48 trillion in 2022, with manufacturing operations concentrated in the United States, European Union, India, China, and Japan. India alone accounts for approximately 20% of global generic drug manufacturing by volume, with an estimated 3.5 million workers directly employed in the pharmaceutical and allied chemical sector[4,5].

Despite this magnitude, the occupational health protection landscape for pharmaceutical workers remains fragmented, inconsistent, and — in many jurisdictions — inadequately enforced. At the international level, four

principal regulatory frameworks shape occupational exposure standards for APIs and pharmaceutical chemicals: the International Council for Harmonisation (ICH) Q3C guideline on residual solvents; the United States Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs); the National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limits (RELs) and hazardous drug guidance; and the European Medicines Agency (EMA) guideline on setting Health-Based Exposure Limits (HBELs) in manufacturing. Each framework differs substantially in its scientific methodology, scope, legal status, update frequency, and practical applicability to worker health surveillance[6-8].

This review provides a critical comparative analysis of these four frameworks, examines supplementary systems including Occupational Exposure Banding (OEB) methodologies developed by the International Society for Pharmaceutical Engineering (ISPE), and draws implications for the design and implementation of occupational health surveillance programmes for the pharmaceutical workforce. The review specifically addresses the scientific bases of each framework, their methodological strengths and limitations, their harmonisation status, and the practical challenges in their implementation within pharmaceutical manufacturing and healthcare settings.

Table 1. Classification of APIs by pharmacological hazard and illustrative occupational health effects

Pharmacological Category	API Examples	Occupational Health Effect	Primary Route of Exposure	Evidence Level
Antineoplastic/ Cytotoxic	Cyclophosphamide; Doxorubicin; Methotrexate; Paclitaxel	Genotoxicity; reproductive toxicity; carcinogenicity; bone marrow suppression; secondary malignancies	Inhalation; dermal; surface contact	Strong (Level A): Multiple cohort and case-control studies
Beta-lactam Antibiotics	Penicillin G; Amoxicillin; Cephalosporins	Occupational asthma; anaphylaxis; IgE-mediated sensitisation; urticaria	Inhalation (API dust); dermal	Strong (Level A): Long established; well characterised sensitisation mechanism
Corticosteroids	Dexamethasone; Beclomethasone; Prednisolone	Adrenal suppression; Cushing-like effects; immunosuppression; skin atrophy on chronic dermal exposure	Inhalation; dermal absorption	Moderate (Level B): Supported by experimental and case series data
Oral Contraceptives/ Sex Hormones	Ethinyl estradiol; Medroxyprogesterone; Testosterone	Menstrual irregularities in female workers; gynaecomastia in males; endocrine disruption; reproductive effects	Inhalation; dermal	Moderate (Level B): Multiple industry case series reports
Cardiovascular Drugs	Nifedipine; Propranolol; Digoxin	Hypotension; bradycardia; arrhythmias; heart block at occupational exposure	Inhalation (dust); dermal	Moderate (Level B): Supported by pharmacological reasoning and occupational case reports
Psychoactive Drugs	Haloperidol; Diazepam; Risperidone; Opioid analgesics	CNS depression; extrapyramidal effects; dependency potential; impaired cognitive function	Inhalation; dermal	Moderate (Level B): Case reports; pharmacokinetic modelling
Antidiabetic Agents	Insulin; Glibenclamide; Metformin	Hypoglycaemia (particularly with insulin and sulfonylureas); lactic acidosis (metformin — theoretical)	Inhalation (insulin aerosols); dermal	Moderate (Level B): Supported by pharmacological reasoning
Antiretrovirals	Zidovudine; Tenofovir; Efavirenz	Genotoxicity; reproductive toxicity; mitochondrial toxicity	Inhalation; dermal	Moderate (Level B): Mechanistic evidence; limited occupational cohort data
Enzymes and Biologicals	Papain; Subtilisins; Factor VIII; mAbs	Occupational asthma; anaphylaxis; high-molecular-weight sensitisation	Inhalation (aerosolisation during production)	Strong (Level A): Well characterised enzyme sensitisation data

2. The Nature of Occupational Hazards from Active Pharmaceutical Ingredients

2.1 Categories of Pharmacological Hazard

APIs present occupational hazards through multiple pathways that are distinct from conventional industrial toxicants. The primary routes of occupational exposure in pharmaceutical manufacturing include inhalation of API-containing aerosols, dust, and vapours; dermal contact with API-containing liquids, powders, and process intermediates; and, to a lesser extent, inadvertent ingestion through contaminated surfaces and inadequate hygiene practices[9,10].

The pharmacological hazard class of an API determines the nature and severity of potential occupational health effects. Highly potent APIs — defined broadly as compounds with a therapeutic daily dose at or below 1 mg/day or with specific high-hazard pharmacological characteristics — represent the most significant occupational concern. These include cytotoxic antineoplastics (alkylating agents, topoisomerase inhibitors, antimetabolites), hormonal agents (corticosteroids, sex hormones, thyroid hormones), highly potent cardiovascular drugs (antiarrhythmics, calcium channel blockers at high doses), immunosuppressants, and emerging biological and gene therapy products.

The principal pharmacological hazard categories, representative APIs, routes of exposure, and evidence levels are summarised in Table 1.

2.2 Routes of Exposure and Influencing Factors

The inhalation route is generally considered the most significant pathway for API exposure in pharmaceutical manufacturing. Airborne API concentrations are influenced by the physicochemical properties of the compound (vapour pressure, particle size distribution, dustiness), the manufacturing process type (open weighing, granulation, milling, tablet coating, vial filling), the engineering controls in place (local exhaust ventilation, isolators, restricted access barrier systems), and work practices. Respirable particles (aerodynamic diameter <10 μm) penetrate the lower respiratory tract, where absorbed doses can be substantial for potent APIs[11,12].

Dermal absorption is increasingly recognised as a significant and often underestimated exposure pathway. Several APIs demonstrate clinically meaningful transdermal penetration — notably fentanyl (the basis for fentanyl patches), oestradiol, testosterone, nicotine, and various cytotoxic agents including carmustine and mechlorethamine. Occupational dermal exposure can occur through direct skin contact with API-containing powders, liquids, and process equipment surfaces. The absence of skin notation in many pharmaceutical OELs — analogous to the OSHA skin notation for conventional chemicals — represents a notable regulatory gap in worker protection for APIs with significant dermal uptake[13,14].

2.3 Highly Potent API Threshold Definitions

The definition of "highly potent" or "potent" APIs varies across regulatory and industry frameworks, which itself creates inconsistency in occupational risk communication. The International Society for Pharmaceutical Engineering defines an API as highly potent when the therapeutic daily dose is ≤1 mg/day, or when the occupational exposure limit is ≤1 μg/m³, or when the compound has high-hazard pharmacological characteristics (genotoxic carcinogen, reproductive toxicant Category 1A/1B, potent sensitiser, narrow therapeutic index). The EMA HBEL guideline uses the Permitted Daily Exposure (PDE) concept — a daily dose below which there is negligible risk of adverse pharmacological effects — as the starting point for deriving occupational exposure limits through inhalation route modelling[15-17].

3. International Regulatory Frameworks for Pharmaceutical Occupational Exposure

3.1 The ICH Q3C Guideline: Residual Solvents in Pharmaceuticals

3.1.1 Scope and Scientific Basis

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3C guideline, first adopted in 1997 and revised in 2016, establishes limits for residual organic solvents in pharmaceutical drug substances and drug products. Although ICH Q3C was designed primarily to protect

patients from residual solvent exposure in finished pharmaceutical products, its classification system and Permitted Daily Exposure (PDE) derivation methodology have been extensively borrowed and adapted in the development of occupational exposure standards for APIs[18,19].

