112 Under the Microscope: EH&S Issues Facing the BioTech & Pharmaceutical Industry

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Faculty Biographies

Andrew B. Cohen

Andrew B. Cohen is associate general counsel at Eisai Inc., the U.S. pharmaceutical subsidiary of Tokyo-based Eisai Co., Ltd. Mr. Cohen is responsible for all legal support at Eisai's manufacturing and research facility in Research Triangle Park, North Carolina. His areas of focus include environmental health and safety, FDA regulation of good manufacturing practices, pharmaceutical distribution, research and development license agreements, and employment law.

Prior to joining Eisai, Mr. Cohen worked in various practice groups at Moore & Van Allen, PLLC as a partner in its Durham, North Carolina office, and at the Raleigh office of Graham & James. Mr. Cohen served for two years as law clerk to U.S. District Court Judge Franklin T. Dupree, in the Eastern District of North Carolina.

Mr. Cohen has performed pro bono work as a cooperating attorney with the American Civil Liberties Union and with local legal services organizations. He has been a member of the eastern district of North Carolina local rules committee and clerk of court selection committee. He has served as chair of the town of Carrboro planning board and is currently a member of the board of directors of the Weaver Street cooperative.

Mr. Cohen is a graduate of Dartmouth College and the Yale Law School.

Steven W. Spector

Steven W. Spector, is senior vice president, general counsel, and secretary of Arena Pharmaceuticals in San Diego.

Prior to joining Arena, Mr. Spector was a partner with the law firm of Morgan, Lewis & Bockius LLP, where his practice focused on representing companies in various industries in corporate and securities matters. Mr. Spector also worked as a member of the litigation department.

Mr. Spector is the president-elect of ACC's Southern California Chapter.

Mr. Spector holds a B.A. and a J.D. from the University of Pennsylvania.

Alan C. Zetterberg

Alan C. Zetterberg is senior corporate counsel/environmental affairs at Pfizer Inc in New York City. He was one of the founding members of Pfizer's environmental health and safety (EHS) program. His current responsibilities include providing counsel on EHS issues to facilities in the U.S., Scandinavia, and Asia. He also provides EHS counsel to Pfizer's research and development site in La Jolla, California. He has been responsible for the EHS aspects of a number of the company's acquisitions and divestitures. He has also had responsibilities in the company's EHS auditing program, EHS corporate compliance program, SEC reporting, management of waste site cases, and defending government investigations.

Prior to joining Pfizer, he worked in private law practice in New York, in government and for a private foundation. He also taught for a year in the Republic of the Philippines.

Mr. Zetterberg is a past chair of ACC's Environmental Law Committee and the PhRMA environmental focus group (law committee). He has been member of the Environmental Law Institute in Washington DC for many years. He is currently involved in conservation and preservation projects with the Nature Conservancy and with Pitzer College, a member of the Claremont Colleges.

Mr. Zetterberg received his B.A. from Pomona College in Claremont, California and his J.D. degree from Columbia University School of Law in New York.

Sample

2006
Annual Safety Refresher Training
Non-Laboratory Staff

Topics

- Injury & Illness Prevention Program
- Hazard Communication
- General Safety
- Medical Emergencies
- Ergonomics
- Fire Safety

Training Objectives

Awareness of the following:

- [Company]'s EH&S programs
- How to prevent Accidents and Injuries
- Procedures for reporting Accidents and Injuries
- Your role in workplace safety and during an incident
- Where to locate [Company]'s written Safety Programs

Injury & Illness Prevention Program

- CCR Title 8, Section 3203 (Cal/OSHA)
- The EH&S Dept. is responsible for implementation
- Requires that [Company] maintain an environment where unsafe or unhealthy conditions are corrected
- Manager/Supervisor & Employee Responsibilities and Rights

Injury & Illness Prevention **Program**

As directed by the IIPP, [Company] provides:

- Training for basic and job specific hazards
- EH&S follow-up on all reported incidents
- An environment where employees are free to communication EH&S problems
- Procedures to ensure EH&S Compliance

The EH&S Department

- ***VP Quality Systems: ____***
- ***EH&S Dept. Manager: _____***
- ***Radiation Safety Officer: _____***
- ***EH&S Specialist: _____***
- ***EH&S Technicians: _____***
- ***EH&S Coordinator: _____***
- ***Consulting Industrial Hygienist: _____***
- ***Consulting Health Physicist: _____***

- ***Chemical Hygiene Officers: _____***
- ***CDF Safety Representatives: _____***
- ***Biological Safety Officer: _____***
- ***Alternate Radiation Safety Officers: _____***

- ***Incident (Spill) Response Team: _____***

Environmental Health & Safety Committee – All departments represented.
BioSafety Committee
Radiation Safety Committee

Managers & Supervisors Safety Responsibilities

- Evaluate the safety performance of all employees
- Counsel employees for disregarding safe practices
- Encourage employees to identify workplace hazards
- Ensure that employees attend Safety Training
- Regularly communicate information to employees regarding safety concerns in the workplace
- Retrain employees when safety performance is deficient

Employee Safety Responsibilities

- Attend required training
- Report unsafe work conditions
- Read (and understand) applicable written safety programs
- Maintain a safe working environment – Follow the rules
- Report all accident, injuries, and near misses ASAP
- Ask Questions, when unsure how to procedure

Reporting Injuries - Accident & Injury Investigation

EH&S is responsible for the following:

- Interview injured workers and witnesses
- Identify factors associated with the accident or exposure
- Corrective action to prevent reoccurrence
- Record the findings and corrective actions
- Report to the necessary regulatory agencies
- Administration of ***Return to Work Program*** for injured workers
- Administration of Workers Comp.

Employees / Managers are responsible for the following:

- Report all injuries
- Submit an Incident Report to EHS (24 hours)
- Be available to assist with the investigation
- Attend all scheduled Doctors appointments
- Adhere to all Doctor / EHS work restrictions

[Company]'s Safety Communication System

Workplace safety and health training programs

- New employee orientation

Regularly scheduled safety meetings

Posted or distributed safety information

Oral instruction about safe work practices

Employee to Supervisor communication

Supervisor to Employee communication

Rewards, Recognitions, and Reprimands (R^3)

EH&S Observation Form

- Triplicate Form (Employee, Supervisor, EH&S)
- Used to document the Three Rs
  - Goal: Primarily used as a reward
- Maintained in the Employee EH&S file
- Issued by the EH&S Manager only
- Formal verbal warning issued by EH&S Manager prior to issuance for a safety violation

Hazard Communication

- Required by CalOSHA
  - 8 CCR Section 5194
- AKA – "Right To Know Law"
- Information Labels on all containers
  - Chemical Hazards
- Material Safety Data Sheets
- Chemical Inventory Program

General Safety

Emergency Action Plan

CCR Title 8, Section 3220

Emergency Procedures

- Fire / Explosion
  - Using a Fire Extinguisher
  - Building Evacuation
  - Fire in the surrounding canyons
- Spills of Hazardous Materials
- Emergency Equipment and Resources
- Medical Emergencies
- Earthquake
- Power Failure
- Etc…

General Safety

Emergency Evacuation

Who can call for an evacuation – YOU!

When to call for an evacuation

- Any unsafe condition – Fire, Spill, Explosion, Earthquake etc…

Follow Evacuation Procedures

Evacuation Drills (2x Annually)

Document Control Room Alarms

General Safety

Emergency Evacuation cont.

Evacuation Procedures

- Calmly, loudly announce “EVACUATE”
- Repeat message, ask for help from others
- Contact 911 if necessary
- Sweepers will be activated once announcement is made

Do Not Jeopardize Your Own Safety!

General Safety

Emergency Evacuation

Immediately contact the front desk x_____ (8 to 5 Mon.-Fri.), Security Guard x_____ (Off Hours)

- Inform the front desk personnel or guard that an evacuation is underway
- State the reason and location
- Give any other pertinent information - 911, injuries etc…

During an Evacuation <u>You Must</u>

- Evacuate immediately when asked
- Secure your area
- Assist others
- Proceed to the designated gathering area - check in
- Remain in the evacuation assembly area until released by EH&S, Director level or above, or Fire/Police Dept.

Medical Emergencies - *Non Serious*

All injuries must be reported to EH&S

First Aid Kit Use

[Workers' compensation health-care provider]

- Occupational Health
- Basic Urgent Care
- Physical Therapy

Types of Non-Serious Injuries

- Minor Burns
- Minor Cuts
- Potential exposure to hazardous material
- Sprain or strain
- Bumps, bruises, scrapes, etc…

Medical Emergencies –***Serious Injuries***

Call 911 – Send some to meet responders

Contact EHS ASAP - Front Desk or Guard - NO VOICE MAIL!!!!

CPR/First Aid Trained Personnel

Automatic External Defibrillators (AED)

Recognition of Serious Injury or Illness

- Obvious chemical exposure
- Chest pain
- Confusion
- Significant loss of blood
- Loss of consciousness
- Head injury
- Broken bone

ERGONOMICS

- The goal of ergonomics is to fit the workspace to the worker.

[Outside consultant]

- [Consultant] is a health promotion company that specializes in work-site health issues.
- [Consultant] conducts all Ergonomic Evaluations at [Company].
- [Consultant] suggests ways we can make your work station more comfortable, including repositioning furniture, adding ergonomic equipment and teaching employees the importance of taking breaks and stretching.

