The Challenge of Working with "Unknowns"

Workplace Evaluation and Control Without Exposure Limits or Monitoring Methods

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THE CHALLENGE

The "New" Pharmaceutical Compound Challenge

- Pharmaceutical compounds are being developed on a record pace and drugs are more potent than ever before
  - More drug innovators
  - High throughput screening
  - Microgram per day doses
- "Targeted" drugs for specific pharmacological activity
  - More molecular targets identified through genomics
  - Many are structural analogs of naturally occurring materials
  - Common to alter molecules for higher activity, longer duration of action and greater specificity

Current Trends in Product Development

- It's a brave new scary world
  - Older molecules shown to be too toxic are making a comeback
  - New ultra-toxic materials are being developed due to advanced delivery systems
  - Linking drugs to antibodies, peptides and PEG
    - Safe patient delivery of some of the most toxic substances in industry history
- Majority of drugs are taken orally or by IV/injection but inhalation is the greatest occupational risk
- Other products may contain drug substances
  - Diagnostics, stents, screening devices, analytical tools

Potential occupational exposure to these materials require greater control

No Limits, No Methods

Rule #1 – *"Do not collect environmental data unless you know what to do with it"*

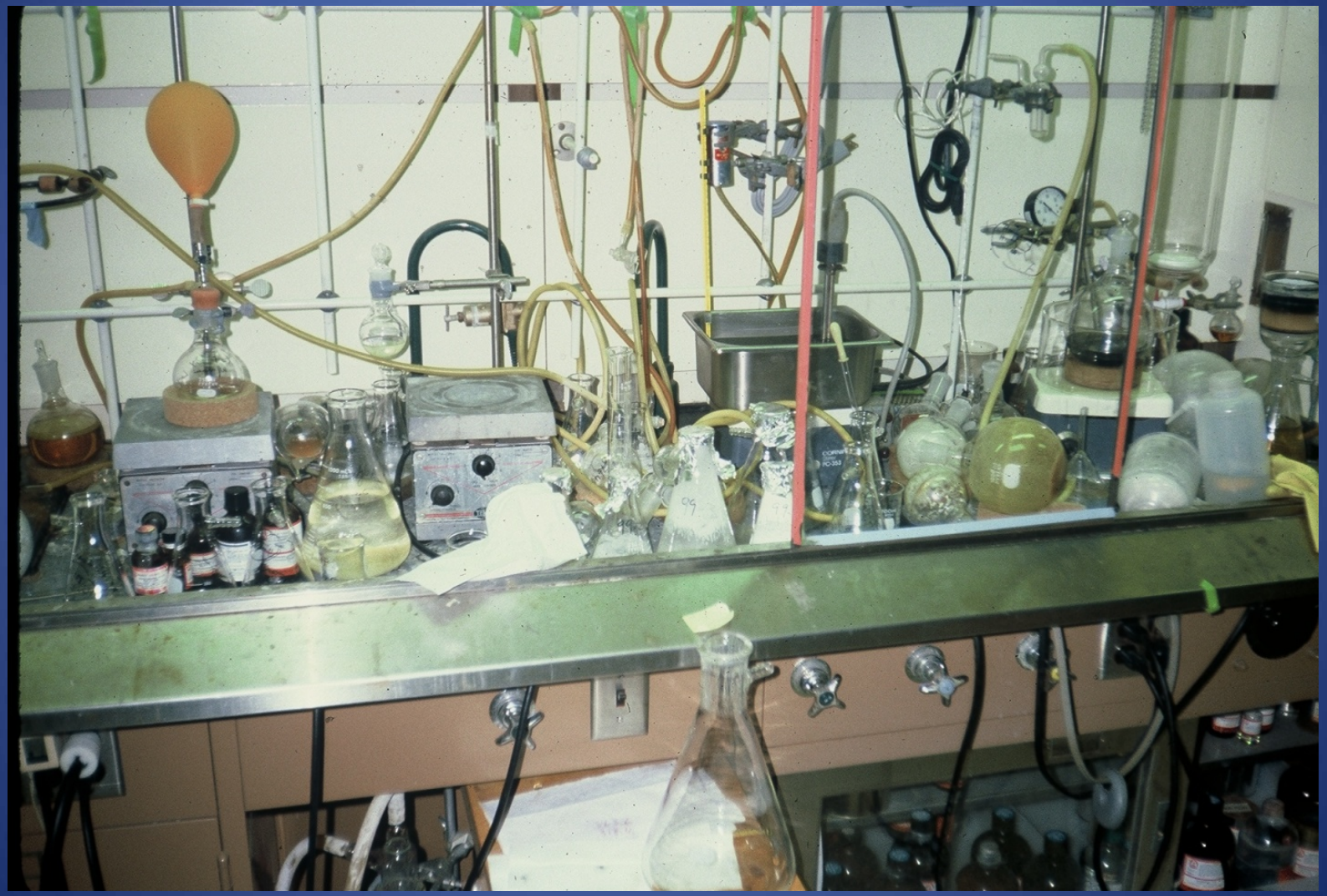
- Qualitative Assessment
  - Look at toxicology data that you have
    - Material characteristics
    - Work with your toxicologists
  - Categorize or default into control band
  - Study the process and use judgment to compare to measured exposures
- Surrogate monitoring
  - Can you replicate process and use comparative data?

CATEGORIZATION AND CONTROL

Control Banding
In the Beginning…

- Concept evolved from an identified need in the pharmaceutical industry
- R&D scientists working with kilos of drug material
  - Novel compounds with little or no pharmacology and toxicology data
  - Several ‘open’ operations
    - Kilogram scale synthetic chemistry
    - Pilot scale process development
    - Formulation development/clinical manufacturing
  - Inability to set exposure limits
  - No target for air monitoring methods

Norm's Hood



What Should We Do?

- Issue arose at the 1988 Pharmaceutical Safety Group (PSG) meeting
  - Ad hoc gathering of 15 pharmaceutical safety directors
- Five companies volunteered to work on the issue
  - Syntex
  - Merck
  - Abbott
  - Lilly
  - Upjohn