ICH Q3C classifies pharmaceutical solvents into three categories based on their toxicological profile and risk potential. Class 1 solvents (known or suspected human carcinogens and environmentally hazardous agents including benzene, carbon tetrachloride, and 1,2-dichloroethane) are to be avoided in pharmaceutical manufacturing. Class 2 solvents (non-genotoxic animal carcinogens or possible causative agents of reversible toxicity; including acetonitrile, chlorobenzene, cyclohexane, methylene chloride, and toluene) are subject to PDE limits. Class 3 solvents (low toxic potential; including acetone, ethanol, ethyl acetate, and isopropanol) carry a general PDE of 50 mg/day unless otherwise specified.

The PDE derivation methodology in ICH Q3C involves identifying the critical study or toxicological endpoint for each solvent from animal or human data; establishing the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) from the most sensitive relevant study; and applying a series of adjustment factors to extrapolate from the experimental scenario to the human occupational scenario, including factors for interspecies extrapolation (F1), intraspecies variability (F2), duration of study (F3), severity and reversibility of toxicity (F4), and no-effect level applicability (F5)[19,20].

$$\text{PDE (mg/day)} = \text{NOAEL} \times \text{Body weight (50 kg)} / (F1 \times F2 \times F3 \times F4 \times F5)$$

3.1.2 *Application to Occupational Settings and Limitations*

While ICH Q3C PDEs have been used as a basis for deriving occupational exposure limits for pharmaceutical solvents — through conversion to airborne concentration limits assuming a standard breathing rate and working hours — their direct applicability to occupational scenarios carries significant limitations[21].

First, ICH Q3C was designed for patient exposure in finished products, where exposure is episodic (dose-to-dose), well-defined in quantity, and involves systemic distribution of a known pharmaceutical substance. Occupational exposure, in contrast, is repeated daily (up to 8-10 hours/day, 5 days/week, over a working lifetime of 40+ years), often involves poorly defined mixed-solvent exposures, and occurs primarily via the inhalation route rather than the oral route assumed in ICH Q3C PDE calculations.

Second, ICH Q3C does not address API dusts, biologically active pharmaceutical substances, or complex pharmaceutical aerosols — the primary occupational exposure concern in drug manufacturing. The guideline is fundamentally a product quality and patient safety tool, not an occupational health instrument, and regulatory agencies including OSHA and EMA have explicitly stated that ICH Q3C PDEs are not intended to serve as occupational exposure limits.

Table 2. ICH Q3C solvent classification system with PDE values and occupational relevance

Solvent Class	Classification Basis	Examples	PDE (mg/day)	Occupational Relevance	OEL (OSHA PEL for Comparison)
Class 1	Known or suspected human carcinogens; environmental hazard	Benzene; Carbon tetrachloride; 1,2-Dichloroethane; 1,1,2-Trichloroethane	Avoid use; ICH Q3C specifies limits only where unavoidable	Highest hazard; IARC Group 1 or 2A carcinogens; requires substitution in occupational settings	Benzene: 1 ppm (OSHA PEL); NIOSH REL: 0.1 ppm; ACGIH TLV: 0.5 ppm
Class 2	Non-genotoxic animal carcinogens; reversible toxicity agents	Acetonitrile; Chlorobenzene; Cyclohexane; Methylene chloride; Toluene; Xylene	Acetonitrile: 4.1 mg/day; Chlorobenzene: 3.6 mg/day; Methylene chloride: 6.0 mg/day; Toluene: 8.9 mg/day	Moderate to high occupational hazard; PDE can be converted to inhalation OEL via breathing rate modelling	Toluene: 200 ppm (OSHA PEL); NIOSH REL: 100 ppm; Methylene chloride: 25 ppm (NIOSH REL)
Class 3	Low toxic potential; widely used pharmaceutical solvents	Acetone; Ethanol; Ethyl acetate; Isopropanol; Methanol	50 mg/day (general limit); methanol: 30 mg/day	Lower occupational hazard; conventional OELs generally applicable	Acetone: 1000 ppm (OSHA PEL); Ethanol: 1000 ppm; Isopropanol: 400 ppm

The ICH Q3C solvent classes, PDE values, and occupational relevance are summarised in Table 2.

3.2 OSHA Permissible Exposure Limits: Legal Authority and Scientific Currency

3.2.1 Legal Framework and Scope

The United States Occupational Safety and Health Administration (OSHA), established under the Occupational Safety and Health Act of 1970, is the primary federal agency responsible for setting and enforcing legally binding workplace chemical exposure standards — Permissible Exposure Limits (PELs) — in the United States. PELs represent the maximum concentration of a chemical substance in workplace air to which an employee may be exposed during an 8-hour time-weighted average (8h-TWA) work shift, or during a 15-min Short-Term Exposure Limit (STEL) window, without experiencing adverse health effects[22,23].

OSHA currently maintains approximately 500 enforceable PELs for specific chemical substances, codified in 29 CFR 1910.1000 (General Industry), 29 CFR 1926 (Construction Industry), and individual substance standards for particularly hazardous chemicals (*e.g.*, 29 CFR 1910.1028 for benzene; 29 CFR 1910.1048 for formaldehyde; 29 CFR 1910.1450 for laboratory chemicals). The legal basis and enforceability of OSHA PELs is unambiguous — violation carries civil and criminal penalties — making them the most legally powerful occupational exposure standard in the United States[23,24].

3.2.2 Scientific Currency and Limitations

Despite their legal authority, OSHA PELs is widely regarded by occupational health scientists and epidemiologists as scientifically outdated, insufficiently protective, and inadequately covering the contemporary pharmaceutical and chemical workforce. The vast majority of current OSHA PELs were adopted in 1971 based on the 1968 ACGIH Threshold Limit Values (TLVs) — a scientific database that is now more than 50 years old and does not reflect the substantial advances in toxicological knowledge, epidemiological evidence, and analytical capabilities achieved over the past five decades[25,26].

A landmark OSHA analysis published in 2014 acknowledged that hundreds of PELs are outdated: NIOSH reviews have identified that for many regulated substances, the current OSHA PEL is insufficiently protective compared with the best available toxicological evidence. OSHA's 1989 Air Contaminants Standard, which attempted to update PELs for 376 substances simultaneously, was vacated by the Eleventh Circuit Court of Appeals in AFL-CIO v. OSHA (1992) on the grounds of insufficient individual risk assessment documentation — a setback from which OSHA PEL reform has never fully recovered[26,27].

For the pharmaceutical sector specifically, OSHA PELs have several critical gaps. First, fewer than 20 APIs have specific OSHA PELs, meaning that the vast majority of the approximately 2,500 APIs currently on the market have no legally enforceable OSHA occupational exposure standard. Second, OSHA PELs for pharmaceutical solvents were not derived with consideration of co-exposure to pharmacologically active API dusts, creating an incomplete risk picture in multi-compound pharmaceutical manufacturing environments. Third, OSHA has no specific standard for "hazardous drugs" — a category that includes approximately 200 antineoplastics, hormonal, antiviral, bioengineered, and other high-hazard pharmaceutical compounds identified by NIOSH.