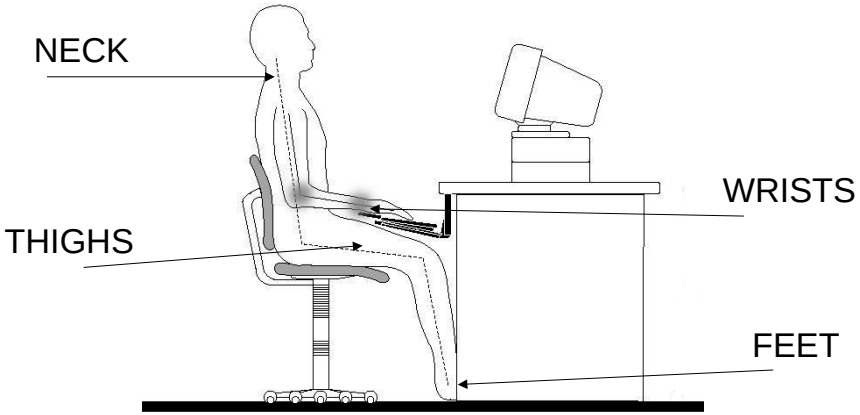
Aspects of Ergonomic Evaluations:

- Physical demands of tasks or job
- Workstation layout and space
- Equipment used and objects handled
- Environmental conditions
- Work organization

Ergonomic Risk Factors

- **Force** – the amount of physical effort required to perform a task or maintain control of tools and equipment
- **Repetition** – performing the same motion or series of motions continually or frequently for an extended period of time
- **Awkward and static postures** – assuming positions that place stress on the body
- **Contact stress** – pressing the body or part of the body against hard or sharp edges

Natural Keyboarding Position



Ergonomic Injuries & Prevention

Common Ergonomic Injuries

- Strain- Back or neck injury
- Cumulative Trauma Disorder (CTD) – Carpal Tunnel Syndrome

Prevention

- Get help lifting, lift with your legs not back, use a mechanical device
- Take breaks
- Request an Ergonomic Evaluation

Ergonomics Program

- We encourage all employees to participate in the Ergonomics Program.
- If you are experiencing discomfort, please let us know right away. In many cases, we can make adjustments to your work station before it becomes a serious injury.

Ergonomics Program

- Please read the hand outs we have provided on Office Stretches and Tips for Computer Users.
- Try to be aware of your posture and positioning while you work.
- To schedule an Ergonomic Evaluation, contact _____.

Speaker Perspective

- Associate General Counsel, Eisai Inc.
- 19th Largest U.S. Pharmaceutical Company
- $2 Billion in Manufacturing Annually
  - **Aricept**® for Alzheimer's disease
  - **Aciphex**® for Acid Reflux
- Research Facility for Potent Compounds
- 16 attorneys in Legal Department

Key to OSHA for Pharma/Biotech

- Innovator company is sole entity with knowledge of compounds – and health and safety risks
- No industry standard for employee protection for a particular compound
- Employee safety profile for each drug is therefore new and unique

Safety and Health Regulations

- Federal Occupational Safety and Health Administration (OSHA)
  - 29 CFR 1910 - General Industry
  - 29 CFR 1903 - Inspections, Citations, Penalties
  - 29 CFR 1904 - Recording/Reporting Injuries
  - 29 CFR 1990 - Occupational Carcinogens

State OSHA Regulations

- Federal OSHA enforced through federally approved state plans (29 CFR 1952)
- Only minor modifications in most states
  - 13 NCAC 07F.0101 (North Carolina)
- Significant modifications in some states
  - California OSHA has incorporated Proposition 65 (Safe Drinking Water and Toxic Enforcement Act)
  - CAL/OSHA Chapter 3.2., Subchapter 1, Article 5, §338 Special Procedures for Supplementary Enforcement of State Plan Requirements Concerning Proposition 65

Pharmaceutical Development Process

Molecule Discovery
⇨
Formulation Research
⇨
Pre-Clinical
⇨
Pilot Scale Manufacturing
⇨
Phase I, II, III Trials
⇨
NDA Submission
⇨
Commercial Manufacturing
⇨

OSHA Issues in Drug Development

- Working with New Chemical Entities
- Drafting Material Data Safety Sheets (MSDS)
- Determining Occupational Exposure Bands (OEB)
- Evaluating Pharmaceutical Synthesis Processes
- Developing Occupational Exposure Limits (OEL)
- Developing Industrial Hygiene and Analytical Methods
- Evaluating Manufacturing Processes
- Medical Surveillance Programs
- Relationship between OSHA Recordables and FDA Adverse Events

Practical Application

- See sample policy:

  "Health and Safety Guidelines for Drug Evaluation and Development"

Working with New Chemical Entities

- Treat conservatively until risks have been assessed
  - Barrier isolation systems
  - No open handling
- Undertake prompt assessment by a health and safety evaluation committee

* * *

See sample policy: "Handling/Containment Guidelines for New Chemical Entities"

Material Safety Data Sheets

- MSDS required as part of Hazard Communication
  - 29 CFR 1910.1200
- MSDS required at certain stages of drug development:
  - Shipping compound, i.e for outside testing
  - Required for all Active Pharmaceutical Ingredients (API)
  - Required for final product if non solid dose

MSDS cont'd

- Concerns regarding confidentiality of MSDS information:
  - 29 CFR 1910.1200 (i) allows trade secret information to be omitted from MSDS
  - Companies must have procedures for providing trade secret information required for emergency medical treatment
  - Can also use Confidentiality Agreements in non-emergency settings
- MSDS information must be consistent with information in New Drug Application (NDA) submitted to obtain FDA approval

Occupational Exposure Band

- Determine OEB using:
  - Pre-clinical toxicology results
  - Chemical class information
- OEB Levels dictate handling methods:
  - Level 1 - Controlled General Ventilation
  - Level 2 - Local Exhaust Ventilation
  - Level 3 - Barrier Isolation Systems
  - Level 4 - Closed Handling Within Isolator

Pharmaceutical Synthesis Process

- Determine health and safety concerns in API synthesis process
  - Process safety testing, i.e. explosivity testing of drug
  - Analysis of potential worker exposure through air monitoring
  - Develop cleaning and analytical methods
  - Develop exposure controls, especially for OEB Level 3 or 4

Occupational Exposure Limit

- OEL should be set prior to Phase IIB, and expanded manufacturing of clinical supplies
- Many tests required for determining OEL are performed as part of drug development:
  - Acute oral toxicity
  - Ames mutagenicity
  - Systemic toxicity
- Additional tests for employee safety:
  - Allergy or skin irritation
  - Eye irritation

Sampling and Analytical Methods

- In conjunction with setting Occupational Exposure Limit, pharmaceutical companies must develop methods for sampling and analyzing air samples
- Work with in-house analytical chemists with knowledge of compound

Manufacturing Process

- Job Hazard Assessment required by 29 CFR 1910.132
- Analyze potential exposure in clinical and commercial manufacturing processes
- Conduct air monitoring and surface testing
- Evaluate whether engineering controls can be used to reduce burden and risk of personal protective equipment (PPE)

Medical Surveillance Programs

- Required by OSHA for certain hazardous substances:
  - 13 listed carcinogens - 29 CFR 1910.1003
  - Also, lead, asbestos, benzene, arsenic, etc.
- Prudent to have medical surveillance for potent compounds not identified in OSHA regulations

* * *

See sample policy: "Medical Surveillance Policy"

See sample protocol: "Medical Surveillance Protocol for Employees Handling Potent Compounds"

OSHA Recordable vs. FDA Adverse Event

- OSHA requires that workplace health problems be recorded or reported
- FDA requires reporting of "adverse events"

OSHA Recordable vs. FDA Adverse Event

- Question: Should a pharmaceutical/biotech company report an employee health problem caused by drug exposure to the FDA as an adverse event?
- Answer: Possibly, depending on whether the path of exposure was similar to the drug delivery mechanism
  - Employee skin rash from topical drug or airborne exposure to inhaled drug may be an FDA adverse event

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HANDLING/CONTAINMENT GUIDELINES FOR NEW CHEMICAL ENTITIES

Introduction

This program provides guidance on minimum precautions to limit exposure while handling new chemical entities (NCEs) in the absence of detailed, worksite-specific risk assessments. The intent of these guidelines is to create uniform NCE handling procedures throughout CompanyName to assist with ranking and prioritizing risks among different NCEs, and to provide basic recommendations to the NCE user on handling precautions. The guidelines also provide a basis for better prioritization of worksite-specific risk assessments, focusing on NCEs and processes posing the greatest potential exposure risk. The guidelines assume that well-applied traditional controls and company safety procedures are in place. In some cases, joint worksite and process-specific health risk assessments by NCE users, their management, and Environmental Health and Safety (EH&S) will be necessary. A detailed risk assessment includes a thorough, written hazard evaluation for each step in a process and may include a worksite visit by EH&S.

The NCE Handling and Containment program should be initiated when an NCE is considered for early development. At that time, the substance is categorized to Occupational Exposure Band 3 (OEB 3) by default. Each OEB has a specific set of handling and containment recommendations designed to minimize potential exposure to NCEs. During drug development, the CompanyName Health Hazard Evaluation Committees (HHEC) will review the available data on each NCE and confirm the default categorization or, based on health hazard potential, reassign a substance to OEB 1, 2, or 4. Representation on each CompanyName Health Hazard Evaluation Committee includes representatives from the CompanyName Environmental Health and Safety Consortium, internal or external Toxicologists, Project Team representatives, and other departmental representatives as needed.