Control Banding

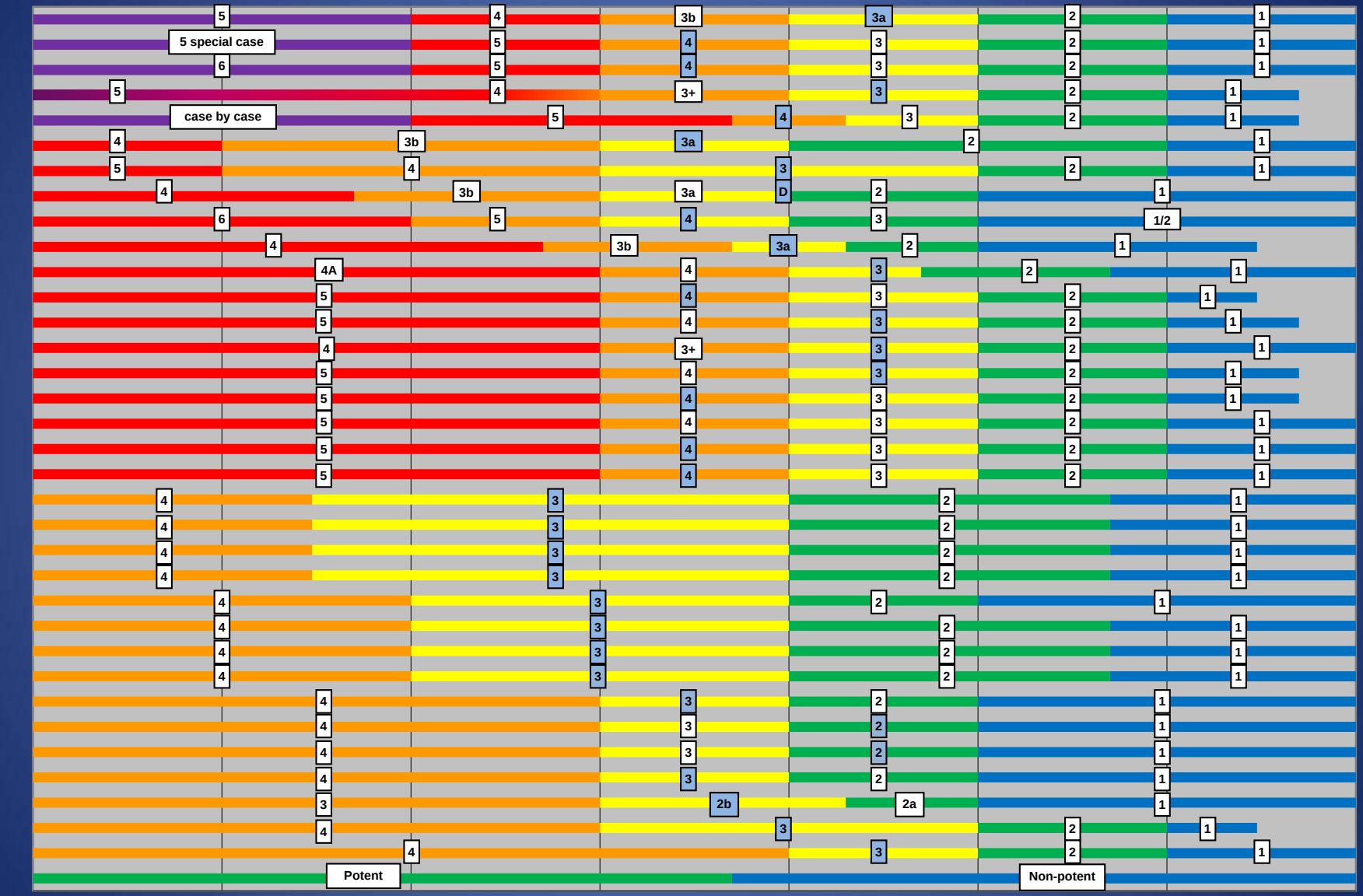
Development of a Concept in Pharma for R&D

- Pharmaceutical approach based on the NIH/CDC Biosafety Level model
- "Hand in glove" system
- Linking pharmaceutical potency and toxicity to safe handling

"You haven't done anything until you have controlled the exposure."

- Control recommendations in a *matrix format* were based on success with compounds having similar characteristics
  - Work environments, process controls, techniques, PPE
  - Air monitoring results to support control levels

BANDING CUTOFFS 2010



Why Are There So Many Different Systems in the Pharma Industry?

- Tried to create a “one size fits all” system to take back to the other companies
  - Clearly the therapeutic substances were different in the five companies
  - The surprise was that the work environments and equipment was also different
- Conclusion was to develop company-specific systems based on the common theme
- Proper implementation depends on customization to match your needs

Toxicity/Potency Categorization of Chemicals (SafeBridge System)

- **Category 1:** Low Potency
  OEL >0.5 mg/m^3
  (aspirin, naproxen)
- **Category 2:** Intermediate Potency
  OEL 10 µg/m^3 - 0.5 mg/m^3
  (insulin, hydrocodone, simvastatin)
- **Category 3:** Potent **(default)**
  OEL 30 ng/m^3 - 10 µg/m^3
  (estradiol 17-β, fentanyl, paclitaxel)
- **Category 4:** Highly potent
  OEL ≤ 30 ng/m^3
  (ethinyl estradiol, leuprolide, sufentanyl)

Category 1
Material Hazard Criteria*

Most Important Factors

- Irritants
- Low Acute/Chronic Systemic Effects
- Low Potency
- None of the "–gens"
- Pharmacological mechanism of action (mild effects)

Other Considerations

- Reversible Effects
- Immediate Onset of Symptoms (minutes to hours)
- Good Warning Properties

* One or more of the above criteria may place a material into this category

Category 2
Material Hazard Criteria*

Most Important Factors

- Moderate chronic or moderate to high acute toxicity
- Moderate systemic toxicity – reversible or low severity
- None of the "-gens"
- Pharmacological mechanism of action (moderate effects)

Other Considerations

- Corrosives and mild to moderate sensitizers
- Moderately absorbed via inhalation or dermal exposure
- Moderate degree of medical intervention required

* One or more of the above criteria may place a material into this category

Definitions

- "Genic" – material that may be:
  - Mutagen – causes mutations in DNA
  - Genotoxicant – causes chromosomal damage
  - Carcinogen – causes cancer
  - Developmental toxicant – causes effects in the offspring when drug is administered to the parent
    - Teratogen – causes structural birth defects
  - Reproductive toxicants – affects fertility or ability to mate

Category 3 (default category)
Material Hazard Criteria*

Most Important Factors

- Pharmacological mechanism of action (significant)
- Serious acute and chronic irreversible systemic effects
- Potent (~10 mg clinical dose; ~1 mg/kg/day in animals)
- "-Genic"
- Sensitizers

Other Considerations

- Poor or no warning properties
- Medical intervention required

* One or more of the above criteria may place a material into this category

Category 4
Material Hazard Criteria*

Most Important Factors

- Pharmacological mechanism of action (serious)
- Severe acute and chronic irreversible systemic effects
- Highly potent (~70 μg/day dose clinically; ~10 μg/kg/day in animals)
- "-Genic" effects
- May affect sensitive subpopulations (e.g. asthmatics)

Other Considerations

- Poor or no warning properties
- High degree of medical intervention required

* One or more of the above criteria may place a material into this category

Most Critical Data for Determining a Category

- Proposed mechanism of action
- Anticipated therapeutic indication
- Anticipated or current dose
- Toxicology data – critical endpoints are “-gens”
- Target organ toxicity (including pharmacological effects)

Paclitaxel - Category 3 of 4

1. MECHANISM: interferes with cell replication by affecting microtubule function leading to cell death
2. TREATMENT: anti-neoplastic
3. CLINICAL EFFECTS: bone marrow suppression, nausea & vomiting, hair loss, possible skin, eye, & lung irritation
4. CLINICAL DOSE: about 12 mg/day (DED)
5. PRECLINICAL TOX.: mutagenicity/carcinogenicity – effects chromosomes, no cancer data; reproductive/developmental toxicity – effects male and female fertility in lab animals, effects viability of fetus in lab animals
6. OEL Range: 0.8 – 10 $\mu g/m^3$

So the Toxicologist Has "Banded" the Material - Now What?

- This is not a "cook book" system
  - **Judgment is required**
  - Knowledge of the process
  - Control advice from guidance documents (matrices)
  - Experience with similar materials and situations
- Proper implementation depends on customization to match needs
  - Understand variable factors – volume, physical form, frequency and duration of operations
  - Consider surrogate testing prior to actual use
- A range of control approaches is likely necessary and appropriate
  - Facility features and process engineering controls
  - Administrative controls
  - PPE

Airborne Concentrations Applied to Banding

- Assign novel entities into band
- Usually 4-6 bands
  - Many companies have adopted this approach
  - Band “cut-offs” vary among companies
- Develop specific handling guidelines for each band (experience-driven, but should be verified)
- Within each band, handling guidelines may vary depending on amounts handled

Handling Practice Guidelines

For each Category (1-4), a handling practice guideline is developed based on:

- Experience with the type of technology/ equipment and its exposure potential
- Known containment capabilities of available devices
- Scale of operations:
  - Laboratory / Kilo plant
  - Pilot plant
  - Full scale production

Laboratory Work Environments Descriptors for Safe Handling of Pharmaceutical Powders

- Control Category 1 - Work on open bench acceptable
- Control Category 2 – Work in fume cupboards and limit surface contamination
- Control Category 3 – Designated areas, no open handling of powder, weighing hoods, clean surfaces daily, contained transfers, laminar air supply
- Control Category 4 - Designated areas, no open handling of powder, work done in isolators, clean surfaces daily, double-contained transfers, laminar air supply; facility features such as air locks depending on scale and type of activity