The pharmaceutical industry has, by necessity, operated largely in the absence of OSHA-specific API OELs. Companies have instead relied on voluntary OEL standards derived by their internal toxicologists, industry consortium OELs (AstraZeneca, GlaxoSmithKline, and other major manufacturers publish OELs for their products on the OEL-at-a-Glance database), ISPE OEB classifications, and NIOSH RELs and hazardous drug guidance[28,29].

3.3 NIOSH Recommended Exposure Limits and Hazardous Drug Framework

3.3.1 NIOSH RELs: Scientific Rigour and Worker Advocacy Focus

The National Institute for Occupational Safety and Health (NIOSH), established under the same 1970 legislation as OSHA but as a research and public health agency rather than a regulatory enforcement body within the Centres for Disease Control and Prevention (CDC), develops Recommended Exposure Limits (RELs) for workplace chemical exposures. NIOSH RELs are non-binding recommendations — they carry no legal enforcement authority — but are the most scientifically current and comprehensive exposure recommendations available for the US pharmaceutical workforce[30,31].

NIOSH criteria documents, on which RELs are based, typically involve a comprehensive review of all available epidemiological, toxicological, and clinical evidence; dose-response analysis; risk characterisation; and — where feasible — quantitative risk assessment targeting a specific excess risk level (typically 1 in 1000 or 1 in 10,000 for carcinogens). NIOSH RELs are substantially more current than OSHA PELs (NIOSH regularly publishes new or updated REL criteria documents), and for many pharmaceutical chemicals, the NIOSH REL is significantly more stringent than the OSHA PEL, reflecting the additional toxicological evidence accumulated since 1971[31,32].

3.3.2 NIOSH Hazardous Drug List and Healthcare Worker Protection

Of particular importance to the pharmaceutical sector is NIOSH's development and periodic update of the List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings — commonly referred to as the NIOSH Hazardous Drug (HD) List. First published in 2004 and updated biennially, the NIOSH HD List identifies pharmaceutical agents that meet one or more of the following hazard criteria in humans or animals: carcinogenicity, teratogenicity or other developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, and new drugs that mimic existing hazardous drugs in structure or toxicity profile[33,34].

The 2024 NIOSH HD List includes more than 200 drugs across three groups: Group 1 (antineoplastic drugs meeting HD criteria), Group 2 (non-antineoplastic drugs meeting one or more HD criteria), and Group 3 (drugs primarily for reproductive risk only — risk to reproductive potential including pregnancy). The NIOSH HD framework has been adopted as the scientific basis for the United States Pharmacopeia (USP) Chapter 800 (Hazardous Drugs — Handling in Healthcare Settings), which establishes standards for receipt, storage, compounding, dispensing, administration, and disposal of hazardous drugs in healthcare entities[33,35].

NIOSH provides specific engineering control recommendations for hazardous drug handling: Biological Safety Cabinets (BSC Class II, Type B2) for closed-system drug transfer and compounding; Compounding Aseptic Containment Isolators (CACIs); Closed System Drug Transfer Devices (CSTDs); and personal protective equipment specifications including chemotherapy-tested gloves (ASTM D6978-05), closed-front impermeable gowns, and respiratory protection during aerosolisation risk activities. These recommendations, while non-binding at the federal level, have become de facto industry standards and are referenced by accreditation bodies including The Joint Commission.

The NIOSH hazardous-drug groups, associated health risks, engineering controls, and healthcare applications are summarised in Table 3.

3.4 EMA Guideline on Setting Health-based Exposure Limits: The Most API-specific Framework

3.4.1 Background and Regulatory Context

The European Medicines Agency (EMA) guideline on setting Health-Based Exposure Limits (HBELs) in the manufacture of different medicinal products in shared facilities (EMA/CHMP/CVMP/SWP/169430/2012), adopted in 2014 and representing the culmination of a decade of regulatory science development, provides the most comprehensive and API-specific methodology for establishing exposure limits for pharmaceutical substances. Although the guideline was developed primarily to address cross-contamination risk — the unintended carry-over of one API into another product manufactured in the same facility — its scientific methodology is directly applicable, and is increasingly applied, to the derivation of occupational exposure limits for API manufacturing workers[36,37].

The EMA HBEL guideline was developed in response to regulatory concerns arising from high-profile product contamination incidents, including the contamination of conventional pharmaceutical products with potent hormonal compounds and drew upon the PDE derivation methodology established in ICH Q3C, extending it comprehensively to API substances[38].

3.4.2 PDE Derivation Methodology Under EMA HBEL

The EMA HBEL methodology requires calculation of a Permitted Daily Exposure (PDE) value — the maximum daily dose of an API that is considered acceptable to be present as a cross-contaminant in another medicinal product intended for daily patient use, without clinical consequence. The PDE is derived using the same mathematical framework as ICH Q3C, applied to the

Table 3. Comparison of NIOSH hazardous drug groups with occupational health implications

NIOSH HD Group	Criteria	Drug Examples	Primary Health Risk	Recommended Engineering Controls	Healthcare Setting Application
Group 1: Antineoplastic HD	IARC or NTP classified carcinogen; teratogenicity; reproductive toxicity; organ toxicity at low dose; genotoxicity	Cyclophosphamide; Doxorubicin; Methotrexate; Vincristine; Paclitaxel; Cisplatin; Fluorouracil	Genotoxicity; carcinogenicity; reproductive toxicity (miscarriage; infertility); bone marrow suppression; organ toxicity	BSC Class II Type B2 or CACI; CSTDs; double chemotherapy-tested gloves; impermeable gown; respiratory protection; dedicated storage	Pharmacy compounding areas; oncology administration units; research laboratories; pharmaceutical manufacturing
Group 2: Non-antineoplastic HD	Meets one or more HD criteria in humans or animals	Thalidomide; Diazepam; Warfarin; Phenytoin; Ribavirin; Ganciclovir; Azathioprine; Sex hormones (injectable)	Teratogenicity; reproductive toxicity; organ toxicity; endocrine disruption; immunosuppression	Risk assessment-based approach; CSTDs recommended for antineoplastic-like risk profiles; appropriate PPE; engineering controls proportional to risk	Pharmacy; hospital wards; community pharmacy; pharmaceutical manufacturing
Group 3: Reproductive Risk only	Reproductive or developmental toxicity in humans or animals; reproductive potential risk during handling	Finasteride; Dutasteride; Misoprostol; Spironolactone; Oral contraceptives (high-dose)	Reproductive toxicity in workers of reproductive potential; teratogenicity; developmental abnormalities in exposed offspring	Precautions especially for workers of reproductive potential; assess risk per individual; appropriate PPE; consider alternative assignment during pregnancy or lactation	Pharmacy; healthcare settings; pharmaceutical manufacturing; dispensing

Abbreviations: BSC = Biological Safety Cabinet; CACI = Compounding Aseptic Containment Isolator; CSTD = Closed System Drug Transfer Device.

comprehensive pharmacological and toxicological data package for each API[36,39].

The key methodological steps in EMA HBEL/PDE derivation are: (i) Identification of the critical effect — the most sensitive, most relevant adverse pharmacological or toxicological effect for the particular API; (ii) Identification of the NOAEL, LOAEL, or pharmacological threshold dose from the available data (therapeutic dose-response, safety pharmacology studies, non-clinical toxicology studies); (iii) Application of adjustment factors (equivalent to the ICH Q3C F factors) accounting for interspecies extrapolation, intraspecies variability, study duration adjustment, severity and reversibility of the critical effect, and NOAEL/LOAEL uncertainty; (iv) Division of the adjusted threshold dose by the daily dose exposure assumption to derive the PDE in mg/day.

