

Assessing Drug Substances to Identify “Highly Hazardous” Compounds for Quality Risk Management Programs



R. Sussman¹, A.R. Schatz², T.A. Kimmel¹, A. Ader³, and B.D. Naumann⁴

¹SafeBridge Consultants, Inc., NY, NY; ²Ashland, Inc., Bridgewater, NJ; ³SafeBridge Consultants, Inc., Mountain View, CA; ⁴Merck & Co., Inc., Whitehouse Station, NJ

Abstract:

Regulatory guidance documents and audits of pharmaceutical drug product manufacturing operations are intended to preserve the quality and safety of active pharmaceutical ingredients (APIs) and drug products. Historically, regulatory authorities have assigned certain APIs to various “categories of concern”, based on their toxicological properties, in the interest of protecting patients from exposure to potentially hazardous contaminants. Equipment used to manufacture multiple products has the potential of becoming cross-contaminated. In the absence of data clearly demonstrating safety, these categories were intended to provide appropriate segregation for the prevention of potential cross-contamination as outlined by current Good Manufacturing Practices. However, the use of specific categories of concern often overlooked other characteristics of the API such as pharmacologic potency and mechanism of action, which might also trigger specific requirements for safe handling and disposal. Drug manufacturers are often asked by contract manufacturing organizations whether or not APIs are “cytotoxic”, “steroids”, or “hormones.” As these terms were never defined, clarification is needed because the pharmacological mechanism of new APIs has dramatically changed since these terms were first introduced. Also, certain compounds may be inappropriately placed in one of these generic categories, giving the impression that segregation or dedication is required when in fact an acceptable daily exposure can be established and sufficient cleaning achieved. This poster discusses the historic use of these categories within the context of assessing their toxicological and pharmacological characteristics to help identify compounds requiring special attention within a quality risk management program.

Background:

- Risk of cross-contamination is a concern with certain drug substances and has resulted in:
 - Dedication
 - Segregation
 - Campaign manufacturing (temporal separation)
- Can we clean pharmaceutical equipment to safe levels?
 - Perform quantitative risk assessment to develop an acceptable daily exposure (ADE), a level of the contamination acceptable by unintended exposure
- If we can clean to an acceptable level that is measurable, then dedication / segregation not needed
- Certain categories of drugs still cause concern due to poorly defined terms and poor understanding of risks.
- Although the tide is turning, some regulators still use these terms today, and will for a while longer.
- Many CMOs have contracts with drug innovators that preclude using facilities / equipment where these types of drugs are handled.

Basic Facts:

- Traditional categories causing concern may be less important:
 - “Certain Cytotoxics”, “Certain Steroids”, “Certain Hormones”, other “Highly Active Drugs”
- Assigning a drug substance to one of these categories overlooks other characteristics, such as:
 - Pharmacologic potency
 - Mechanism of action
 - High risk situations with less potent drugs (exposures not controlled)

“Cytotoxic”

- Historically = Anti-cancer compounds
- Characteristics: Cell death due to direct actions on DNA or DNA-macromolecules demonstrating or predicted to cause genotoxicity *in vivo* and rapid and non-specific cell death in healthy as well as abnormal cells.
- Examples: alkylating agents, anti-metabolites, mitotic inhibitors, topoisomerase inhibitors (although the latter 3 have thresholds).

“Cytostatic”

- Characteristics: Preferentially toxic to tumor cells over normal cells due to a specific genetic defect, non-genotoxic and have toxic effects that display thresholds below which no effects are expected.
- Should these be lumped in with cytotoxic?
- Example: kinase inhibitors

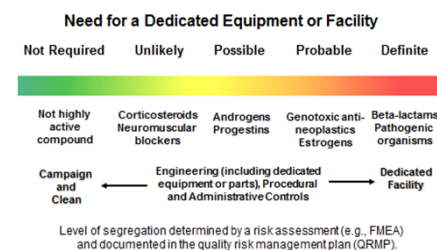
Hormones and Hormone-like Drugs

- Historically = Steroidal sex hormones
- Characteristics: Act as a chemical messenger, either remotely (endocrine), locally (paracrine), or intracellularly (autocrine), recognized by a specific hormone receptor protein that may be intracellular or associated with the cell membrane, and relays and/or amplifies the received message leading to a cellular response.
- Includes: endogenous hormones, synthetic hormones, hormone-receptor agonists (full or partial).

Highly Active Drugs

- Genotoxic compounds that are known to be, or highly likely to be, carcinogenic to humans, or
- Compounds that can produce reproductive and/or developmental effects at low doses, or
- Compounds that can produce serious target organ toxicity at low doses
 - Clinical doses <1-10 mg/day or dosages <0.1-1 mg/kg/day in animal studies.

Degrees of Segregation



Summary:

- No standardized definitions = segregation expectations
- Evaluate all endpoints, including potency
- Set Acceptable Daily Exposures, regardless of category
- Segregation/dedication not required if adequate cleaning is demonstrated
- Principle endorsed by FDA and supported by EMA
- Standardizing the evaluation of drugs of concern will:
 - Identify those requiring special scrutiny
 - Facilitate the assessment of CMOs
 - Improve communication of hazards
 - Provide better protection of patients; and
 - Focus regulatory agencies on compounds of highest concern.