Production Work Environments Descriptors for Safe Handling of Pharmaceutical Powders

- Control Category 1 - LEV and/or enclosure at dust-generating points, open handling acceptable for low dust-generating operations or solutions

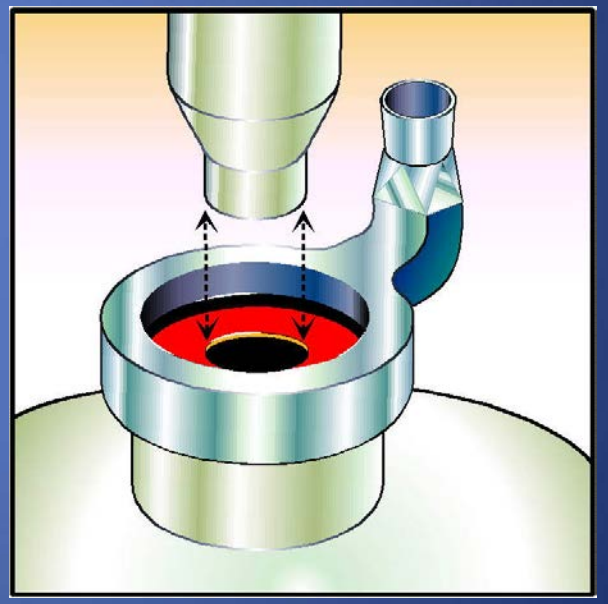
- Control Category 2 - LEV and/or enclosure at dust-generating points, emphasis placed on closed material transfer and process containment with limited open handling of powders, weighing hoods, specialized cleaning procedures

Articulating Arm Connections

- Basic emissions control at source
- Articulating arm supports the hood
- Provides ability to move hood into position and out of the way

Charging Hood

Custom Designs for Equipment
Combination Technologies (charging canister)



Bulk Powder Handling

Flow Sciences

Labconco

Pharmaceutical Compound Powders Production Work Environments (2)

- Control Category 3 - Closed material transfers, process containment/isolation, no open handling of powder, weighing hoods, clean-in-place, separate gowning and degowning rooms, decontamination areas (misting showers), negative/positive air pressure relationships w/buffer zones, access restricted

- Control Category 4 - Complete process containment and isolation plus above facility requirements

Flexible Containment

ILC Dover

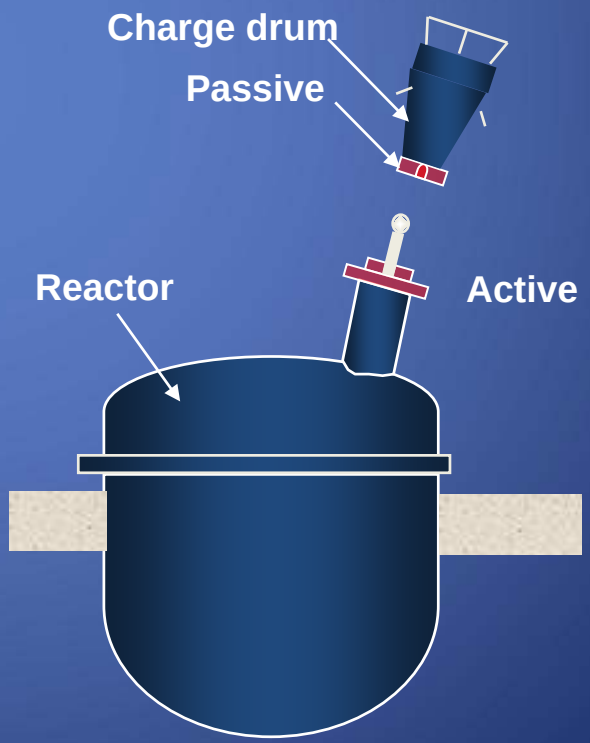
Drum Discharge and Receiving

ILC Dover

Continuous Liner

Split Butterfly Valves
Closed Powder Transfers

- **Charging into Vessels**
  - Handling active materials safely around the plant
  - Handling lubricants and additives
  - Access for sampling or cleaning
  - Suitable for automated docking



Isolators

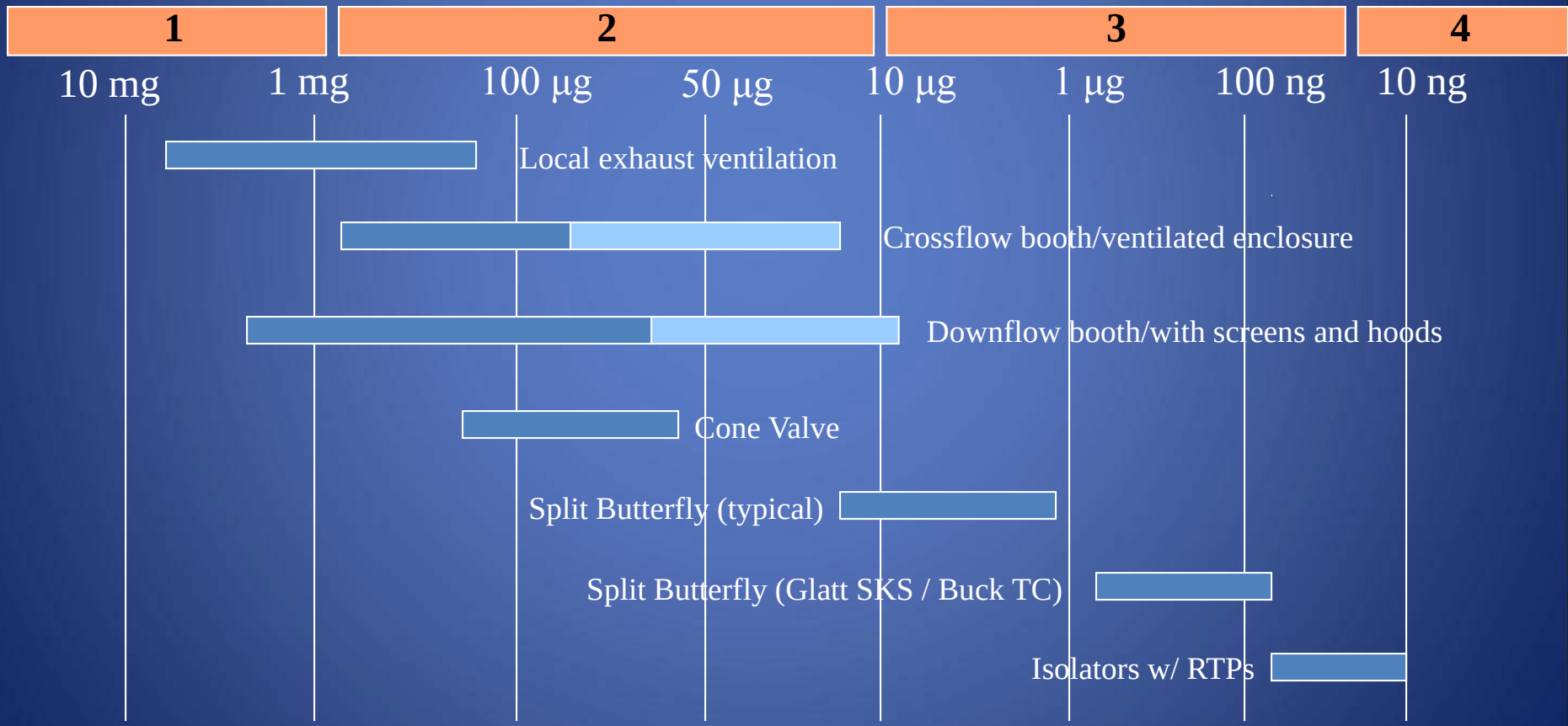
Weighing and Dispensing

Product Charging

Typical Containment Levels

for greater than Kilo Scale Applications + SafeBridge Categories

Categories 1-4 and OEL (mg, µg & ng /m^3)