Hazard categories (i.e., OEBs) for each NCE are made available to the NCE user through means such as written programs and on-line CompanyName or CompanyAffiliate WebPages. As more information becomes available about an NCE, the handling and containment category may change. Such changes are conveyed by electronic mail, updates to Web-accessible pages, and by notifying department management, who then notify staff. As an NCE enters full development, its CompanyName Health Hazard Evaluation Committee will review the composite dataset collected on the NCE and estimate an Occupational Exposure Limit (OEL). The OEL is an airborne exposure limit at which workplace exposure can occur without detectable pharmacological or toxicological effect. In general, an OEL is established for each NCE prior to latter phases of clinical trials (Phase II / III) when plans indicate high likelihood of further progression. However, in some instances an OEL is established sooner based on the toxicity of the NCE.

How to use NCE Handling and Containment Guidelines

1. Search CompanyName or CompanyAffiliate websites, or contact a Health Hazard Evaluation Committee member to determine the OEB or OEL for the substance(s) of interest. Assume OEB 3 unless clear guidance to do otherwise has been given.

2. Each OEB (1– 4) corresponds to an associated set of NCE handling and containment guidance; refer to the handling/containment guidelines for the applicable category. For NCEs to which an OEL has been assigned (generally substances for which clinical Phase II investigation has been completed), general guidance on handling and containment may be obtained by using the following table to match OEL values to handling and containment categories:

OEL Value (mcg/m^3)	Use NCE Handling and Containment OEB Guidelines
> 500	1
10 - 500	2
1 - 10	3
< 1	4

3. Review and plan any handling of the NCE to comply with recommended protective measures found herein. The selection of the most appropriate engineering control depends largely on the scale of operation, the job activity, and site-specific procedures. For example, laboratory "fume" hoods are not designed to handle dust but if the scale of work is small enough and with EH&S Department approval, lab hoods may be used effectively with the addition of certain procedural controls. The use of ventilated balance safety enclosures (VBSEs) or containment technology (e.g., gloveboxes) should be considered for larger scale operations with NCEs or other pharmacologically potent or toxic substances.

The Environmental Health and Safety department at each CompanyName location may be able to measure and assess the effectiveness of the selected control strategy (depending upon the availability of a validated analytical method for the chemical substance of interest). Such assessments help to validate that the selected control is providing adequate protection.

NCE Handling/Containment Guidelines for OEB 1

General Requirements for all operations

- Review MSDS or other relevant safety information
- Appropriate eye protection, gloves, lab coat must be worn.
- Lab coats must be cleaned on a regular basis
- Wash hands before leaving work area.
- Label and handle all waste according to company waste procedures
- Work surfaces should be cleaned and/or lab bench absorbent paper changed on a regular basis (e.g., daily)
- Personnel should be knowledgeable on the most suitable solvent(s) for cleaning.
- When transporting containers containing the NCE, secondary containment should be used.
- Performance specifications for Local Exhaust Ventilation (LEV) must be set and LEV must be routinely monitored.
- Personal Protective Equipment (PPE) must be changed if it becomes contaminated.
- All work done in fume hoods must be completed with hood sashes positioned no higher than designated by the calibration sticker. All work must be completed at least 6” inward from the front edge of the fume hood.
- All emission control devices (e.g., VBSE, glove box) must be approved by EH&S Department
- When handling the compound, slow, deliberate movements must be used so as to prevent aerosolization of the compound.
- Be careful not to touch your eyes, mouth, or other body areas while working.
- Industrial hygiene evaluations (e.g., air and/or surface monitoring) to be performed, if available

1. **Laboratory Scale Operations**
   - General room ventilation
   - Open handling permitted for all but dusty processes**.** While emissions control equipment is always a preferred means of dust control; where it is not practical, feasible, or before it is operational, a particulate respirator should be used.
     - A laboratory fume hood, although designed for extraction of vapors, may be an acceptable means of emission control equipment for dust. Contact EH&S Department.

Solutions Handling

- Solutions can be handled outside of local exhaust ventilation (e.g., laboratory fume hood, biosafety cabinet) during procedures with no potential for aerosolization. Fume hood must be used for aerosol generating procedures.

2. Pilot Plant Scale Operations

- Same as in Laboratory Scale Operations, plus:

- Emission control equipment at dust generating process points is recommended. Particulate respirator required in absence of sufficient control equipment, based on EH&S Department guidance.
- Consideration should be given to minimize transfer points and use direct connections where feasible.
- For dusty processes, nylon coveralls or disposable Tyvek suit, disposable booties, and disposable gloves must be worn.
- Protective garments must not be worn outside of the work area.
- Negative/positive air pressure relationships and buffer zones are required.

Solutions handling
- Gloves must be protective against solvents in use

3. Commercial Manufacturing Operations
- Emissions control equipment should be utilized if feasible for dust control.
- A particulate respirator is required without sufficient emissions control equipment, based on EH&S Department guidance.
- Negative/positive air pressure relationships and buffer zones are required.
- For dusty processes, nylon coveralls or disposable Tyvek suit and disposable booties and disposable gloves must be worn.
- Documented procedures for PPE decontamination prior to degowning. Personnel must use wet methods for decontamination (e.g., spray bottles/wipes and the buddy system to effectively decontaminate PPE), or utilize a HEPA filtered vacuum system.

NCE Handling/Containment Guidelines for OEB 2

General Requirements for all operations
- Review MSDS or other relevant safety information
- Appropriate eye protection, gloves, lab coat must be worn.
- Lab coats must be cleaned on a regular basis
- Wash hands before leaving work area.
- Label and handle all waste according to company waste procedures
- Work surfaces should be cleaned and/or lab bench absorbent paper changed on a regular basis (e.g., daily)
- Personnel should be knowledgeable on the most suitable solvent(s) for cleaning.
- When transporting containers containing the NCE, secondary containment should be used.
- Performance specifications for Local Exhaust Ventilation (LEV) must be set and LEV must be routinely monitored.
- Personal Protective Equipment (PPE) must be changed if it becomes contaminated.
- All work done in fume hoods must be completed with hood sashes positioned no higher than designated by the calibration sticker. All work must be completed at least 6" inward from the front edge of the fume hood.
- All emission control devices (e.g., VBSE, glove box) must be approved by EH&S Department
- When handling the compound, slow, deliberate movements must be used so as to prevent aerosolization of the compound.
- Be careful not to touch your eyes, mouth, or other body areas while working.
- Industrial hygiene evaluations (e.g., air and/or surface monitoring) to be performed, if available.

1. Laboratory Scale Operations
- Emission control equipment at dusty process points (e.g., ventilated balance safety enclosure (VBSE) HEPA filtered and exhausted to room) or other approved LEV must be used. Ventilation will be approved on a task specific basis.
  - A laboratory fume hood, although designed for extraction of vapors, may be an acceptable means of emission control equipment for dust. Contact EH&S Department
- Open handling of powder must be approved by EH&S Department on a task specific basis.
- In absence of sufficient emission control equipment, a particulate respirator is required.

Solutions Handling
- Solutions can be handled outside of local exhaust ventilation (e.g., laboratory fume hood) during procedures with no potential for aerosolization. Fume hood must be used for aerosol generating procedures.

2. Pilot Plant Scale Operations

- Same as in Laboratory Scale Operations, plus:
- Emission control equipment at dust generating process points. Particulate respirator required in absence of sufficient control equipment, based on EH&S Department guidance.
- Transfer points should be minimized and direct connections utilized where feasible
- For dusty processes, nylon coveralls or disposable Tyvek suit, disposable booties, and disposable gloves must be worn.
- Protective garments must not be worn outside of the work area.
- Negative/positive air pressure relationships and buffer zones are required.

Solutions handling

- At a minimum, emission control equipment should be utilized for work activities with aerosol-generating potential (e.g., sampling, opening manway on tanks)
- Gloves must be protective against solvents in use

3. Commercial Manufacturing Operations

- Emissions control equipment utilized for dusty processes.
- At a minimum, a particulate respirator is required without sufficient emissions control equipment, based on EH&S Department guidance.
- Negative/positive air pressure relationships and buffer zones are required.
- Nylon coveralls or disposable Tyvek suit and disposable booties must be worn.
- Double gloves and tyvek sleeve covers must also be worn
- Documented procedures for PPE decontamination prior to degowning, as well as procedures which designate process gowning required areas**.** Personnel must use wet methods for decontamination (e.g., spray bottles/wipes and the buddy system to effectively decontaminate PPE), or utilize a HEPA filtered vacuum system.

NCE Handling/Containment Guidelines for OEB 3

General Requirements for all operations

- Review MSDS or other relevant safety information
- Appropriate eye protection, gloves, lab coat must be worn.
- Lab coats must be cleaned on a regular basis
- Wash hands before leaving work area.
- Label and handle all waste according to company waste procedures
- Work surfaces should be cleaned and/or lab bench absorbent paper changed on a regular basis (e.g., daily)
- Personnel should be knowledgeable on the most suitable solvent(s) for cleaning.
- When transporting containers containing the NCE, secondary containment should be used.
- Performance specifications for Local Exhaust Ventilation (LEV) must be set and LEV must be routinely monitored.
- Personal Protective Equipment (PPE) must be changed if it becomes contaminated.
- All work done in fume hoods must be completed with hood sashes positioned no higher than designated by the calibration sticker. All work must be completed at least 6” inward from the front edge of the fume hood.
- All emission control devices (e.g., VBSE, glove box) must be approved by EH&S Department
- When handling the compound, slow, deliberate movements must be used so as to prevent aerosolization of the compound.
- Be careful not to touch your eyes, mouth, or other body areas while working with compounds.
- Industrial hygiene evaluations (e.g., air and/or surface monitoring) to be performed, if available.