For occupational purposes, the PDE can be converted to an inhalation-based occupational exposure limit by accounting for the inhalation absorption efficiency of the API, the breathing rate of a pharmaceutical worker during typical work activities (assumed to be 10 m^3 over an 8-hour working shift in ISPE and industry guidance), and whether the API is present as a respirable aerosol or vapour. This conversion, while straightforward in principle, requires knowledge of the API's physical form (particle size distribution), its pulmonary absorption fraction, and the work scenario's specific breathing rate[40,41].

The EMA HBEL guideline explicitly acknowledges the applicability of PDE-based limits to occupational scenarios, noting that "if the derived PDE is of similar magnitude to the Occupational Exposure Limit

(OEL), an OEL may be used instead of the PDE." This acknowledgement has driven significant adoption of the EMA HBEL methodology in pharmaceutical company occupational hygiene programmes across Europe and globally, where companies routinely derive occupational exposure limits from their product-specific HBELs using the inhalation conversion approach.

3.4.3 Key Distinctions from other Frameworks

The EMA HBEL approach is distinguished from other frameworks by several important characteristics. First, it is inherently API-specific, derived from the pharmacological and toxicological data package of each individual compound, rather than relying on a generic chemical toxicity database. Second, it explicitly requires consideration of the most relevant adverse pharmacological effect as the critical endpoint, rather than general organ toxicity — an approach that is scientifically more appropriate for pharmacologically targeted API molecules. Third, the EMA framework is regularly updated through a rolling review process and is applied to all new medicinal products granted marketing authorisation in the EU, ensuring that HBELs are available for the contemporary pharmaceutical portfolio. Fourth, the EMA HBEL guideline has global regulatory reach through its adoption by PICS (Pharmaceutical Inspection Co-operation Scheme) member countries and reference by regulators including FDA, Health Canada, and TGA Australia[36,42,43].

4. Occupational Exposure Banding: Bridging Regulatory Gaps

4.1 The Rationale for Occupational Exposure Banding

The pharmaceutical industry routinely encounters a fundamental operational challenge: new APIs are developed and brought into manufacturing before sufficient toxicological data are available to derive a conventional OEL through the full ICH/EMA PDE methodology. This is particularly acute in early-stage pharmaceutical development, where a candidate drug may be synthesised in kilogram quantities for Phase I/II clinical trials years before the comprehensive non-clinical toxicology package required for OEL derivation is complete. During this interim period, workers handling the novel API have no scientifically grounded occupational exposure standard to guide engineering control selection, exposure monitoring design, or health surveillance protocols[44,45].

Occupational Exposure Banding (OEB) systems were developed by major pharmaceutical companies and the International Society for Pharmaceutical Engineering (ISPE) to address this gap. OEB assigns a compound to one of several exposure bands — each associated with a defined airborne concentration range and corresponding engineering control and PPE requirements — based on a semi-quantitative assessment of available hazard data, without requiring the complete toxicological dataset needed for a full OEL derivation. As toxicological data mature, band assignments can be refined or converted to formal OELs.

4.2 ISPE OEB Framework

The ISPE Good Practice Guide on Assessing the Particulate Hazards of Compounds in Pharmaceutical Manufacturing, which has undergone multiple revisions and is now in its third edition, defines five primary occupational exposure bands (OEB 1 through OEB 5) for APIs, with OEB 5 being further subdivided by some organisations (*e.g.*, using OEB 5A and OEB 5B) to distinguish compounds requiring conventional engineering containment from those requiring pharmaceutical isolator-grade containment. The ISPE OEB definitions are based on the airborne concentration range below which no adverse health effects are expected (the expected or target OEL range) and the corresponding engineering control requirements[45,46].

The ISPE occupational exposure bands, concentration ranges, hazard characteristics, and control requirements are summarised in Table 4.

4.3 Quantitative OEB Approaches: Control Banding and Nano Mapper

Multiple quantitative or semi-quantitative OEB methodologies have been developed to improve the reproducibility and scientific defensibility of band assignments. The Pfizer Global OEB System, the GlaxoSmithKline Hazard Assessment Framework, AstraZeneca's OEB system, and the PhRMA (Pharmaceutical Research and Manufacturers of America) OEB framework represent company-

Table 4. ISPE occupational exposure banding system: Definitions, concentration ranges, and engineering control requirements

OEB Band	OEL Range (µg/m³)	API Potency Descriptor	Pharmacological Hazard Characteristics	Engineering Control Requirements	Examples (illustrative)
OEB 1	≥1,000 µg/m³ (1 mg/m³)	Low potency; minimal hazard	High therapeutic doses (>1 g/day); no significant systemic toxicity at likely occupational exposure levels; not sensitising; not genotoxic or carcinogenic	Standard industrial hygiene controls; general dilution ventilation; minimal PPE requirements	Antacids; bulk vitamins at high doses; certain excipients with pharmacological activity
OEB 2	100-1,000 µg/m³	Moderate potency	Therapeutic dose 100 mg-1 g/day; some systemic effects possible at high occupational exposures; not genotoxic; not significant sensitiser	Local exhaust ventilation (LEV) for dusty operations; basic respiratory protection for high-dust tasks; standard chemical-resistant gloves	Many analgesics; antihypertensives at moderate doses; common antibiotics (non-beta-lactam)
OEB 3	10-100 µg/m³	Moderately high potency	Therapeutic dose 10-100 mg/day; pharmacological effects possible at occupational exposure; possible reproductive effects; moderate sensitisation potential	Engineered containment for open handling; LEV with HEPA filtration; half-face respirator with P100 filter; appropriate gloves and gowns; awareness training	Many cardiovascular drugs; corticosteroids; antidepressants; moderate-dose hormonal agents
OEB 4	1-10 µg/m³	High potency	Therapeutic dose 1-10 mg/day; significant pharmacological effects at low concentrations; potential reproductive toxicity; significant sensitisation possible	Dedicated equipment; powder transfer isolators or split butterfly valves; supplied air or full-face PAPR; appropriate chemotherapy-type PPE; routine biomonitoring	Many antiepileptics; potent cardiovascular drugs; highly potent hormonal agents; certain antineoplastics
OEB 5	<1 µg/m³ (often <0.1 µg/m³)	Highly potent/ extreme potency	Therapeutic dose <1 mg/day; active at nanogram level concentrations; genotoxic carcinogen; reproductive Category 1A/1B toxicant; extreme sensitiser; narrow therapeutic index	Pharmaceutical-grade isolators; negative-pressure containment; continuous air monitoring; full supplied-air PPE; comprehensive biological monitoring programme; strict medical surveillance	Cytotoxic antineoplastics; sex hormones (medroxyprogesterone; ethinyl estradiol); potent biologicals; gene therapy products; certain immunosuppressants

specific approaches that have been published in the peer-reviewed literature. In addition, academic and consortium-developed tools including the RISKOEB system (developed by Levin *et al.*[47]) and the Band-in-a-Box rapid assessment tool have been applied in pharmaceutical development settings[48].

Common input variables across quantitative OEB systems include: the pharmacological potency indicator (target OEL if known, or therapeutic dose as a surrogate); carcinogenicity classification (IARC Group, NTP classification, GHS/CLP Category 1A/1B/2); reproductive and developmental toxicity classification (GHS Category 1A/1B/2); sensitisation potential (skin and respiratory); target organ toxicity profile (single and repeated dose); genotoxicity data (Ames test, *in vitro* chromosomal aberration, in vivo micronucleus); and any Structure-Activity Relationship (SAR) alerts generated by computational toxicology tools.