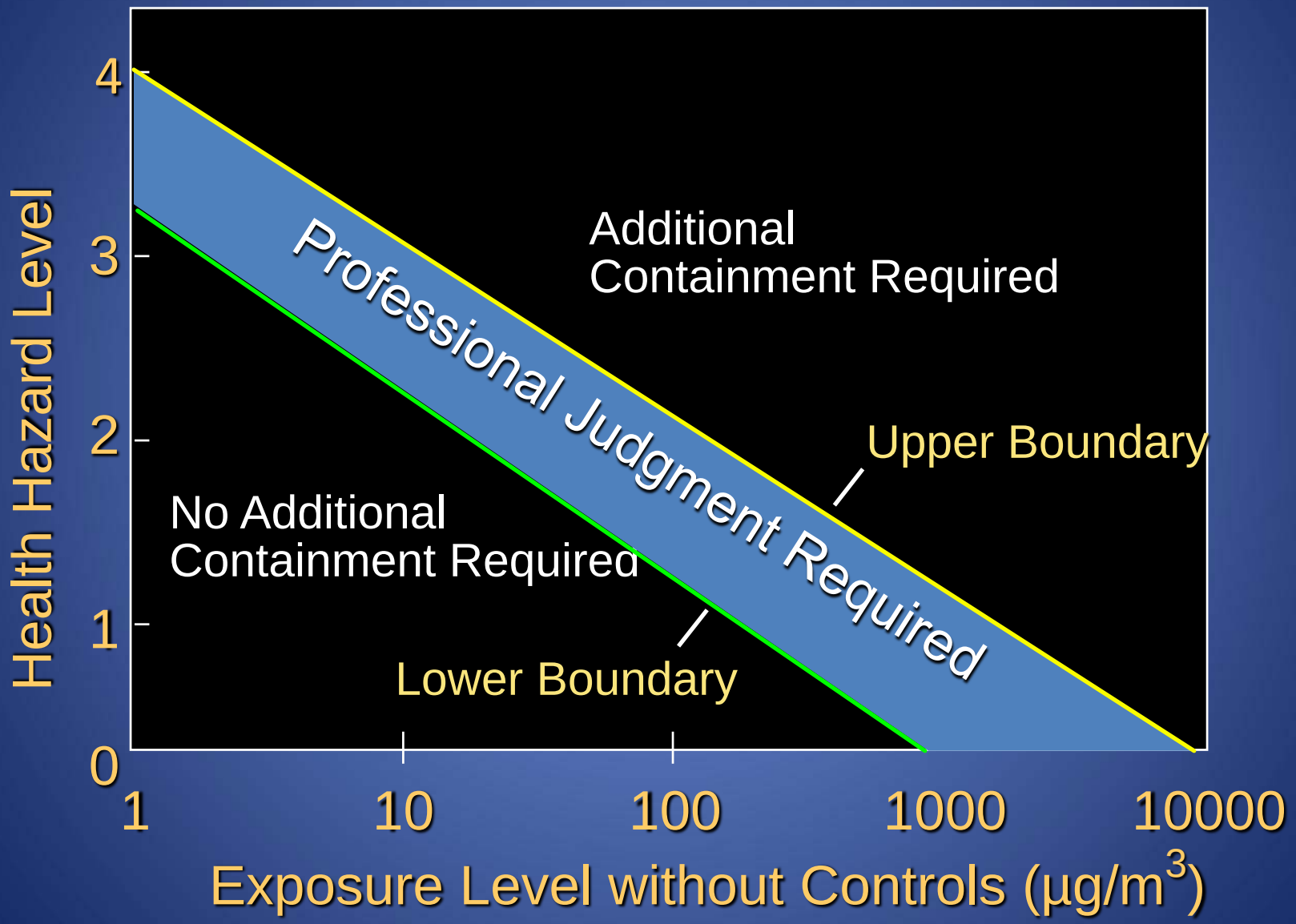
Actual performance varies as a result of installation and use

Pharmaceutical Formulation Manufacturing Control Matrix

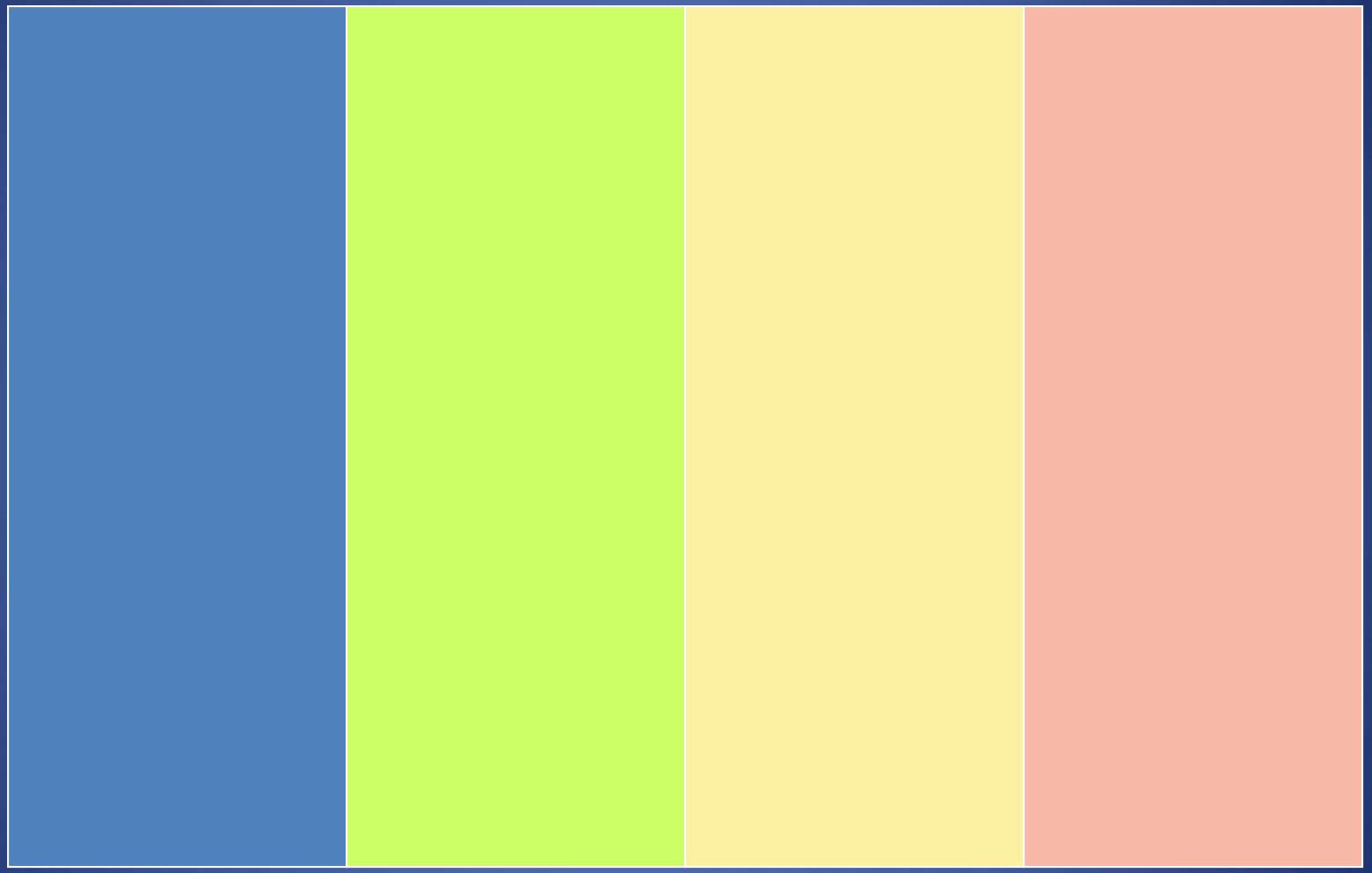
Unit Operation	Category 1	Category 2	Category 3	Category 4
Weighing and Dispensing APIs	Standard ventilation controls.	Engineered ventilated Balance Enclosure	Engineered ventilated balance enclosure for small quantities (i.e., amounts to be weighed up to 100 grams), Larger quantities must be handled in an isolator, glove bag or other system verified by IH monitoring.	Use isolator for all quantities. Dispensing and receiving containers should be mated to the isolation system.