1. Laboratory Scale Operations

- No open handling. A ventilated balance safety enclosure (HEPA filtered and connected to house exhaust) or other approved LEV must be used. Ventilation will be approved on a task specific basis.
- Clearly defined areas for handling material (e.g., glovebox, hood, biosafety cabinet, or VBSE) must be designated.
- Substance must be in non-dusty form (e.g., solution or suspension) prior to removal from hood or enclosure or within secondary containment. NCE container must be decontaminated prior to removal from containment.
- Only persons with appropriate training are permitted in the work area.
- When handling the compound, slow, deliberate movements must be used so as to prevent aerosolization of the compound.
- Equipment and work surfaces must be cleaned daily (wet-wiping of potentially contaminated surfaces with a suitable solvent until visible clean at minimum). If lab bench absorbent paper is used, it must be changed at least daily.

- Written procedures for handling spills may be required, based on EH&S department guidance.
- Wet methods or a HEPA filtered vacuum system must be used for spill containment and clean up.

Powders handling
- Powder handling operations must be done in a VBSE, a glove box, or other equivalent ventilation containment system. Where containment or local ventilation is not available, a Powered Air-Purifying Respirator (PAPR) or Supplied Air Respirator (SAR) must be worn by all personnel in the immediate area.
- Equipment and surfaces must be decontaminated after manipulating powder (wet-wiping of potentially contaminated surfaces with a suitable solvent until visibly clean at minimum).
- Double gloves and disposable sleeve covers must be worn

Solutions handling
- Solutions can be handled outside a containment system or without local exhaust ventilation during procedures with no potential for aerosolization.
- If the procedures have a potential for aerosolization, they should be handled in a containment system or with LEV. In situations where this is not feasible, a PAPR or SAR must be worn by all personnel in the immediate area.

2. Pilot Plant Scale Operations
- Same as in Laboratory Scale Operations, plus:
- The use of intermediate bulk containers (IBCs) equipped with split butterfly valves (SBVs) or equivalent is encouraged if direct connections are not possible.
- Process steps should be combined to minimize transfer points.
- High-energy operations must only be done within an approved emissions control or containment system. Where sufficient emissions control or containment is not available, a PAPR or SAR must be worn by all personnel in the immediate area.
- Nylon coveralls or disposable Tyvek suit and disposable booties must be worn.
- Protective garments must not be worn outside of the work area.
- Clean/dirty/decontamination areas must be established, as well as procedures for PPE decontamination prior to degowning.
- Negative/positive air pressure relationships and buffer zones are required.

Powders handling
- Emphasis must be placed on closed material transfer systems and process containment, with no open handling of powders.
- Clean-in-place equipment is preferred.
- Where possible, paperless or dedicated notebooks and batch records are required unless another means of contamination control can be documented.

Solutions handling
- Enclosed systems must be used where possible.
- Processing tanks must be kept covered.
- Process samples must be taken from sample ports if feasible
- Gloves must be protective against solvents in use

3.0 Commercial Manufacturing Operations

- Closed transfer operations, as well as usage of specialized emissions control equipment should be utilized.
- The use of intermediate bulk containers equipped with split butterfly valves or equivalent is encouraged if direct connections are not possible.
- Negative/positive air pressure relationships and buffer zones are required.
- For open operations, a hooded PAPR or SAR must be worn by all personnel in the immediate area. The level of respiratory protection required may be reduced by EH&S Department dependent on air monitoring data and known or suspected health hazard information.
- Nylon coveralls or disposable Tyvek suit and disposable booties must be worn.
- Double gloves and tyvek sleeve covers must also be worn
- Proactively change outer gloves after manipulating powder or uncoated tablets
- Documented procedures for PPE decontamination prior to degowning, as well as procedures which designate process gowning required areas. For PPE decontamination, a specialized decontamination shower is recommended, however at a minimum personnel must use spray bottles/wipes and the buddy system to effectively decontaminate PPE or utilize a HEPA filtered vacuum system.
- When handling the compound, slow, deliberate movements must be used so as to prevent aerosolization of the compound. EH&S Department can provide operator training on procedural techniques to minimize aerosolization during charging/transfer steps.
- Written procedures for handling spills

Powders handling
- Emphasis must be placed on closed material transfer systems and process containment, with no open handling of powders.
- Clean-in-place equipment is preferred.
- Where possible, paperless or dedicated notebooks and batch records are required unless another means of contamination control can be documented.

Solutions handling
- Enclosed systems must be used where possible.
- Processing tanks must be kept covered.
- Process samples must be taken from sample ports if feasible
- Gloves must be protective against solvents in use

NCE Handling/Containment Guidelines for OEB 4

General Requirements for all operations

- Review MSDS or other relevant safety information
- Appropriate eye protection, gloves, lab coat must be worn.
- Lab coats must be cleaned on a regular basis
- Wash hands before leaving work area.
- Label and handle all waste according to company waste procedures
- Work surfaces should be cleaned and/or lab bench absorbent paper changed on a regular basis (e.g., daily)
- Personnel should be knowledgeable on the most suitable solvent(s) for cleaning.
- When transporting containers containing the NCE, secondary containment should be used.
- Performance specifications for Local Exhaust Ventilation (LEV) must be set and LEV must be routinely monitored.
- When handling the compound, slow, deliberate movements must be used so as to prevent aerosolization of the compound.
- PPE must be changed if it becomes contaminated.
- Be careful not to touch your eyes, mouth, or other body areas while working with compounds.
- All work done in fume hoods must be completed with hood sashes positioned no higher than designated by the calibration sticker. All work must be completed at least 6" inward from the front edge of the fume hood.
- All emission control devices (e.g., VBSE, glove box) must be approved by EH&S Department
- Industrial hygiene evaluations (e.g., air and/or surface monitoring) to be performed, if available.

1. Laboratory Scale Operations

- No open handling.
- While working with potent compounds, signage must be placed on all doors to the laboratory. For example, "Caution-Potent Compound work in Progress-Restricted Access". Hoods and other equipment must also be labeled.
- Only persons with appropriate training are permitted in the work area.
- Substance must be in non-dusty form (e.g., solution or suspension) prior to removal from hood or enclosure or within secondary containment. NCE container must be decontaminated prior to removal from containment.

Powders handling

- Powder handling operations must be done in a glove box, or other equivalent containment system. Where containment is not available, a Powered Air-Purifying Respirator (PAPR), tyvek suit, shoe covers, double gloves, and tyvek sleeve covers must be worn.
- Powder should be put into solution or a tightly capped container before being removed from powders weighing hood/glove box.
- Any reconstitution of powder should be performed inside a containment system (VBSE, addition of solvent to stoppered vial containing lyophilized powder, etc).
- Equipment and surfaces must be decontaminated after manipulating powder (wet-wiping of potentially contaminated surface with a suitable solvent until visibly clean at minimum).

Solutions handling

- If the procedures have a potential for aerosolization, they must be handled in a containment system or with LEV. In situations where this is not feasible, a PAPR or SAR must be worn by all personnel in the immediate area.

2. Pilot Plant Scale Operations

- Same as in Laboratory Scale Operations, plus:
- Nylon coveralls or disposable Tyvek suit and disposable booties must be worn.
- Protective garments must not be worn outside of the work area.
- Clean/dirty/decontamination areas are must be established
- Negative/positive air pressure relationships and buffer zones are required.
- High-energy operations must only be done within an approved emissions control or containment system. Where containment is not available, a PAPR or SAR must be worn by all personnel in the immediate area.
- The use of intermediate bulk containers (IBCs) equipped with split butterfly valves (SBVs) or equivalent is encouraged if direct connections are not possible.
- Process steps should be combined to minimize transfer points.

Powders handling

- Emphasis must be placed on closed material transfer systems and process containment, with no open handling of powders.
- Clean-in-place equipment is preferred.
- Where possible, paperless or dedicated notebooks and batch records are required unless another means of contamination control can be documented.

Solutions handling

- Enclosed systems must be used where possible.
- Processing tanks must be kept covered.
- Process samples must be taken from sample ports if feasible
- Gloves must be protective against solvents in use

3.0 Commercial Manufacturing Operations

- Closed transfer operations and process containment, as well as usage of specialized emissions control equipment are required. Open handling of powder must be eliminated.
- The use of intermediate bulk containers (IBCs) equipped with split butterfly valves (SBVs) or equivalent are required if direct connections are not possible.

- As deemed appropriate by EH&S, personal protective equipment may be necessary in addition to emission control equipment. For example, a PAPR or SAR may be required to ensure adequate respiratory protection.
- Negative/positive air pressure relationships and buffer zones are required.
- Nylon coveralls or disposable Tyvek suit and disposable booties must be worn.
- Double gloves and tyvek sleeve covers must also be worn
- Proactively change outer gloves after manipulating powder or uncoated tablets
- Documented procedures for PPE decontamination prior to degowning, as well as procedures which designate process gowning required areas. For PPE decontamination, a specialized decontamination shower is required.
- When handling the compound, slow, deliberate movements must be used so as to prevent aerosolization of the compound. EH&S Department to provide operator training on procedural techniques to minimize aerosolization during charging/transfer steps.
- Written procedures for handling spills

HEALTH AND SAFETY GUIDELINES FOR DRUG EVALUATION AND DEVELOPMENT ACTIVITES

I. Development and Update of a Material Safety Data Sheet (MSDS)

The MSDS is needed for regulatory compliance, and employee health and safety consideration. Appropriate information flow is necessary to facilitate the development of the proper information on the MSDS. Several key time frames occur in drug evaluation, which require development and update of this information, as follows.