These inputs are typically scored, weighted, and combined through a decision algorithm or scoring matrix that generates a band assignment. The key advantage of quantitative OEB approaches over expert judgment alone is improved inter-rater reliability and auditability — critical considerations for regulatory inspection and worker health protection programmes. Validation studies have demonstrated that well-designed OEB systems achieve agreement with formally derived OELs in 70-90 % of cases across a range of pharmaceutical compound datasets[49,50].

Table 5. Comparative matrix of four regulatory frameworks for pharmaceutical occupational exposure limits

Criterion	ICH Q3C	OSHA PEL	NIOSH REL	EMA HBEL
Primary Regulatory Purpose	Patient safety (residual solvents in pharmaceuticals)	Worker health protection (legal enforcement)	Worker health protection (advisory/ research)	Product cross-contamination prevention / patient safety (applicable to OEL derivation)
Legal status	Voluntary (regulatory guideline for product approval)	Legally binding in US workplaces (enforced via OSHA Act 1970)	Non-binding recommendations (no legal enforcement authority)	Required for EU marketing authorisation applications (legally binding for product quality; voluntary for occupational OELs)
Scope of coverage	Pharmaceutical organic solvents (Classes 1-3)	~500 chemical substances in general industry (very few APIs specifically)	~700+ substances including carcinogen risk assessments; NIOSH HD List for ~200 hazardous drugs	All APIs requiring marketing authorisation in the EU; applicable to ~8,000+ medicinal products
Scientific basis (year range of evidence)	Toxicological data available up to guideline revision date (2016); solvent-specific literature review	1968 ACGIH TLV scientific basis for most substances; very few updates post-1971 reform failure	Ongoing review; criteria documents typically reflect evidence up to 5 years before publication	Rolling updates; reflects contemporary drug development Toxicology package; evidence current to date of product authorisation
Derivation methodology	NOAEL/LOAEL × adjustment factors (F1-F5); PDE in mg/ day; converted to air concentration for OEL application	Historical industrial hygiene practice (1960s-70s); variable methodology by substance	Comprehensive literature review; quantitative risk assessment for carcinogens; explicit risk characterisation (1/1000 or 1/10,000 excess risk target)	NOAEL/LOAEL from critical pharmacological or toxicological study × adjustment factors (identical structure to ICH Q3C); PDE in mg/day; explicit pharmacological endpoint focus
Update frequency	Infrequent; major revision 2016; individual PDE updates through ICH Q3C addenda process	Extremely infrequent; 1971 and 1989 (1989 vacated); no systematic review programme for most PELs	Ongoing: individual REL criteria documents published continuously; 2024 occupational carcinogen update	Rolling: HBEL derived for each new marketing authorisation; scientific basis updated with each new drug application; guidelines periodically revised (2014; revision ongoing)
Applicability to highly potent APIs	Limited: designed for solvents; not applicable to API dust, biologicals, or nanomedicines	Minimal: <20 APIs have specific OSHA PELs; hazardous drug standard absent despite legislative authority	Substantial: NIOSH HD List covers ~200 hazardous APIs; RELs exist for carcinogenic APIs and solvents	Comprehensive: Covers all APIs on EU market; most applicable to occupational scenarios through PDE-to-OEL conversion
Global harmonisation status	ICH membership: USA, EU, Japan, Canada, Switzerland, China (observer); high global adoption in pharma industry	USA only; significant influence on other national occupational safety standards historically but not a harmonised international standard	USA primarily; CDC/NIOSH guidance adopted internationally by many national occupational health programmes	EU and PICS member countries (38+ countries); increasingly referenced globally; cited by FDA, TGA, Health Canada for shared facility inspections
Biological monitoring guidance	None: Focused on product testing, not worker biomonitoring	Limited: Biological Exposure Indices (BEIs) developed by ACGIH, not OSHA directly; few pharma-specific BEMs	Limited: Biological exposure guidance for select substances; NIOSH HD alert recommends urine/ blood monitoring for cytotoxic drugs	None directly: HBEL guideline is a product quality document; biological monitoring for workers is addressed in complementary occupational health guidance

5. Comparative Analysis of Regulatory Frameworks

5.1 Scientific Methodology Comparison

The four regulatory frameworks under review differ fundamentally in their approach to the scientific derivation of exposure limits. OSHA PELs, for the majority of substances, represent the adoption of 1968 ACGIH TLVs without systematic independent scientific review — a "snapshot" of 1960s occupational toxicology that does not incorporate subsequent mechanistic understanding, epidemiological findings, or risk assessment methodologies. NIOSH RELs employ a systematic literature review and quantitative risk assessment approach similar to regulatory risk assessment in environmental toxicology, with explicit risk characterisation and target excess risk levels for carcinogens.

ICH Q3C PDE derivation follows a structured adjustment factor methodology that is scientifically transparent and reproducible but was designed for patient safety in pharmaceutical products rather than occupational health — a fundamental misalignment that limits its direct utility in setting OELs. The EMA HBEL methodology is the most API-specific and scientifically sophisticated of the four frameworks, incorporating the pharmacological mode of action, the most sensitive human therapeutic dose-response data, and a comprehensive adjustment factor approach that explicitly addresses pharmacological effects as the critical endpoint[36,42].

A comparative matrix of the four principal regulatory frameworks is presented in Table 5.

5.2 The OEL Derivation Comparison: A Worked Example

To illustrate the practical differences between frameworks, it is instructive to consider how each would approach establishing an exposure limit for cyclophosphamide — a nitrogen mustard alkylating antineoplastic agent that is a NIOSH Group 1 hazardous drug, an IARC Group 1 human carcinogen (sufficient evidence of carcinogenicity in humans), and a reproductive Category 1A toxicant. Cyclophosphamide is widely used in oncology practice and requires preparation by pharmacy compounding personnel and administration by nursing staff — populations at documented occupational exposure risk[33,51].

Under the OSHA framework, there is no specific OSHA PEL for cyclophosphamide. Workers handling cyclophosphamide in healthcare compounding pharmacies are technically only subject to the general duty clause (Section 5(a)(1) of the OSH Act), which requires employers to provide workplaces free from recognised serious hazards — a provision that requires OSHA to prove both recognition of the hazard and feasibility of abatement but does not specify a quantitative exposure limit. This is a stark regulatory gap for one of the most well-characterised occupational carcinogens in healthcare.

NIOSH, in its 2016 technical report on workplace controls and exposures to antineoplastic drugs in healthcare settings, does not establish a specific REL for cyclophosphamide but recommends the use of all engineering controls, closed-system transfer devices, and PPE consistent with its hazardous drug classification. NIOSH further notes that "no safe level of exposure can be recommended" for genotoxic carcinogens such as cyclophosphamide — a position consistent with the linear no-threshold model of carcinogen risk assessment but practically challenging for occupational hygiene programme design[35,52].

The EMA HBEL for cyclophosphamide (as a drug present in shared manufacturing facilities) has been publicly derived by several toxicology consultancies and pharmaceutical companies, yielding PDE values in the range of 0.005-0.02 mg/day for the oral route. Converting to an inhalation OEL assuming 10 m^3/shift breathing volume and 50% pulmonary absorption yields an occupational air concentration limit of approximately 0.001-0.004 µg/m^3 — an OEB 5 compound by the ISPE framework, requiring pharmaceutical-grade isolator containment for open handling. Several major oncology drug manufacturers apply OELs in the range of 0.001-0.01 µg/m^3 for cyclophosphamide, broadly consistent with EMA HBEL derivation.