CONCEPT REALITY CHECK

Control Level



Continuum of Potency



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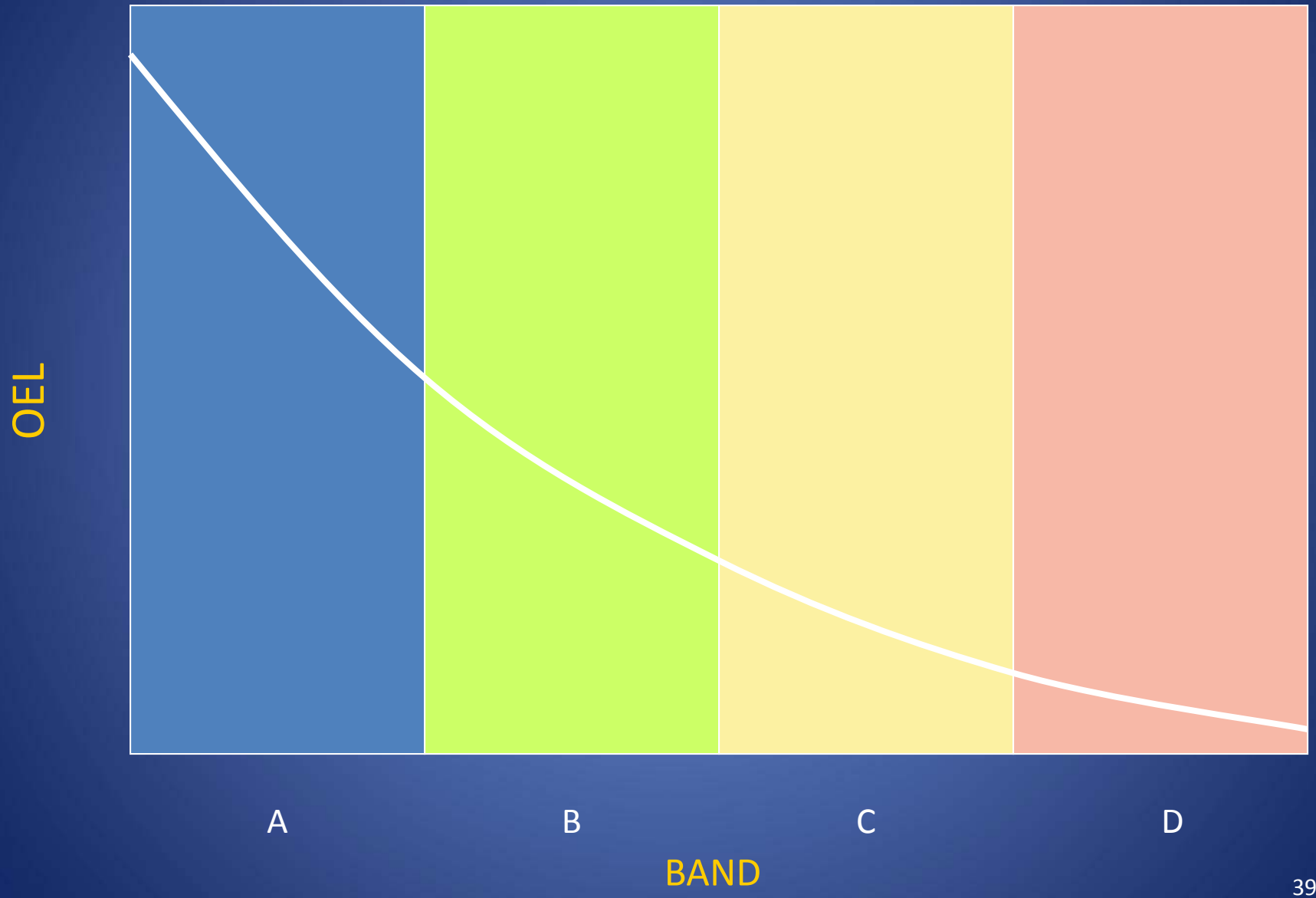

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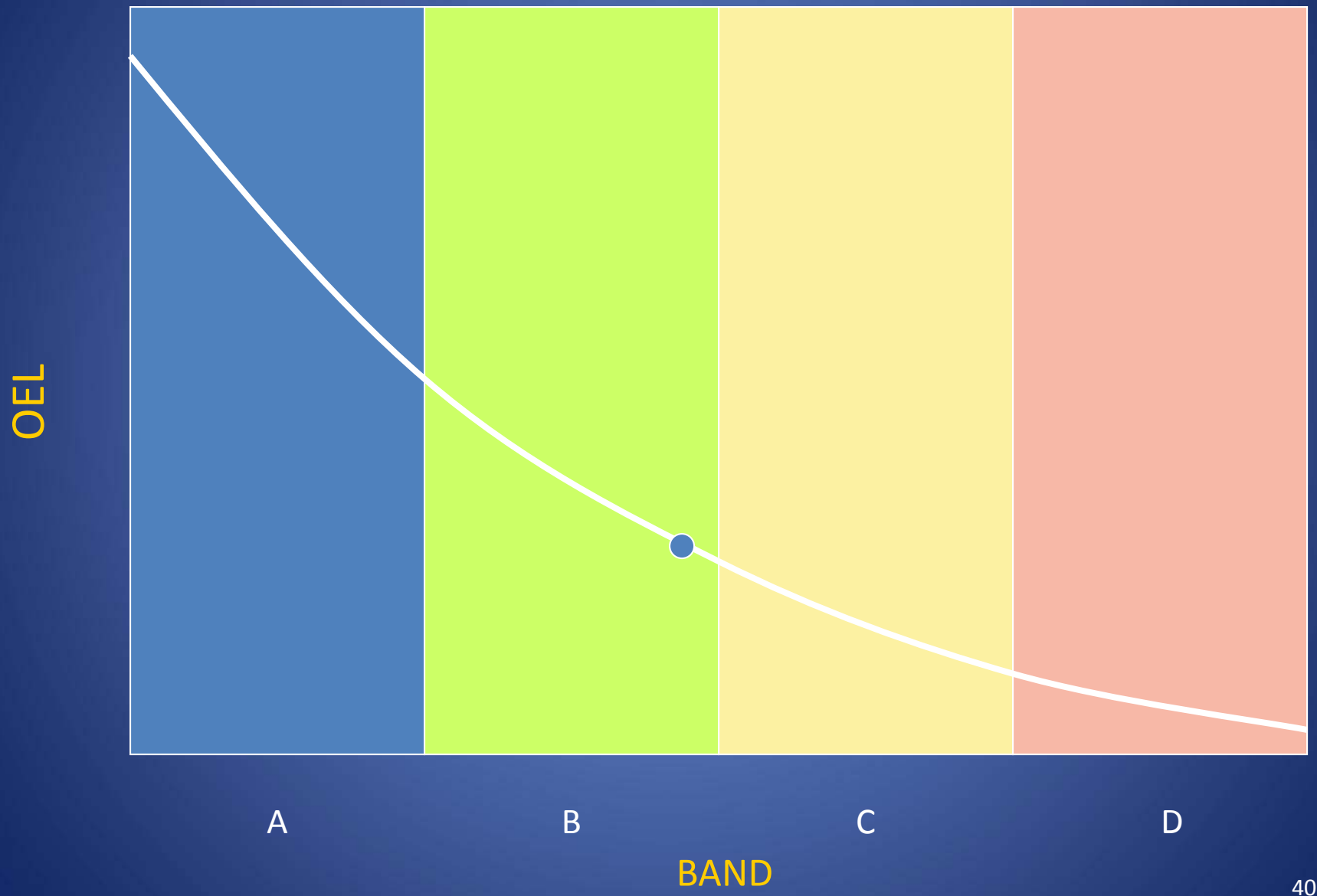