1. An MSDS is required when a compound is within the Project Entry phase, especially if the compound is to be shipped outside the company, e.g., a mutagenicity testing laboratory.
2. As more information is gathered, the MSDS will be updated and distributed to the appropriate people. The revision date will be noted on the MSDS.
3. If the final drug product is a non-solid dosage form, i.e., not a pill or tablet, it is required by U.S. regulations to have a completed MSDS.
4. There must be a completed MSDS prior to importing/exporting non-solid dosage form drug product.
5. Active pharmaceutical ingredients (API) and intermediates are required to have an MSDS.
6. It is required that the MSDS for drug substances and drug products reaching an NDA/NADA submission be consistent with information contained in the NDA, including the Environmental Assessment reports submitted to FDA or comparable regulatory authorities.

The Project Team must provide the Safety and Health Consortium (the Consortium) with formulation information to allow for development of an MSDS for API, intermediates, and non-solid dosage form drug product.

II. Determination of an Occupational Exposure Band (OEB)

An occupational health categorization scheme (OEB 1, 2, 3, or 4) based on toxicity and potency has been developed as an effective tool in communicating potential risk in handling new chemical entities. These guidelines provide minimum precautions to limit exposure while handling new chemical entities (NCEs) in the absence of detailed, worksite-specific risk assessments. The guidelines create uniformity in NCE handling procedures throughout CompanyName.

When a compound moves from Project Entry into Candidate Selection, data needed to establish an OEB must be collected and reviewed. The Project Team is responsible for providing information to the Consortium so the OEB can be determined. This may include preclinical toxicology test results, chemical class information, etc. If there is not enough data to establish an OEB, additional information will be requested from the Project Team by the Consortium.

III. Perform Pharmaceutical and Chemical Synthesis Process EH&S Evaluations

The pharmaceutical and chemical synthetic processes for the drug product and drug substance respectively must be evaluated to determine if there are any associated potential health or safety concerns. Evaluation activities must occur once the processes are defined or reach development stage, whichever occurs earlier. As changes are made to the chemical synthesis process, re-evaluation must occur. Early resolution of potential health or safety concerns will allow for rapid and efficient transfer of these processes to development and commercialization. Evaluation activities include:

- Preparing a preliminary materials balance for the IND process and verification for the information as processes change
- Performing process safety hazard analyses for the processes prior to the IND
- Conducting process safety testing, e.g., explosivity testing on the drug substance or drug product
- Determining exposure control issues, especially for Category 3 and 4 compounds
- Development of cleaning methods
- Development of spill control plan
- Analysis of potential worker exposure issues as determined by air monitoring

IV. Development of an Occupational Exposure Limit (OEL) on the Drug Substance

To develop an OEL, a minimum test battery is needed to determine its potential to cause toxicity. For the drug substance, most studies needed for occupational hazard determination (acute oral toxicity, Ames mutagenicity, systemic toxicity) are already performed as part of drug evaluation. Additional testing to assess the occupational hazard potential for the drug substance and drug product may be necessary to determine the potential of these materials to cause skin or eye irritation and allergic sensitization to the skin.

Testing may also be necessary on the isolated intermediates in the chemical synthetic pathway. Samples should be collected for occupational toxicity testing when the process has been defined or when the first pilot plant batch has run. Tests to be conducted on each of the isolated intermediates, may include skin and eye irritation, acute oral and dermal toxicity, and skin sensitization tests and an Ames mutagenicity assay. Conduct of these tests will also allow for flexibility for the Project Team to import intermediates into Europe as there are certain regulatory required tests to be conducted on any chemical, including pharmaceutical intermediates, shipped into the European Union.

Results of these tests must be communicated to employees via MSDSs, batch sheet records, and hazard communication training by health and safety staff and supervisors

An OEL is should be determined prior to Phase IIB clinical trials or when a compound reaches repeated pilot plant scale at the research, chemical, or pharmaceutical manufacturing facilities. The purpose of an OEL is to develop a safe level that will be an acceptable limit for workers to potentially be exposed without adverse health effects. An OEL may is necessary not only for the final drug substance but also for intermediates in the drug synthesis pathway.

The draft OEL will be reviewed by individuals familiar with the toxicological and clinical data as well as by individuals within the Consortium. Once accepted, the appropriateness of the OEL will be re-evaluated as new toxicological and clinical data become available during the drug development process. The Consortium will review the draft OEL recommendation and, if appropriate, adopt it as a company standard. After the drug is launched, the appropriateness of the OEL will be reviewed at least once every three years, based on actual experience with handling the drug in the workplace and worker health surveillance information.

V. Development of an Industrial Hygiene Sampling and Analytical Method

Development of an industrial hygiene sampling and analytical method to analyze air samples for the drug substance taken in the workplace must occur in parallel to the development of an OEL for the drug substance or intermediate. Once the analytical method has been validated, the Consortium will implement special requirements for collecting and shipping samples to the laboratory for analysis.

VI. Industrial Hygiene Evaluation of Chemical and Pharmaceutical Plant Processes

When the OEL and industrial hygiene sampling and analysis method have been completed, an analysis of potential exposures in the chemical manufacturing and pharmaceutical plants must be undertaken. Air monitoring results will be shared with all facilities handling a certain chemical. Based on these evaluations, containment design of the processes may need to be modified.

MEDICAL SURVEILLANCE POLICY

I. SCOPE

All employees who have been identified by their supervisor as having a significant (i.e., daily or weekly) potential exposure to a specific health hazard from their job are included in the Medical Surveillance Programs. These jobs include laboratory and pilot plant personnel who may handle hazardous chemicals, pharmaceuticals and research compounds. All personnel required to wear a respirator are included in the Respiratory Protection Program with OSHA-mandated medical surveillance.

II. MEDICAL SURVEILLANCE PROGRAMS

The following medical surveillance programs are offered by CompanyName (*see separate protocols for each program*):

1. Potent Compound Medical Surveillance Protocol
2. Respiratory Protection Program
3. Hearing Conservation Program
4. Laboratory Animal Occupation Health Program
5. Hepatitis B Vaccination Program

Each program will be reviewed annually by CompanyName, and will remain in compliance with any federal and state OSHA standards or guidelines as applicable.

III. GENERAL POLICY

The specific surveillance program(s) for a given employee is driven by their job position and potential job exposures. Employees receive medical surveillance on the following occasions:

a. Pre-placement to establish a baseline prior to or shortly after the initial assignment to an area with identified workplace hazards or exposures.
b. Annually (or as determined for specific compounds and/or the medical examiner) for as long as the employee is assigned to a job in an area with identified workplace hazards or exposures.
c. At the time of reassignment to an area with identified workplace hazards or exposures.
d. Post exposure when a specific incident or occurrence takes place.

IV. SCHEDULING

Specific scheduling of surveillance is determined by the employee's date of hire and the recommended frequency of exams for each program (e.g., annually, other). Each month CompanyName EH&S will review and ask each eligible employee to be seen at MedicalProvider for routine baseline and periodic surveillance. Confidential Medical Surveillance Questionnaire(s) relating to Potent Compounds, Laboratory Animals, or Respirator Medical Clearance will be provided to the employee to fill out and return to MedicalProvider for review. In addition, any physical exam or laboratory testing should be scheduled as per each program.

V. RECORDKEEPING AND NOTIFICATION

OSHA requires that records are maintained and retained on any exposure measurements, and made available for employee review. CompanyName will maintain records of exposure measurements for employees to review for the periods specified by state law and OSHA Standard 29 CFR 1910.1020. Any specific medical surveillance exams (e.g., baseline, periodic, compound specific) are to be documented and maintained in the employee's medical chart at MedicalProvider during their employment by CompanyName. Once an employee terminates their employment with CompanyName, MedicalProvider will be notified and the employee's medical records will be kept by CompanyName for 30 years. Access to employee exposure data and medical records will be in compliance with state law and OSHA 29 CFR 1910.1020. Employees are entitled to one free copy of their medical and exposure records upon written request to MedicalProvider or CompanyName. If MedicalProvider confirms a new onset or aggravation of an occupational illness or injury, the case will be entered into the OSHA 300 log by CompanyName.

VI. EMPLOYEE NOTIFICATION BY MEDICAL PROVIDER

A completed and signed report of medical surveillance notification shall be provided by MedicalProvider to the employee. All new hire candidates and employees will be offered copies of any medical tests performed during baseline or periodic medical surveillance by MedicalProvider. Copies of abnormal test results will be provided to all new hire candidates or employees by MedicalProvider with instructions for follow-up evaluations, referral or treatment when indicated.

VII. EH&S NOTIFICATION BY MEDICAL PROVIDER

The completed report of medical surveillance shall be provided to the EH&S Department or designated CompanyName staff indicating if the employee has:

1. Any work restrictions for assigned duties
2. Clearance to use respiratory protection or other personal protective equipment required for his/her job if indicated
3. Any detected conditions possibly related to work exposures
4. Any referrals for further evaluation and treatment if conditions are work-related or affect work availability

Employees with normal examinations will be medically cleared by MedicalProvider. The employee will be advised by EH&S to follow established health and safety guidelines including appropriate use of protective equipment, and voluntary annual medical surveillance through MedicalProvider.