6. Occupational Health Surveillance: Framework Implications and Programme Design

6.1 The Purpose and Components of Occupational Health Surveillance

Occupational health surveillance for pharmaceutical workers serves multiple complementary functions:

Table 6. Recommended biological monitoring approaches for selected API categories in pharmaceutical settings

API Category	Biological Marker	Biological Matrix	Analytical Method	Timing of Sample	Biological Exposure Index (if established)	Regulatory Reference
Alkylating cytotoxics (cyclo phosphamide; ifosfamide)	Cyclophosphamide; ifosfamide parent compound and metabolites	Urine	LC-MS/MS; GC-MS (after SPE or LLE extraction)	End of shift; end of work week	No established BEI; NIOSH suggests LOQ as action level (~0.1 µg/L cyclophosphamide in urine as alert level used by some institutions)	NIOSH 2010 Technical Report; ASHP Guidelines
Platinum-based cytotoxics (cisplatin; carboplatin; oxaliplatin)	Total urinary platinum; speciated platinum by LC-ICP-MS	Urine	ICP-MS; ICP-OES; LC-ICP-MS	End of shift following platinum drug handling	No established BEI; background urinary platinum <5 ng/L; occupational alert level: >5 ng/L	NIOSH 2010 Technical Report; published European oncology pharmacy studies
Antimetabolites (methotrexate; fluorouracil)	Methotrexate (urine; plasma); 5-FU and metabolites	Urine; plasma	ELISA (methotrexate); LC-MS/MS (5-FU and metabolites)	End of shift; post-infusion preparation session	No established BEI; detectable methotrexate in urine (any concentration) suggests inadequate containment	NIOSH 2010 Technical Report; published nursing and pharmacy cohort studies
Beta-lactam antibiotics	Specific IgE to penicilloic determinants (skin prick test or RAST/ Immunocapture)	Serum; skin prick test response	Specific IgE RAST (radioallergosorbent test); Immuno CAP fluorescence enzyme immunoassay	Pre-employment baseline; annual surveillance; symptom-triggered	No BEI; positive specific IgE to penicilloyl-polylysine or minor determinants = sensitised; removal from exposure recommended	NIOSH; European Pharmaceutical Aerosol Group guidelines
Corticosteroids	Morning cortisol; 24-hour urinary cortisol; low-dose ACTH stimulation test (if adrenal suppression suspected)	Serum; urine	Chemiluminescent immunoassay; LC-MS/MS	Morning (fasting); 24-hour urine collection	Serum cortisol <5 µg/dL (9:00 AM) may indicate adrenal suppression; ACTH stimulation test for confirmation	No formal BEI; clinical judgement combined with exposure assessment recommended
Sex hormones (oral contraceptives; androgenic steroids)	Serum oestradiol; FSH; LH (females); serum testosterone; LH (males); menstrual cycle tracking	Serum	Chemiluminescent immunoassay; LC-MS/MS	Pre-employment baseline; six-monthly surveillance	No established pharmaceutical-specific BEI; comparison with population reference ranges for sex and age	No formal regulatory standard; specialist endocrinology review recommended for abnormal values
Industrial pharmaceutical solvents (toluene; xylene; acetonitrile)	Urinary hippuric acid (toluene); urinary methyl hippuric acid (xylene); urinary mandelic acid + phenyl glyoxylic acid (ethylbenzene)	Urine	Colorimetric; HPLC; GC-MS	End of shift	Toluene: 1.6 g hippuric acid/g creatinine (ACGIH BEI); Xylene: 1.5 g methyl hippuric acid/g creatinine (ACGIH BEI)	ACGIH BEI documentation; OSHA analytical methods; NIOSH NMAM methods

Abbreviations: BEI = Biological Exposure Index; LOQ = Limit of Quantification; TWA = Time-Weighted Average.

early detection of work-related health effects in exposed individuals (medical surveillance); monitoring of biological markers of exposure or early effect to verify the adequacy of engineering controls (biological exposure monitoring); population-based tracking of health outcomes to identify occupational disease clusters and inform OEL adequacy (epidemiological surveillance); and regulatory compliance documentation. Effective pharmaceutical occupational health surveillance programmes require integration of all four components, anchored to the OEL framework in use at the facility[7,53].

6.2 Biological Monitoring in Pharmaceutical Settings

Biological monitoring — the measurement of chemicals or their metabolites or reaction products in biological media (urine, blood, exhaled air) to estimate absorbed dose — is the most direct method for assessing actual worker exposure to APIs, accounting for all routes of exposure (inhalation, dermal, incidental ingestion) simultaneously. Biological monitoring provides a personalised, integrated measure of exposure that complements (but does not replace) area and personal air monitoring[54].

For cytotoxic antineoplastics, urinary mutagenicity assays (Ames test on urine concentrates), wipe sampling of workplace surfaces, and direct urinary measurement of the drug or its metabolites (*e.g.*, urinary cyclophosphamide by LC-MS/MS; urinary platinum for platinum-based chemotherapy) are established biological monitoring approaches. For hormonal APIs, serum hormone level monitoring in exposed workers can provide evidence of pharmacological effect, though distinguishing occupational from endogenous or exogenous non-occupational hormonal variation requires careful baseline assessment and longitudinal monitoring design.

Recommended biological monitoring approaches for selected API categories are presented in Table 6.

6.3 Health Surveillance Programme Design based on OEL Framework

The specific regulatory framework guiding OEL establishment in a pharmaceutical facility should directly inform the design of the occupational health surveillance programme. In US facilities governed by OSHA PELs, statutory medical surveillance requirements exist for specific substances (29 CFR 1910.1028 for benzene workers, 29 CFR 1910.1048 for formaldehyde-exposed workers), but for the vast majority of APIs, medical surveillance is not legally mandated by OSHA and is implemented voluntarily by employers or required by pharmaceutical GMP expectations[7,23].

In European facilities operating under EMA HBEL guidance and national transpositions of the EU Directive on Chemical Agents at Work (Directive 98/24/EC) and the EU Carcinogens, Mutagens, and Reprotoxic (CMR) Directive (Directive 2004/37/EC), health surveillance is a statutory requirement for workers exposed to defined categories of hazardous substances — including carcinogens and reproductive toxicants — at concentrations above specified action levels. The EU framework thus creates a stronger legal mandate for occupational health surveillance in pharmaceutical environments than its US OSHA counterpart for the majority of APIs.

An evidence-based pharmaceutical occupational health surveillance programme should include: pre-placement medical assessment (baseline health status; identification of pre-existing conditions that may increase susceptibility to API pharmacological effects; baseline biological monitoring); periodic surveillance (frequency proportional to OEB classification — minimum annually for OEB 4/5 compounds, bi-annually for OEB 3, every 3 years for OEB 1/2); task-specific health monitoring for new or unusual API exposures; symptom-based surveillance (respiratory questionnaire for sensitising APIs; neurological assessment for neurotoxic APIs; endocrine assessment for hormonal APIs); and exit examination for workers leaving API-exposed roles[55].