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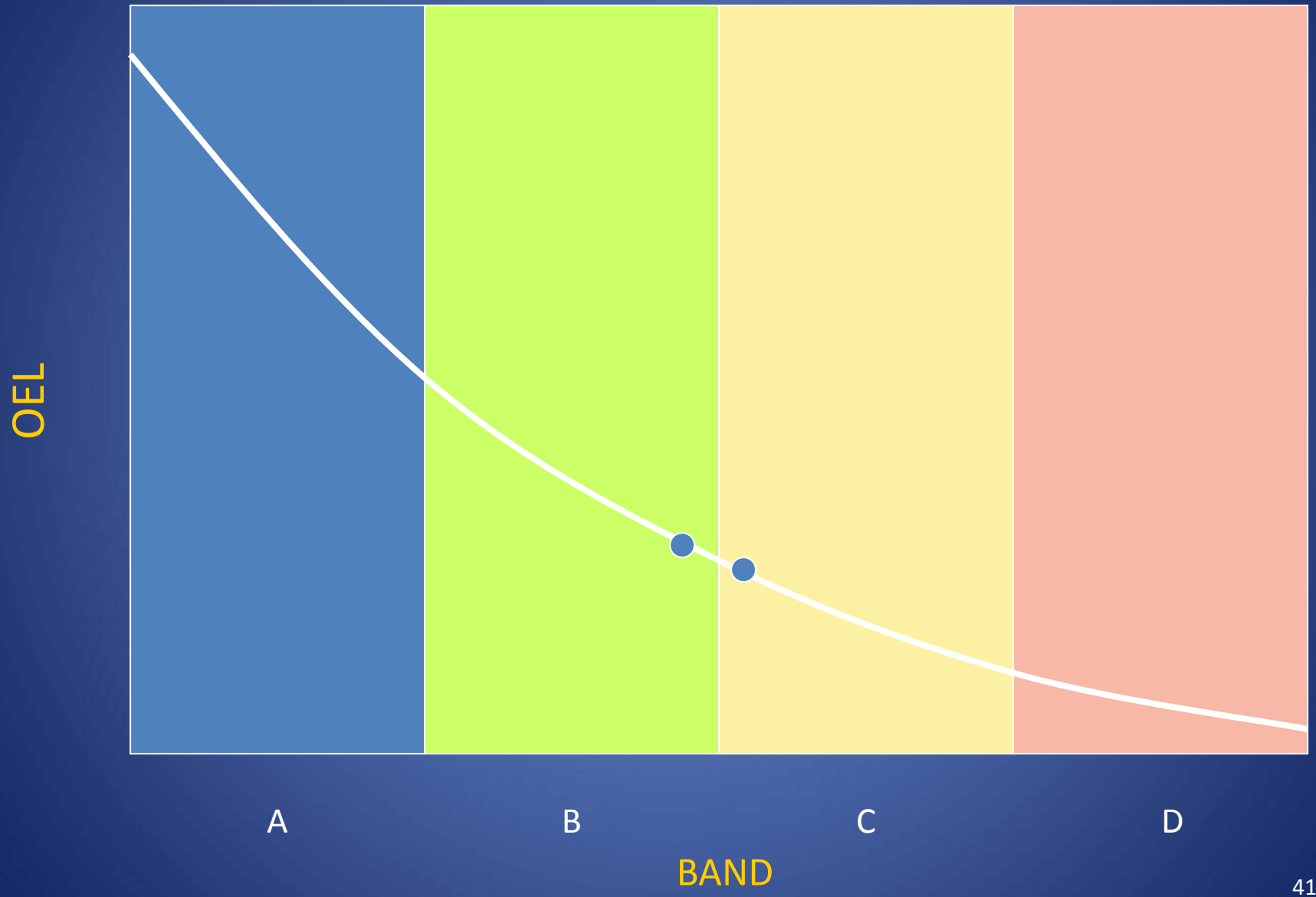
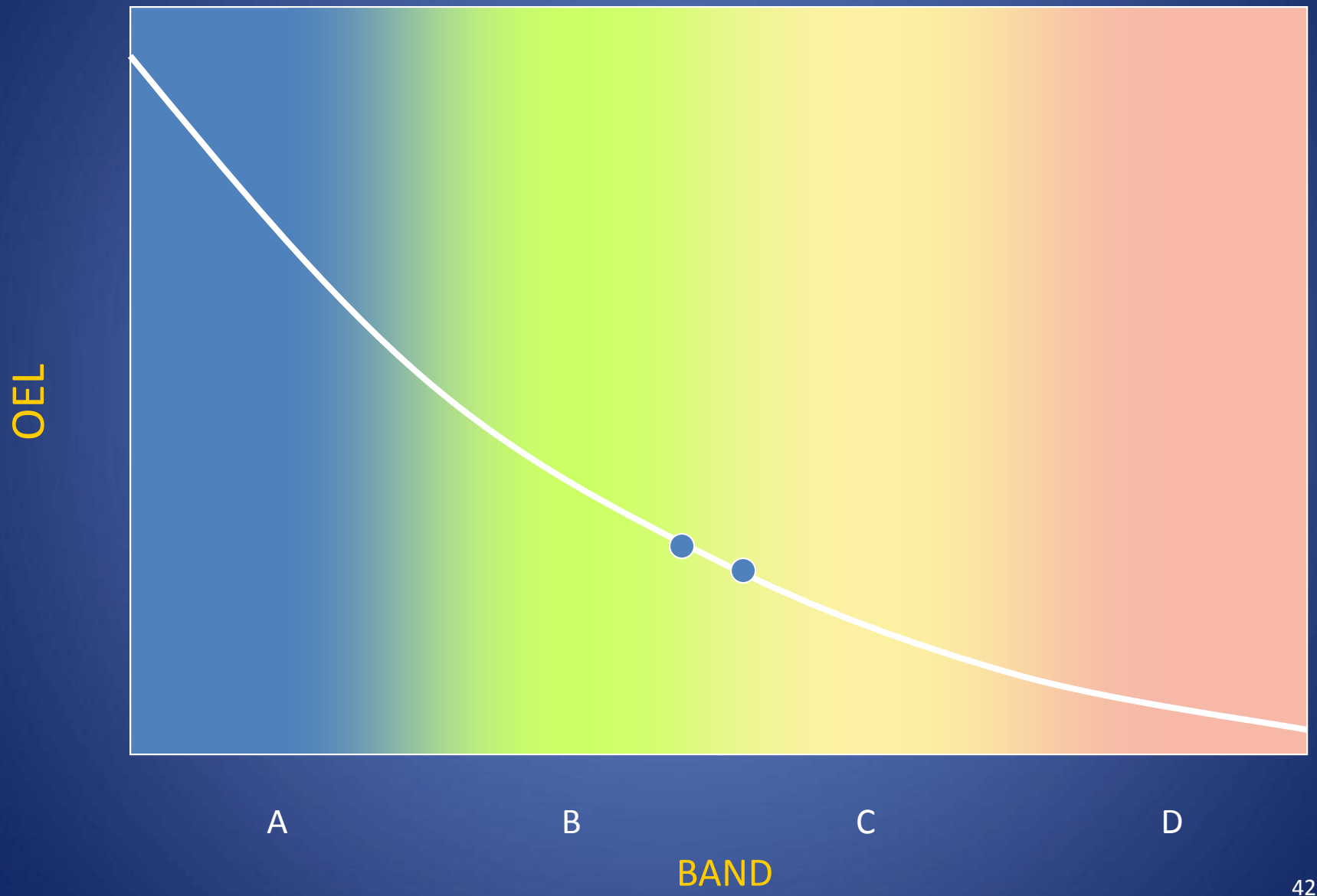