MEDICAL SURVEILLANCE PROTOCOL FOR EMPLOYEES HANDLING POTENT COMPOUNDS

I. PURPOSE AND OVERVIEW

The purpose of the CompanyName Medical Surveillance Program protocol for Potent Compounds is early detection of known adverse health effects of potentially harmful work exposures, early detection of new and/or unrecognized health effects, and screening for health conditions that could predispose an individual to health-related problems from workplace exposures. The goal is to prevent or limit any known adverse health effects from exposures to potent or hazardous drug compounds at CompanyName. However it is recognized that the use of feasible engineering controls (e.g., laboratory bench hoods, ventilation, and isolation), personal protective equipment (e.g., gloves, gown, chemical splash goggles), training and proper work practices are the first choice in preventing work related illnesses.

Potent compounds, in addition to cytotoxic agents (e.g., antineoplastic drugs), shall include all drugs characterized as hazardous in the OSHA Technical Manual, Section VI, Chapter 2: Controlling Occupational Exposure to Hazardous Drugs (1999, January 20). The categorization of drugs as potent or hazardous shall be based upon professional pharmacology and toxicology reviews, using the characteristics described by OSHA and other professional societies. Health, safety and environmental evaluations of known or suspected potent or hazardous drugs are to be completed by CompanyName staff and its professional consultants prior to use of a hazardous drug. A medical review of the potential health hazards with recommendations for appropriate baseline, periodic and postexposure health assessments may be considered for each compound.

II. POTENTIAL HAZARDS

A) Characteristics which can each be considered potentially hazardous include genotoxicity; carcinogenicity; teratogenicity or fertility impairment; and serious organ or other toxic manifestation at low doses in experimental animals or treated patients (American Society of Hospital Pharmacists Technical Assistance Bulletin, 1990).

B) Cytotoxic agents are considered potentially hazardous substances. Workers who handle these agents may be at risk of developing acute and long-term health problems. The primary routes of exposure during the preparation and handling of cytotoxic agents and other hazardous drugs are through inhalation of airborne or aerosolized drug, direct skin contact, and less often through accidental ingestion or inadvertent contact (touching of surfaces that have contacted the drug). The risks to personnel who handle these agents are generally a result of the concentration in air or degree of contamination on surfaces and duration of exposure to these toxic agents while at work.

C) Current data have not fully established the potential carcinogenic or reproductive risk to personnel who handle hazardous or cytotoxic agents although several studies have demonstrated absorption of cytotoxic drugs and biological changes in healthcare personnel during preparation, handling, and administration of various drugs.

D) Investigational or research drugs should be categorized and handled as potentially potent or hazardous drugs (Category 3) until adequate toxicological and clinical data are available to exclude them.

III. MEDICAL SURVEILLANCE

CompanyName will make specified medical examinations and consultations available on the following basis:

- Preplacement (or baseline) on all employees handling or potentially exposed to potent compounds in the workplace on a routine basis
- Periodically based upon the potential for exposure, duration of exposure, and at the discretion of the examining clinician based upon an employee's medical history
- Postexposure following an incident (e.g., spill, accident) with direct employee exposure or when environmental monitoring levels are above recommended exposure levels (when available)
- As soon as possible, following notification by an employee or their supervisor that an employee has developed signs or symptoms of possible overexposure to a potent compound
- Upon termination or transfer to a position with no known exposures to potent compounds (exit examination)

IV. PROCEDURE

A) Examination Scope and Content
Whenever possible, evaluation and testing will include specific assessment for known outcomes or adverse health effects associated with certain compounds or chemicals (such as potent pharmaceuticals, hormones and other potent biologic modulators).

1. Pre-placement (Baseline) Exams:
The following medical examination will be scheduled upon the initial hiring or transfer of an employee into a position where the preparation, handling or disposal of potent compounds and/or materials associated with hazardous drugs is performed.

a) A complete preplacement medical history including past hematopoietic, malignant or hepatic disorders, and a work history including potential exposures to hazardous drugs or research

compounds (see Initial Hazardous Drug questionnaire). Targeted questionnaires for certain potent compounds may be developed/used based on a specific chemical if known (e.g., hormone modulators).

b) A targeted physical examination with emphasis on the skin, mucous membranes, cardiopulmonary, liver, and lymphatic systems.

c) A complete blood count with differential, liver enzymes (ALT, AST), BUN, creatinine, urinalysis and any additional studies if medically indicated based upon positive responses or findings on the history or examination (e.g., pregnancy testing) or as recommended for any specific drugs (i.e., biomonitoring).

2. Periodic Examinations:
All employees handling or potentially exposed to hazardous drugs or potent research compounds will be offered annual medical surveillance. At the discretion of CompanyName or the examining clinician the interval of examination may vary depending upon the category of drug(s) handled, potential for exposure and duration of exposure (e.g., postproduction) or an employee's personal health or risk factors, respectively.

The content of the exam includes:

a) Periodic questionnaire(s) regarding exposure and health history to be sent to all eligible employees for completion within 5 days (see Periodic Medical Questionnaire for Potent Compounds).

b) Those employees with positive responses to health or exposure questions will receive appropriate medical follow-up, including a targeted physical examination and pertinent laboratory testing if indicated.

3. Postexposure or Symptom-based Exams: as indicated by the nature and intensity of exposure and any reported symptoms.

4. Exit Examination:
An exit examination will be provided to employees leaving employment or transferring to another position that does not provide medical surveillance. The same elements and follow-up of the periodic examination will be offered and should be guided by the employee's history of exposures.

B) Information to MEDICAL PROVIDER

CompanyName shall make the following information available to the examining clinician:

1. A description of the affected employee's duties as they relate to the employee's exposure and any exposure monitoring records or anticipated exposure levels.

2. A description of any engineering controls (e.g., laboratory bench hood or biosafety cabinet, ventilation, isolator) and personal protective equipment (e.g., respirator, gown, gloves, goggles) used or to be used.

3. Information from previous medical exams of the affected employee that is not otherwise available to the examining physician.

C) Reproductive Health Considerations:
Pregnant or breastfeeding employees, and male or female employees planning or actively trying to conceive a child should be fully informed of the potential reproductive hazards of these drugs. Appropriate consideration for accommodation or transfer to other duties that do not involve direct handling of potent compounds will be handled according to company policy.

D) Results Notification and Referral

The occupational health care provider (MedicalProvider) will provide the employee with a written "Report of Medical Surveillance" after each evaluation or questionnaire review indicating any work restrictions or medical follow-up needed. A copy should be provided to the CompanyName Environmental Health & Safety (EH&S) Manager for their records. Any known or suspected occupational illnesses or injuries should be confidentially reported to the EH&S Manager for further investigation as indicated below. If MedicalProvider confirms a new onset or aggravation of an occupational illness or injury, the case will be entered into the OSHA 300 log by CompanyName.

Abnormal Baseline Evaluation:

The occupational health care provider shall review all medical information and lab results with the employee and advise the employee regarding any abnormalities, work accommodations and any recommended follow-up with their health care provider. The employee should be provided with written notification of their exam results plus a copy of any abnormal lab tests with instructions for follow-up with their health care provider.

Candidates with any significant history or examination findings of medical conditions which might limit their ability to work with hazardous drugs or potent compounds should be counseled about risk factors (including potential occupational exposures) with the assistance

of CompanyName and/or an occupational medicine specialist. Consideration of further protective measures, work restrictions or accommodations from exposure to hazardous drugs or potent compounds will be considered on a case-by-case basis by CompanyName.

Abnormal Periodic/Postexposure/Termination Evaluation:

The occupational health care provider will review all medical information and lab results (if any) with the employee and advise the employee regarding any abnormalities, work restrictions, and any recommended follow-up. A targeted physical examination should be done in consultation with an occupational medicine specialist. CompanyName should be notified to evaluate/review any work exposures and perform monitoring if indicated. Specialist referral may also be recommended for any employee whose health history or lab results indicate a possible problem associated with work exposures to hazardous drugs or potent compounds. Employees with abnormalities unrelated to work exposures should be referred to their personal health care provider for follow-up, if indicated.

INITIAL MEDICAL QUESTIONNAIRE FOR POTENT COMPOUNDS

NAME: _____ JOB TITLE: _____
PHONE:
Home_____Work_____ SUPERVISOR: _____

This CONFIDENTIAL questionnaire will aid CompanyName's Occupational Health Provider (MedicalProvider) in the surveillance of personnel who routinely prepare, handle or dispose of hazardous drugs or potent compounds. If you have any questions, please call the Manager of Environmental Health and Safety.