7. Challenges in Global Harmonisation of Pharmaceutical OELS

7.1 Barriers to Harmonisation

The achievement of globally harmonised OELs for APIs faces a complex set of scientific, regulatory, economic, and political barriers. At the scientific level, OEL derivation is inherently a value-laden process that involves choices about acceptable risk levels, the weight given to animal versus human data, and the selection of adjustment factors — choices that reflect different national and regulatory cultures. The United States traditionally applies a worker protection philosophy that relies heavily on feasibility analysis (technical and economic feasibility of achieving

a given OEL), while the European approach prioritises the health-based derivation of the safest achievable OEL followed by a separate feasibility assessment.

At the regulatory level, the fragmentation of national occupational health authorities — with separate agencies often responsible for different industry sectors, worker categories, or chemical classes within the same country — creates inconsistencies even within national systems. In India, for example, pharmaceutical worker chemical exposure standards are primarily governed by the Factories Act 1948 and its Schedule to Rule 73 (which lists threshold limit values), supplemented by the Mines Act 1952, but without a dedicated pharmaceutical occupational safety standard comparable to US USP 800 or EU CMR Directive requirements. The Indian pharmaceutical workforce — the world's largest in generic drug manufacturing — thus operates in a regulatory environment with significantly less worker protection from API exposure than comparable workers in the United States or European Union[4,5].

7.2 Ongoing Harmonisation Initiatives

Several international initiatives are working toward greater harmonisation of pharmaceutical occupational exposure standards. The ICH's work programme includes consideration of occupational safety guidance as a priority area for future guidelines. ISPE's collaborative Risk-MaPP (Risk-Based Manufacture of Pharmaceutical Products) baseline guide provides a common framework for hazard assessment and OEL derivation that has been adopted across ICH member country pharmaceutical industries. The International Labour Organisation (ILO) Chemical Hazards in the Work Environment programme provides non-binding guidance applicable to pharmaceutical chemical safety that is referenced by many developing country occupational safety agencies. The Global Alliance for Chronic Diseases (GACD) and WHO-linked occupational health programmes have called for inclusion of pharmaceutical worker health protection in global occupational health agendas[46,47].

8. Implications for Worker Health Surveillance in Pharmaceutical Settings

8.1 Strengthening OEL-surveillance Integration

The most important implication of the comparative framework analysis presented in this review is the urgent need for pharmaceutical occupational health surveillance programmes to be explicitly grounded in the most scientifically current and API-relevant OEL framework available for each compound handled, rather than relying exclusively on any single regulatory system. In practice, this means applying EMA HBEL-derived OELs where available, supplemented by NIOSH RELs and HD guidance for classified hazardous drugs, and ISPE OEB classifications for novel compounds lacking formal OELs — while maintaining awareness of the legal requirements imposed by OSHA PELs in US facilities as a minimum compliance baseline.

For multi-national pharmaceutical companies operating in both the US and EU, the "highest common standard" approach — applying the more stringent of the applicable national and international OELs — represents best practice and is increasingly an expectation of regulatory inspectors. A 2019 EMA reflection paper on shared manufacturing facilities noted that where company-derived OELs based on HBELs are more stringent than national occupational health standards, the more stringent company OEL should be applied — a position that effectively elevates EMA HBEL-based standards to de facto mandatory status in EU pharmaceutical manufacturing environments[42].

8.2 Health Surveillance Gaps and Research Priorities

Systematic reviews and epidemiological studies consistently identify several critical gaps in pharmaceutical occupational health surveillance. First, surveillance is heavily weighted toward cytotoxic antineoplastics — a priority category that is well-justified given the carcinogenicity evidence but that may result in under-attention to hazards from non-antineoplastic high-potency APIs (hormonal agents, immunosuppressants, antiretrovirals) that are often handled with less rigorous containment. Second, surveillance data are rarely pooled across companies or facilities to enable the statistical power needed to detect rare but serious occupational health outcomes — an issue that could be addressed through de-identified industry consortium surveillance programmes similar to the UK-based EPIDERM national occupational skin disease surveillance system.

Third, the shift toward biopharmaceutical and advanced therapy medicinal product (ATMP) manufacturing — gene therapies, cell therapies, mRNA medicines — creates novel occupational exposure scenarios

for which no OELs or surveillance frameworks yet exist. Workers handling viral vectors, lipid nanoparticles, mRNA constructs, and ex vivo genetically modified cells face potential exposures whose long-term health implications are unknown and for which regulatory frameworks have not yet been developed. Prospective longitudinal cohort studies in these emerging pharmaceutical manufacturing settings are an urgent research priority[4,55].

9. Future Directions in Pharmaceutical OEL Science and Regulatory Policy

9.1 Computational Approaches to OEL Derivation

The integration of computational toxicology, Quantitative Structure-Activity Relationship (QSAR) modelling, and read-across methodologies into the OEL derivation pipeline represents a significant emerging opportunity for the pharmaceutical sector. For novel APIs in early development — where the toxicological dataset may consist only of in vitro cytotoxicity data, a basic Ames mutagenicity assay, and a single-dose rodent tolerability study — computational QSAR models trained on structural alerts for toxicological endpoints (carcinogenicity, reproductive toxicity, sensitisation potential, organ toxicity) can provide a rapid, scientifically defensible basis for provisional OEB classification[48,49].

Several computational tools are now in active use for pharmaceutical hazard assessment: the OECD QSAR Toolbox for structural alert identification and read-across; the Leadscope QSAR models for pharmaceutical carcinogen prediction; Derek Nexus (Lhasa Limited) for expert-rule-based toxicity prediction; Sarah Nexus for reproductive toxicant prediction; and Toxtree for EU classification prediction. The integration of these tools into a formalised, auditable OEB derivation workflow — validated against compounds with known OELs — would substantially accelerate the provisional OEL assignment process for novel pharmaceutical compounds entering manufacturing development.

9.2 Physiologically Based Pharmacokinetic Modelling in OEL Derivation

Physiologically Based Pharmacokinetic (PBPK) modelling, which describes the Absorption, Distribution, Metabolism, and Excretion (ADME) of a compound using mathematical representations of organ compartments and physiological parameters, offers a powerful tool for route-to-route extrapolation in OEL derivation. For APIs with extensive clinical pharmacokinetic data from therapeutic use, PBPK models can be used to predict the internal dose at a given inhalation exposure concentration, enabling more accurate conversion of PDEs derived from oral therapeutic data to inhalation OELs[50,51].

This is particularly valuable for APIs where pulmonary absorption kinetics differ substantially from oral bioavailability — notably poorly water-soluble APIs where respirable particle deposition in the lower respiratory tract may result in a substantially different absorbed dose than would be predicted from simple breathing rate-based conversion of the oral PDE. PBPK models for pharmaceutical OEL derivation have been published for a small number of APIs and represent a growing area of regulatory toxicology research with significant potential to improve the scientific accuracy of occupational exposure standards.

9.3 Real-time Exposure Monitoring Technology

Advances in real-time airborne monitoring technology for pharmaceutical environments offer the prospect of continuous, ambient monitoring of API aerosol concentrations in manufacturing areas, compounding pharmacies, and healthcare administration settings. Photoionisation Detection (PID), Surface Acoustic Wave (SAW) sensors, aerosol mass spectrometry, and miniaturised electrochemical sensors have demonstrated applicability in pharmaceutical pilot studies for select volatile compounds. For non-volatile API aerosols, real-time monitoring remains technically challenging, but advances in nanoparticle characterisation technology and ambient aerosol mass spectrometry offer longer-term potential.