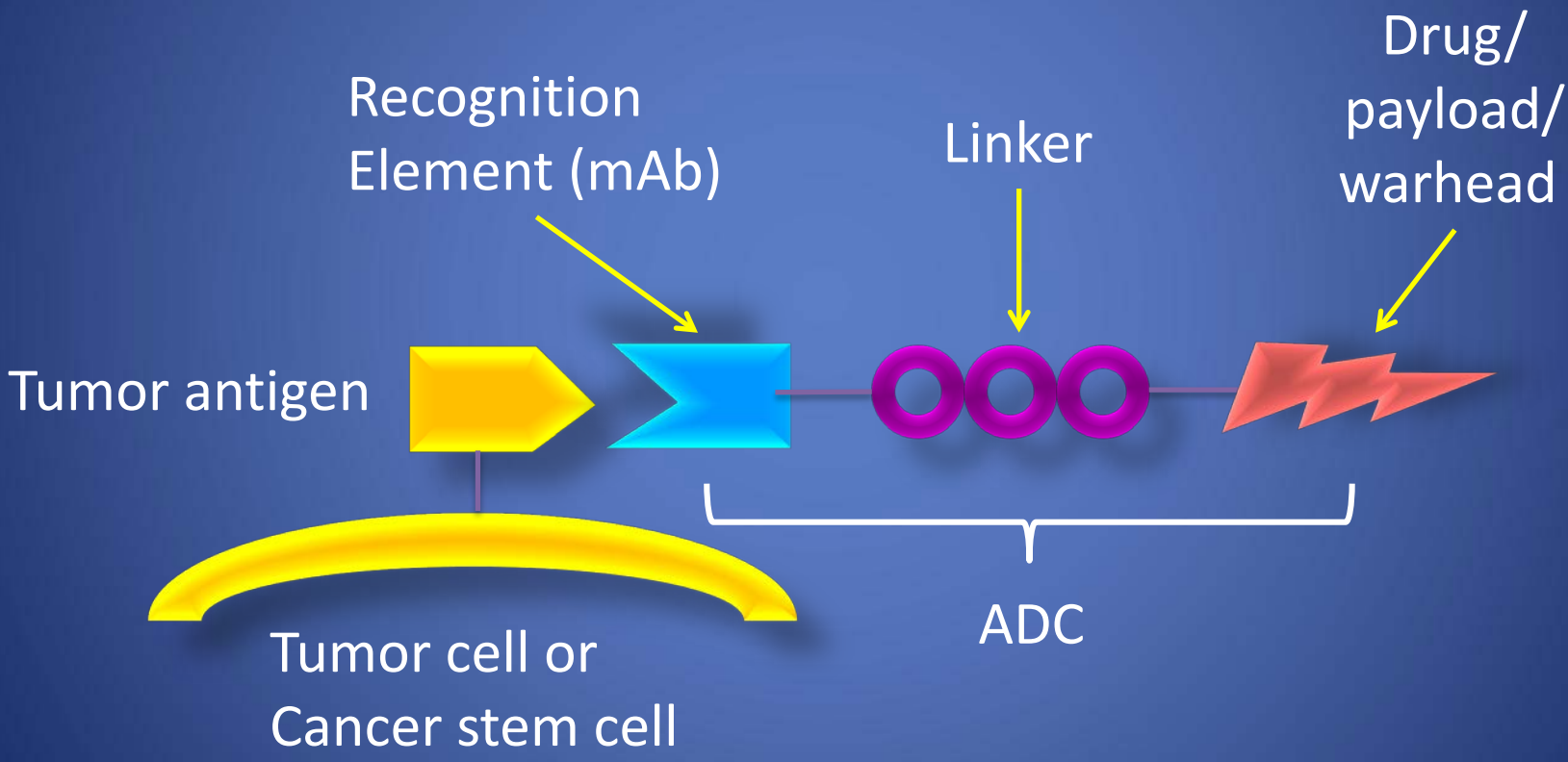
Continuum of Potency



HIGHER POTENCY / GREATER RISK

Antibody Drug Conjugate Components

(courtesy J.Gould, BMS)



PBD - Category 4 of 4
(pyrrolobenzodiazepine)

1. MECHANISM: PBD to be conjugated to tumor specific antibody that releases payload after reaching cell
2. TREATMENT: Cancer chemotherapy
3. CLINICAL DOSE: Related PBD, dose was 30 µg/m^2/day x 5 days every 3 weeks (13 µg/day)
4. CLINICAL EFFECTS: Likely to be similar to other anti-cancer agents (e.g., liver, blood and nerve toxicity, GI effects; also may impair fertility, cause birth defects, secondary cancers; skin/eye irritation)
5. NON-CLINICAL TOX.: Likely to be similar to other anti-cancer agents (e.g., liver toxicity, blood toxicity, peripheral neuropathy, GI effects, acute toxicity, including skin and eye irritation, genotoxicity, probable impaired fertility and birth defects).
6. OEL: 1 ng/m^3 (Preliminary from others)