Job Description
1) What projects are you currently working on?
_____
_____

2) What quantities of active pharmaceutical ingredients (API) and Intermediates compounds do you or will you be handling (largest amount)? If the answer to this question has not been identified, please solicit assistance from colleagues/supervisor.
_____
_____
_____

3) What form is the drug substance or drug product you will be handling (check one)?
____ Liquid (in solution) ____ Solid ____ Both

4) What engineering controls are in place (check all that apply)?
____ Laboratory hood
____ Local exhaust ventilation
____ Vented Balance Safety Enclosure
____ Glove box
Other (describe):_____

5) What personal protective equipment are you or will you be wearing (check all that apply)?
____ Gloves (list type):_____
____ Tyvek clothing
____ Air line or powered air purifying respirator
Other (describe): _____

Health Information
1. Have you ever had any blood diseases or bleeding disorders?
❑ YES ❑ NO
If YES, please explain:_____

2. Have you ever had any liver disorders (such as hepatitis or jaundice)?
❑ YES ❑ NO

If YES, please explain:_____

3. Have you ever had any cancers or malignant disorders?
   ❑ YES ❑ NO
   If YES, please explain:_____

4. Have you ever had any other active serious medical conditions, e.g., kidney problems, lung disease?
   ❑ YES ❑ NO
   If YES, please explain:_____

5. Do you have any medical conditions that might affect immune system function, e.g. taking Prednisone or other corticosteroids?
   ❑ YES ❑ NO
   If YES, please explain:_____

6. Any prescription medications that you take on a regular basis?
   ❑ YES ❑ NO
   If YES, please explain:_____

7. Are you or your spouse planning a family or currently pregnant?
   ❑ YES ❑ NO

8. Do you have any questions for the clinician or Occupational Health Services regarding hazardous drugs?
   ❑ YES ❑ NO

_____ _____
Employee Signature Date

PERIODIC MEDICAL QUESTIONNAIRE FOR POTENT COMPOUNDS

NAME: _____ JOB TITLE: _____
Phone: _____ Supervisor: _____

This questionnaire will aid CompanyName in the surveillance of personnel who routinely sample, analyze, handle or dispose of potent compounds or hazardous drugs. Please answer the following **CONFIDENTIAL** questions as part of your Medical Surveillance. If you have questions, please ask the physician or nurse at MedicalProvider or your supervisor.

1. How many times in the past month have you handled potent or hazardous compounds (sample, analyze, handle, or dispose)? _____ In the past year? _____

2. Do you wear Personal Protective Equipment (gloves, tyvek suit, respirator) while handling or disposing of potent or hazardous drugs?

   ❑ YES ❑ NO

3. Have you had any incidents that resulted in a direct exposure of hazardous drugs onto your unprotected skin, face, eyes, mouth OR have you directly inhaled one of these agents?

   ❑ YES ❑ NO
   If *yes*, please explain:_____

4. Have you had any problems with bleeding, bruising, frequent infections, excessive fatigue since your last exam?

   ❑ YES ❑ NO

5. Do you have any new and *unexplained* medical problems since your last examination?

   ❑ YES ❑ NO
   If *yes*, please list:_____
   _____

6. Do you feel the medical problem(s) may be related to handling potent or hazardous drugs at work?

   ❑ YES ❑ NO

7. Do you have any questions regarding hazardous drugs and your reproductive health?
   ❑ YES ❑ NO

8. Are you pregnant or planning a family?

❑ YES ❑ NO

_____ _____
Employee Signature Date

Medical Evaluation Declination Form
Potent Compound

Directions: *Use this form when the designated employee elects NOT to participate in the Medical Surveillance Program. Maintain the form in the employee's medical file.*

EMPLOYEE'S NAME: _____

I have been informed that due to the nature of my occupational exposure to Potent Compounds I may be at risk of acquiring a disease. CompanyName has established a medical surveillance program for early detection, diagnosis and treatment of occupational illnesses. I have been provided a copy of the program. I have read and understand it. I also understand that the records from the program are confidential and that all expenses are paid by the company. However, at this time, I choose to NOT participate in the Potent Compound Medical Surveillance Program. I am aware that I may be at risk of acquiring an occupational illness. If in the future I continue to have occupational exposure to potent compounds while employed at CompanyName and I elect to participate in the medical surveillance program, I may do so at no charge to myself.

_____ _____
Employee's Signature *Date*

_____
Print Name

SAMPLE

Listing of EHS Regulatory Agencies affecting the San Diego Biotech Industry and Associated Documents, Plans and Policy.

- **County of San Diego – Department of Environmental Health – Hazardous Materials Division** (Certified Unified Program Agency – CUPA)
  - **Regulatory Agencies & Scope:**
  - *Annual Inspection & Fees*
  - California Health and Safety Code - Medical Waste Management Act – Biohazardous /Medical Waste
  - Federal Aboveground Petroleum Storage Act
  - Department of Toxic Substances Control (DTSC) / Cal EPA – Hazardous Waste Management
  - Storm Water (run off) Management
  - Accidental Release Reporting
    - **Documents:**
      - Hazardous Materials Business Plan
      - Hazardous Material Health Permit
      - Medical Waste Management Plan
      - Spill Prevention and Counter Measure Control Plan (SPCC)
      - Chemical Hygiene Plan Section: Hazardous Waste Guidelines, Spill Prevention and Reporting
      - BioSafety Manual Section: Biohazardous Waste Guidelines
      - Stormwater Pollution Control Plan (SWPCP)
      - Hazardous Waste Manifest Records
      - Medical Waste Tracking Records
      - Biennial Report to DTSC (Hazardous waste types and amounts)
      - DTSC Verification Questionnaires (Large Quantity Generator annual manifest fee)

- **County of San Diego- Air Pollution Control District**
  - **Regulatory Scope:**
  - *Annual Inspection & Fees*
  - Emissions monitoring

SAMPLE

  - Diesel Generator Permitting
    - **Documents:**
      - Emergency Generator Operating Permits
      - Emergency Generator Operation and Maintenance Records

- **California Department of Health Services - Radiological Health Branch** (Co-op with the Federal Nuclear Regulatory Commission, the State of CA- DHS, and Local County of SD- DEH)
  - **Regulatory Scope:**
  - *Inspection Every 5 years, Annual Fees*
  - Radiation Use
    - **Documents:**
      - Radioactive Use License and Amendments
- **County of San Diego – Radiological Health Program**
  - **Regulatory Scope:**
  - *Co-managed w/the DHS*
  - Performs Radiation Use Inspections
    - **Documents:**
      - All RAM management documents: inventory and package receipts, waste tracking, contamination surveys, equipment calibration, x-ray machines, building decommissioning reports, incidents involving RAM, sewer release totals, staff training, etc…)

- **City of San Diego – Metropolitan Waste Water District**
  - **Regulatory Scope:**
  - *Inspection every 3 years, annual permit fees*
  - Industrial Discharge (city sewerage system)
    - **Documents**
      - Industrial User Discharge Permits (includes water usage accountability for each address)
      - Industry Self Monitoring Best Management Practices Forms (annual)
      - Solvent User Management Certification (semi-annual)

- **California Code of Regulations, Title 8 (Industrial Relations) Chapter 4 (Division of Industrial Safety) AKA: Cal/OSHA**

SAMPLE

- **Regulatory Scope:**
- *Inspections only following and serious incident or employee complaint /Authority to issue citation with a fine*
- Occupational Health and Safety: General Industry and Construction
  - **Documents:**
    - Injury and Illness Prevention Plan
    - Chemical Hygiene Plan
    - Emergency Action Plan
    - Biosafety Manual (Includes Exposure Control Plan required by the Bloodborne Pathogen Standard)
    - Respiratory Protection Plan
    - Fire Prevention Plan
    - Access to employee medical records administrative requirements
    - Cal/OSHA Postings (protection on the job)
    - Cal/OSHA Carcinogen registration report
    - Formaldehyde monitoring program registration
    - Methylene Chloride monitoring program
    - Hazardous Communication Plan
    - Lock Out -Tag Out Program
    - New Hire Safety Manual (meets initial training Requirement)
    - Confined Space Entry Program
    - Forklift Safety Program
    - Electrical Safety Plan
    - OSHA 300 Log
    - CalOSHA Form 5150 records (cal/OSHA First Report of Injury)
    - Ergonomics Program
    - Job Hazard Assessments
    - Site Quarterly Safety Audit Program
    - Accident and Incident Investigation records
    - Employee Safety Training Records
    - CalOSHA Carcinogen Inventory Report
    - Various EHS Written Standard Operating Guidelines (written to demonstrate formal procedures regarding specific safety issues):

SAMPLE

- Safe Handling of Active Pharmaceutical Ingredients
- Personal Protective Equipment
- Initial Reaction Hazard Assessment
- Process Safety – Process Hazard Analysis
- Working with Biohazardous Material
- CDF Hazardous Waste Mangement
- Supplied Breathing Air System
- Emergency Evacuation of cGMP Areas
- Medical Emergencies within the cGMP Areas

- **San Diego Fire Department**
  - **Regulatory Scope:**
  - *Annual Inspection / Fees*
  - Fire and Life Safety
  - Building Occupancy Permits
  - System Permits (gases, process piping)
  - Annual Inventory
    - **Documents:**
      - Retention of all related permits, applications and inspections

- **US Drug Enforcement Agency (DEA)**
  - **Regulatory Scope:**
  - *Unannounced Inspections / Annual Fee*
  - Controlled Substances Program
  - Encapsulating / Caplet making equipment
    - **Documents:**
      - EHS Standard Operating Guideline: Controlled Substance Program

- **Department of Transportation – Hazardous Materials Division**
  - **Regulatory Scope:**
  - *Unannounced Inspections / Authority to issue a citation with a fine*

SAMPLE

- Hazardous Materials Transportation (by Ground)
  - **Documents**
    - Hazmat Security and Safety Plan (in progress)
    - Hazmat Employee DOT Training Records

- **U.S. Department of Treasury- Alcohol and Tobacco Tax and Trade Bureau**
  - **Regulatory Scope:**
  - Industrial Alcohol / Ethanol Use
    - **Documents:**
      - Industrial Alcohol User Permits (each address)
      - Ethanol Special Tax (exemption) Stamp

- **Federal Aviation Administration (FAA) / International Air Transport Association (IATA)** (Authority given by the Department of Homeland Security and Department of Transportation)
  - *Unannounced Inspections /Authority to issue fines*
  - Dangerous Good Shipments (by Air)
    - **Documents:**
      - EHS Standard Operating Guidelines: Dangerous Goods Shipping
      - Retention of all Dangerous Goods shipment records
      - DG Shipper (IATA) Training Records

ACC Association of Corporate Counsel

Speaker Perspective

- General Counsel, Arena Pharmaceuticals
- Losses of $77.1 million for the year ended December 31, 2005; accumulated deficit of $278 million from April 1997 through June 30, 2006
- Approximately 340 employees (290 in R&D) on a single campus in San Diego
- 4 clinical stage programs:
  - All orally bioavailable/small molecules
  - Most advanced scheduled to begin Phase 3 trial for obesity
  - 2 partnered (Phase 2 with Ortho-McNeil; Phase 1 with Merck)
- Pilot plant/chemical development facility: production of intermediates and other compounds for R&D, and production of API for clinical trials through Phase 2 development

Speaker Perspective (cont.)