In the immediate term, the most impactful technological advance for pharmaceutical exposure monitoring is the development and validation of sensitive, specific, and deployable wipe sampling assays and personal breathing zone sampling methods — coupled with low-cost, high-throughput analytical platforms (LC-MS/MS with automated sample preparation) — that enable routine exposure assessment for the breadth of APIs encountered in complex pharmaceutical manufacturing

environments. Standardisation of wipe sampling and air sampling analytical methods for common hazardous drugs, coordinated by organisations such as NIOSH, ISPE, and the European Pharmaceutical Aerosol Group, would substantially advance the evidence base for occupational health surveillance[52,53].

10. A Framework for Integrated Pharmaceutical Occupational Health Surveillance

Based on the comparative analysis presented in this review, Figure 1 presents a proposed integrated framework for pharmaceutical occupational health surveillance that synthesises the most useful elements of each of the four regulatory systems reviewed, supplemented by OEB methodology and biological monitoring.

The cornerstone principle of this integrated framework is proportionality: the intensity and scope of exposure monitoring and health surveillance should be commensurate with the pharmacological and toxicological hazard of the API, as quantified by its OEB classification or formal OEL. This proportionality principle prevents the resource allocation challenges that arise when attempting to apply uniform, maximum-intensity surveillance to all APIs encountered in a complex pharmaceutical manufacturing environment — an approach that is neither scientifically justified nor operationally feasible, and that risks diluting surveillance quality across the board by spreading limited occupational health resources too thinly[54,55].

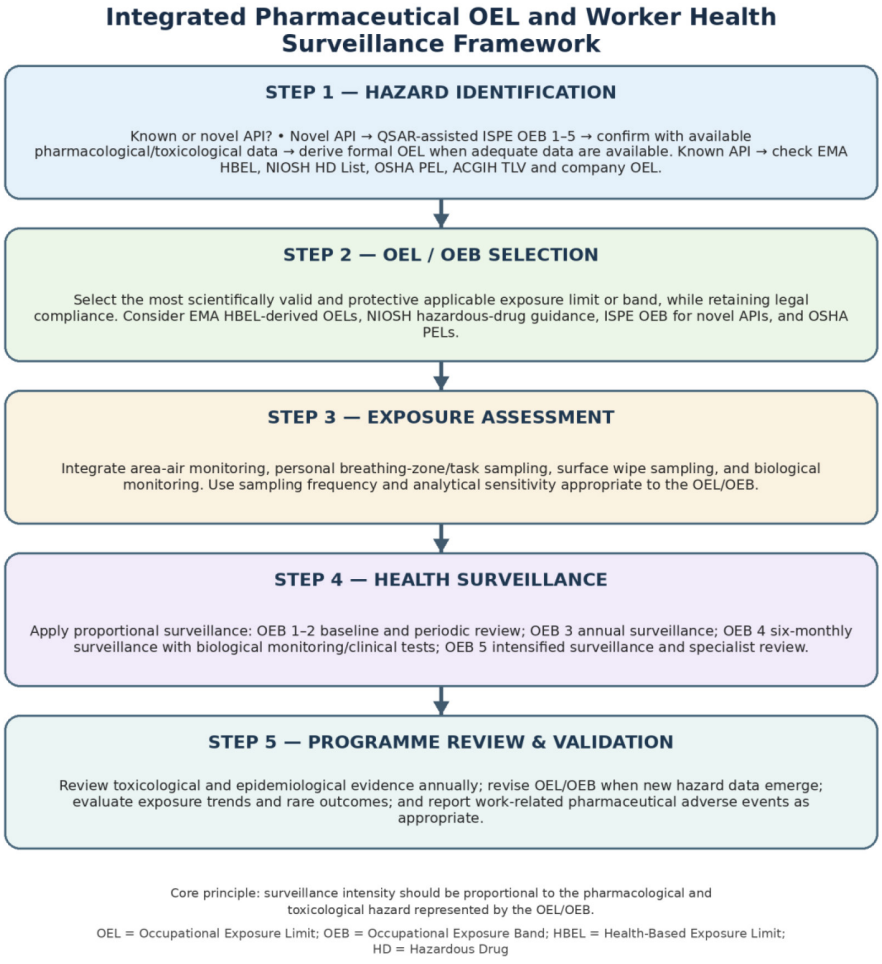


Figure 1. Proposed integrated framework for pharmaceutical occupational health surveillance.
Abbreviations: TWA = Time-Weighted Average; OEL = Occupational Exposure Limit; OEB = Occupational Exposure Band; HBEL = Health-Based Exposure Limit; HD = Hazardous Drug.

11. Conclusion

This review has examined four major regulatory frameworks governing occupational exposure limits for active pharmaceutical ingredients — ICH Q3C, OSHA PELs, NIOSH RELs, and EMA HBELs — and has critically analysed their scientific bases, methodological approaches, regulatory status, global applicability, and implications for worker health surveillance in pharmaceutical and healthcare settings. The analysis reveals a landscape of substantial regulatory heterogeneity, with each framework contributing important but incomplete coverage of the occupational health protection needs of the pharmaceutical workforce.

OSHA PELs, while legally enforceable and administratively important, are scientifically outdated for the vast majority of substances and provide virtually no API-specific guidance — a critical inadequacy given the pharmacological complexity of the contemporary pharmaceutical manufacturing environment. NIOSH RELs and the NIOSH Hazardous Drug framework represent the most current and worker-health-focused regulatory guidance in the US context, but their non-binding status limits their operational impact in workplaces not proactively committed to exceeding minimum compliance standards. ICH Q3C provides a scientifically rigorous PDE derivation methodology for pharmaceutical solvents that has been widely adapted for occupational purposes, but remains fundamentally a product quality tool not designed for the inhalation hazard profile of API dusts encountered in manufacturing.

The EMA HBEL guideline, while also primarily a product quality standard, provides the most comprehensive, API-specific, and scientifically sophisticated framework available, with direct applicability — through inhalation route conversion — to occupational exposure limit derivation. The EMA HBEL framework should be the preferred scientific basis for OEL derivation for marketed APIs in pharmaceutical manufacturing environments globally, supplemented by NIOSH HD classification for hazardous drug handling programmes and ISPE OEB methodology for novel APIs in early development.

Worker health surveillance in pharmaceutical settings must be explicitly grounded in the OEL/OEB framework applied, with surveillance intensity proportional to the hazard class of the API handled. Biological monitoring, where technically feasible, provides the most comprehensive assessment of actual absorbed API dose — accounting for all exposure routes simultaneously — and should be a core component of surveillance for OEB 4/5 compounds and all NIOSH-classified hazardous drugs.

Priority research needs identified in this review include: development and validation of QSAR-based OEB assignment tools for novel pharmaceutical APIs; integration of PBPK modelling into route-to-route extrapolation for OEL derivation from therapeutic clinical data; standardisation of wipe sampling and personal air monitoring analytical methods for hazardous drugs; establishment of industry consortium longitudinal surveillance programmes; and development of occupational health frameworks for emerging biopharmaceutical and ATMP manufacturing environments. Progress on these fronts will require sustained collaboration among regulatory agencies, the pharmaceutical industry, academic occupational health researchers, and worker representative organisations — with the shared goal of ensuring that the workforce that produces life-saving medicines is itself comprehensively protected from the pharmacological hazards its work entails.

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Author Contribution

All authors contributed to the conception and design of the review, literature identification and synthesis, manuscript drafting and critical revision, and approval of the final manuscript.

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