Howorth Kilo Lab Hood

ADC Isolator Connected to Hood

Photo courtesy of Howorth

ADC Isolator for Reactor Charging

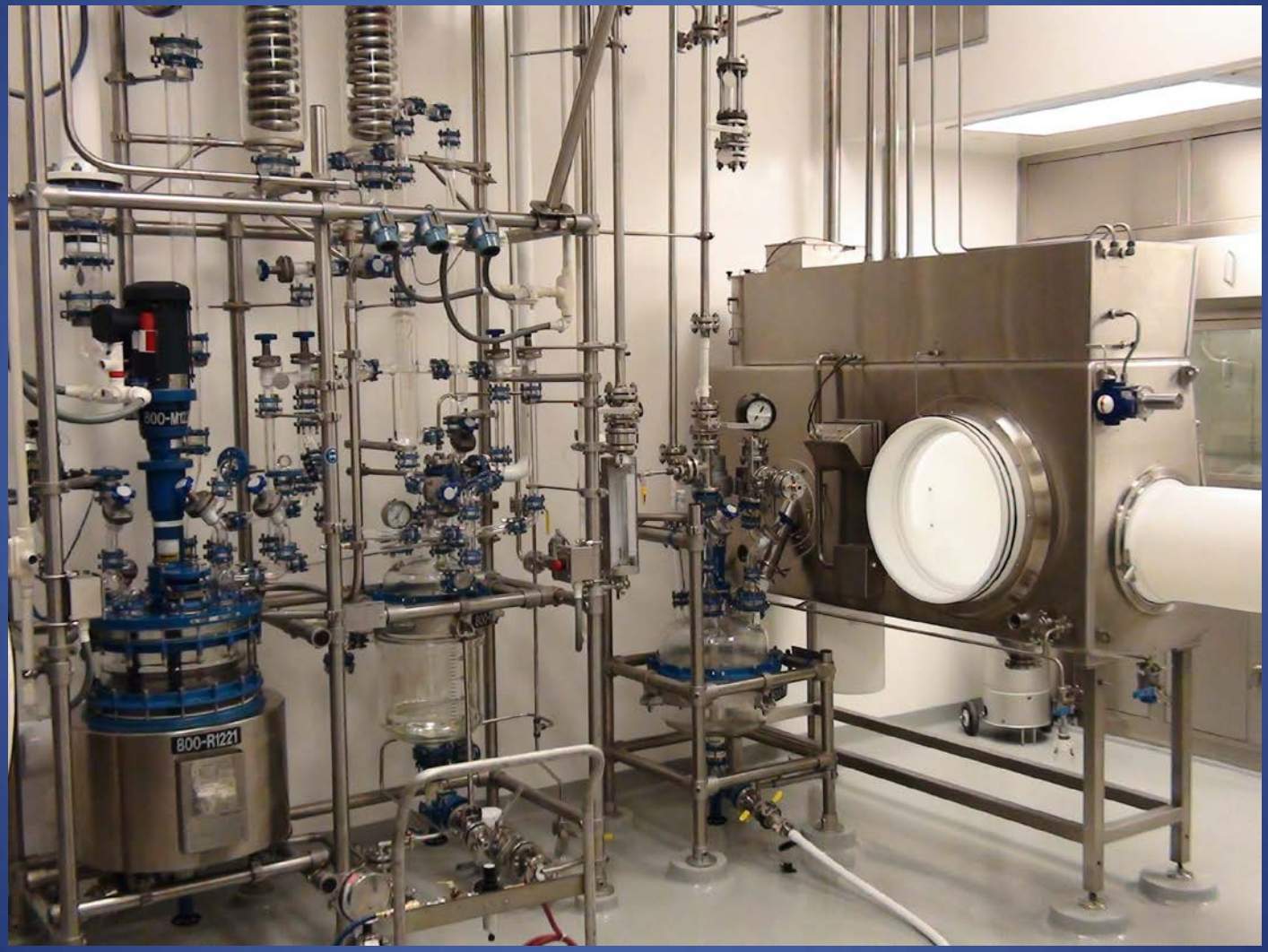


Photo courtesy of Howorth

EVOLUTION OF THE SYSTEM

Implementation and Benefits of the System

- Control advice documents can put you on the right path
- Proactive training and planned ‘roll out’ essential
- Potentially an excellent risk communication tool
- Presents the ‘default’ concept for unknowns (the “precautionary” principle)
- Widely accepted to date by research scientists

Limitations of the System

Does not replace limit setting and air monitoring

- Does not demonstrate a health protective environment
- Placement of compounds is based on characteristics not exposure limits
- Compounds need to be reevaluated as new data become available
- Requires experienced toxicologists and industrial hygienists to get it right
- Not adequate by itself to satisfy regulators for Big Pharma and Big Chem in UK and Eire

Evolution and Spread of the Concept

- Merck published paper in AIHA Journal – January 1996
- Association of the British Pharmaceutical Industry (ABPI) picked up the idea
  - Published two technical guides in 1995
- UK Health and Safety Executive
  - COSHH Essentials developed in 1999
- New applications are being developed
  - NIOSH developing applications in general industry
  - OSHA acceptance in some cases

VERIFICATION

No Limits, No Methods

Rule #1 – *"Do not collect environmental data unless you know what to do with it"*

- Qualitative Assessment
  - Look at toxicology data that you have
    - Material characteristics
    - Work with your toxicologists
  - Categorize or default into control band
  - Study the process and use judgment to compare to measured exposures
- Surrogate monitoring
  - Can you replicate process and use comparative data?

Surrogate Monitoring
What Do You Want to Know?

- Representative and Maximal Case Exposure Potentials?
- Task-oriented exposure potentials?
- Potential for migration out of an area?
- Potential surface contamination?
- Potential for cross-contamination?
- Predicable levels of containment performance for equipment?

What Do You Do If You Don't Have a Method?

- Develop one and/or perform surrogate sampling
- Choose surrogate that will replicate your compound of interest
  - Particle size
  - Structure
  - Analytical sensitivity compared to OEL
  - Cleanability
- Possible choices include:
  - Lactose, mannitol, acetaminophen, sodium naproxen
  - SF6 Tracer gas studies

Operator Exposure Monitoring

- Understand the range of acceptable results
- Try to replicate the actual operation as closely as possible with surrogate operations.
- Always sample the operator and change media as tasks change
  - Care in handling samples to avoid contamination
- Is the material getting out of the work area?
  - Sample inside the room door and out in the “clean” area

Surrogate Control Evaluation

- Focus sampling on the control or containment device
- Place area samples close to the “action”
- Assess results against a control performance target concentration (CPT), over the task period.
- Compare the results against the CPT using an objective test:
  - EN 689: 1996 or Bayesian Decision Analysis

- Rule #2 - *“Its hard to draw conclusions based on one data point”*

Surrogate Monitoring Results for Specific Tasks in Clinical Scale Operations ($\mu g/m^3$)

No Control Technology	Range	Mean
▪ Granulation, drying (2)	947.2 - 1534	1240.6
Very Limited LEV		
▪ Granulation, drying (6)	93.3 – 671.1	283.5
▪ Screening (2)	153.6 – 176.4	165.0
▪ Blending, sieving (6)	77.0 – 752.8	347.5
▪ Compression (6)	64.3 – 531.1	203.1
▪ Encapsulation (4)	40.0 – 59.0	54.1
Area Samples (process room +)		
▪ Airlock – no controls (1)	88.6	n/a
▪ Airlock – Limited LEV (12)	0.153 – 3.87	2.32
▪ Outer corridor (12)	0.049 – 0.475	0.182

CPT = 1 $\mu g/m^3$

How Many Samples Do You Take?

- Try to have three different operators perform the same task
- Sample each operator at least two times
  - Attempt to collect a minimum of six data sets
- Decide what is significant to the effort
- Always limited by time, availability and money

Rule #3 - *"Something is better than nothing but no data is better than bad data"*

MAKING IT HAPPEN

Active Project Principles

- Thorough research of toxicity data
- Process evaluation
  - Quantities
  - Ability to generate airborne contaminants
  - Frequency
  - Emission points
- Review of controls options
  - Facility
  - Process
  - Technique
  - PPE
- Review of IH data
- Selection of specific controls based on judgment

Passive Project Principles

- Safety Data Sheet alone
- Assume process in question is just like others
- As long as the control is in the band it must work
  - Most vs. least conservative options
- No limits, no methods, no IH data
- One size fits all
- “Nobody told me”

Active Project Principles

- Controls based on advice and experience
  - Document decisions
- Written SOPs for safe handling and disposal
- Training program implementation
- Identification of limits & monitoring methods
  - Development of them if not available publically
- Do air monitoring to verify control banding decisions
  - Consider surrogate monitoring and/or modeling if necessary
- Reevaluation as toxicity data become available, as monitoring is done, as processes change

Passive Project Principles

- Control banding does not demonstrate a health protective environment
- Pick a number
- Control bands do not necessarily behave as orders of magnitude
- You still may have regulatory challenges in some parts of the world without limits and surveys
- Requires experience in toxicology and industrial hygiene to get control banding right

Basic Considerations

- Number of bands in a system is determined by number of different workplace environments with controls that can be described
  - Airborne emissions don't necessarily behave by factors of 10
- How reliant will you be on RPE?
  - If you don't know the OEL will you assume it falls at high, mid or low end of the band?
- Systems evolve due to changes in manufacturing technology, containment options, product innovations and health effects

Areas in Need of Improvement

- Communication
- Participation
- Researching Alternatives and Combinations
- Productivity Matters
- Demonstration of Control
  - Air and Surface Monitoring
  - Active ingredients and surrogates
- Periodic Reassessment

Things to Think About

- Do enough data exist to get the controls right within a given band
  - Identify data gaps and decide how to address
- Have you thought through the entire process to ensure estimates of emissions and potential exposures are identified
- How much redundancy do you want and will the production group accept?
- Will your qualitative assessment stand up to scrutiny?
- Who may have done this before and where can you get help?

Summary

- Qualitative Assessment
  - Can be done when no limits or methods are available
  - Chemical categorization and banding system evolved for this purpose
  - Base judgements on situations where you have data
  - Lines between bands are “soft” rather than “hard”
  - Err on the side of conservatism
- Surrogate Monitoring
  - Planning is required to do a meaningful study
    - Develop a CPT
  - Determine objectives carefully
    - If you have an OEL, develop a method and meet OEL
  - Judgment is required as to what is important
  - Use only validated methods that are sensitive enough

More Information

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Thank you for the opportunity to speak with you today.

Questions?

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