-
- Dedicated, full-time legal EH&S resources: 0
- EH&S department: 6 employees
  - Mission: protect employees, contractors, visitors and the local environment from any operations at Arena
  - "Full-service" model
  - Overview of environmental and safety responsibilities
    - Regulatory compliance education, counseling and reporting
    - Obtain necessary permits
    - Audit program, including disposal sites
    - Abate violations
  - Report to VP, Quality Systems / Facilities Operations
- Arena Compliance Officer: General Counsel
  - Supervising a non-reporting area
  - Limited resources compared to larger pharmaceutical companies

Challenge for Biotech R&D Companies

- Growing Scope and Complexity of EH&S regulations
- Limited staff and financial resources prior to commercialization phase
- Evolving business plans (R&D to commercialization)

Top current* EH&S issues facing Arena

- Ergonomics
  - Key issue: time and $
  - Non-laboratory repetitive motion and back injuries
- Cal OSHA
  - Key issue: historical lack of participation in industry groups
    - Changing?
  - Key issue: no regular audits
  - Case study: Ethanol spray bottles
    - Industry practice
    - Fire marshal approved
    - Safe
    - Bottom line: violation

Top current* EH&S issues facing Arena (cont.)

- NCEs
  - SOP/guidelines for all compounds (including MSDS post optimization)
- Hazardous waste
  - Key issue: expense
  - Requires in-depth knowledge of chemical capabilities and hazards
  - Local pilot program between San Diego DEH and biotech industry
    - Tracking violations
    - Goal: show low risk industry and reduce regulatory oversight
- Radiation safety
  - Key issue: length of time for amendments
  - Key issue: decommissioning lab or entire facility
  - California is an agreement state; interact with the state and not directly with the NRC

Top current* EH&S issues facing Arena (cont.)

- Complexity and overlapping regulations
  - Key issue: Worker compliance with myriad of policies
  - Case study: Emergency generator
    - Competing guidelines: APCD, fire department, SPCC (spill prevention, control and countermeasure), SDG&E and manufacturer instructions
  - Resource materials: *See listing of EHS regulatory agencies affecting San Diego Biotech Industry and associated documents, plans and policies*
- Proactive vs. reactive
  - Compliance requires both top-down management support and bottom up knowledge of regulations
  - Resource materials: *See sample annual safety refresher training for non-laboratory staff (laboratory staff is more detailed and science-oriented)*

Current* lower risk regulations

- Air
  - Rule 11 exemption for most activities (volatile organic compounds, etc.)
  - Gray areas?
- Water
  - Arena is a zero discharge facility

Arena legal department and compliance function

- Meet regularly with both VP, Quality Systems / Facilities Operations and EH&S manager
  - Best practice
  - Sarbanes-Oxley: Section 404 and internal controls
- "Audit" the audit?
- Balance proactive vs. reactive
- Education
  - Ensure regular training by EH&S
  - Part of Code of Conduct training
  - Whistleblower policy

Arena legal department and compliance function (cont.)

-
- Incorporated into performance reviews
- EH&S involvement on disclosure committee and SEC filings
- Monitor BIOCOM (or other trade organization) EH&S committee

Speaker Perspective

- Pfizer Inc Overview
  - Pharmaceutical Research, Sourcing & Sales
    - Rx Products for Humans and Animals and Consumer Products
  - $51 Billion Annual Sales
  - 106,000 Employees World wide
  - Manufacturing Operations in 31 Countries
  - Major Research Operations in 4 Countries

Pfizer Inc - Resources

- Legal EHS Resources
  - Legal division has 400+ attorneys worldwide
  - 6 full time attorneys in EHS Group
    - Part of interdisciplinary strategic corporate group
- Facilities
  - 76 manufacturing plants worldwide (expected to go down to 63)
  - 8 major R&D locations worldwide: U.S., U.K. France, Japan

Pfizer Inc – Recent History

- Some Recent Highlights
  - 2000 Acquired Warner-Lambert
  - 2003 Acquired Pharmacia (Upjohn, Searle)
  - 2004-07 Integration & Rationalization
  - 2006 Agreement to sell Consumer Health Care Business to J&J ($16.6 billion)
  - July 28, 2006 General Counsel appointed CEO

Recent California Biotech Acquisitions

- Examples Include:
  - Agouron, La Jolla (through W-L, 2000) - now site of Pfizer La Jolla R&D Facility
  - Sugen, South San Francisco (through Pharmacia, 2003)
  - Rinat Neuroscience, South San Francisco (2006)

Pfizer – EHS Legal Group

- Overview of Responsibilities
  - Regulatory Compliance Counseling & Internal Reporting
  - Negotiate Major Environmental Permits
  - Defend Enforcement Actions
  - EHS Aspects of Transactions
  - Assist with EHS Audit Program
  - Manage & Defend EHS Claims including, e.g., CERCLA
  - Environmental Related SEC Disclosure
  - Advice on Environmental Reserves & Liabilities (FAS 5/FIN 45/FIN 47)
  - EHS Aspects of Product Use

Environmental Issues - Air

- Federal Issues
  - Threshold Determination: Major/Minor Source
  - Application of Pharmaceutical MACT: >10/25 tpy HAPs
    - General exemption for R&D
    - Potential applicability of other MACT Standards
  - Applicability of CAA 112(r) (RMP, GDC)
  - Protection of Stratospheric Ozone – Refrigerant Leak Repair (40 CFR 82)

Environmental Issues - Air

- State and Local Requirements
  - Attainment/Non-Attainment Areas
  - Permits to Operate (Minor Source)
  - Prop 65 Environmental Exposures
  - Local Agency: San Diego Air Pollution Control District
    - Areas of Interest
      - Rule 11 R&D Exemption
      - Air Toxics Control Measures (ATCM)
      - Toxic "Hot Spots" Program/Rule 1200
      - Regulation of Boilers
      - Inspections

Environmental Issues - Waste Water

- Federal Issues
  - Direct Discharger - NPDES Permit
  - Pharmaceutical Effluent Guidelines (PEG)
    - Applies to Direct and Indirect Dischargers
    - Applicability to Research Operations
      - Research Subcategory (40 CFR 439)
    - Applicability to Pharmaceutical Manufacturing
      - Fermentation Operations
      - Extraction Operations
      - Chemical Synthesis
      - Mixing, Compounding and Formulating
  - Stormwater Permit Considerations

Environmental Issues - Waste Water

- State & Local Requirements
  - Indirect Discharger—Local User Tie-In Permit
  - Local Agency: San Diego Municipal Waste Water Authority
    - Areas of Interest
      - Obtaining a local permit
      - Four categories of users
      - "Purple Water" - Reuse

Environmental Issues - Solid Waste

- Federal Issues
  - RCRA Compliance
  - Large Quantity Generator/Small Quantity Generator
    - Satellite storage
    - Lab waste management
    - Storage Areas

Environmental Issues - Solid Waste

- State & Local Requirements
  - Local Agency: County of San Diego – Department of Environmental Health – Hazardous Materials Division (Certified Unified Program Agency – CUPA)
  - California Medical Waste Management Act
  - Emerging Issues
    - Unused Medicines
    - Elementary Neutralization/AB2155
- Risk Reduction Efforts
  - Moving from hazardous waste to recycling/reuse
  - Management of expired, off-spec product and chemicals

Environmental Issues - Low-Level Radioactive Materials

- Licensing
  - NRC
    - Includes those subject to Naturally Occurring Radioactive Materials (NORM)
  - State Licensing including California
    - California is an "Agreement" State (33 in all)
    - Title 17, Department of Health Services Regulations
    - License from DOH Radiological Health Branch
      - License includes letters and other communications

Environmental Issues - Low-Level Radioactive Materials

- Reducing Risk
  - Use of consultants
  - Managing inspections
  - Staying current, e.g., Barclays Service
  - Site Management of Low-Level Radioactive Materials
  - Off-Site Treatment, Storage & Disposal

Environmental Issues - Transactions

- Major Business Acquisitions & Divestitures
- Property/Asset Acquisitions & Divestitures
- Leases for Smaller Research and Manufacturing Start-Up Companies

Environmental Issues - Pharmaceuticals in the Environment (PIE)

- P*h*RMA is Working to Better Understand PIE
  - Looking at Human Health-no apparent risk
  - Aquatic Life Impacts-additional studies underway
  - Proper Disposal of Unused Medicines
  - Patient Use is Main Source of PIE
  - P*h*RMA Committed to a Science-based Approach
    - Development of sound data
    - Goal of better understanding of environmental impacts of PIE

Environmental Issues - Emerging Issues

- Proposed Biomonitoring Rule/SB 1379
- Proposed "Super TSCA" in California
  - Mini "REACH" Program
- Chemical Policy in California/Berkeley Study/Green Chemistry
- California Climate Change Policy