# API Risk Communication Case History

## Building a potent compound matrix to communicate with CMOs

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As the Environmental Health & Safety (EH&S) manager of a small but growing drug discovery company, I developed a potent compound control program in 2004-2005. The program was similar in many ways to those that already exist in the pharmaceutical industry, but it focused more on the discovery side of the equation than the finished products side.[1,2,3] As my company's development of novel compounds expanded and efforts progressed into the clinic, larger quantities of materials were needed. It was decided as a general rule that we would use contract manufacturers to produce clinical material beyond the second toxicological lot. We would contract to produce the needed material after proof of production technique had been completed.

This strategy has proved to be an excellent leverage of our discovery resources. By limiting the production of time-consuming large-scale runs and by contracting with companies that are well positioned to produce large kilo-scale reactions, we can keep our focus on what we do the best: drug discovery.

### Challenge

The outsourcing of active pharmaceutical ingredient (API) production to contract manufacturing organizations presents a challenge. The EH&S department did not have difficulties in communicating hazard information of our API to our employees, but with outsourcing we were called upon to communicate with CMOs.

Immediate concerns were raised about confidentiality, intellectual property (IP) protection and what safety data was appropriate to share. It is standard procedure that all CMOs execute confidentiality agreements, but it is also necessary to ensure that IP remains protected. This would call for limiting the information shared. EH&S was caught in the middle of this quandary. We want to be sure that we share sufficient toxicology information with the CMO so that they may take necessary precautions, but what data points were we to share? What subjective — but well-thought-out — decisions should we share? We work in an environment where clinical data may be absent or in the process of being generated. The data we do have consists of potency assays, comparisons to marketed and premarketed drugs, rodent model studies and expert knowledge of the method of action.

### Communicating Hazard Information

To overcome these challenges we created written descriptions of the company system categories. Later, we added a matrix to capture the numeric data and subjective classifications made to compare with appropriate parameters. The categories are presented in Table 1.

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**Table 1:** API Categories

**Category** - The relative scale seeks to place an API into a scale of 1 to 4, based on toxicity, target organ, availability and sensitive end point.

**Category 1**

Compounds that are relatively non-toxic and produce no significant adverse systemic effects.

**Category 2**

Compounds that have low adverse pharmacological effects and generally have low systemic toxicity. Overexposure to these materials requires only first aid or simple medical treatment.

**Category 3**

Compounds that typically have short-term effects that are normally reversible, but may produce effects that are slowly or not completely reversible, especially following prolonged exposure. These effects are generally not life-threatening or incapacitating, and overexposures can be satisfactorily managed medically.

**Category 4**

Compounds that can produce life-threatening effects, with symptoms that may be incapacitating and may require immediate medical intervention. They may also have short-term or long-term effects that are not reversible and could have disabling consequences.

Category disclosure, coupled with the release of the description of categories, could be used more freely because it contains little or no information that was considered to be proprietary. Now we always include the category in our nominated compound material safety data sheets (MSDSs). As is apparent by inspection, these category descriptions allow for practically universal hazard communication. What neither the category nor description includes is information that allows another to independently evaluate the categorization method.

## Matrix Solution

Now that we had created a description of our categories, the challenge was to create a method to communicate numeric data and our consensus decisions of the appropriate answer to a specific parameter. To accomplish this goal we created a matrix using criteria, description, data and reference values. Table 2 provides an example matrix (see page 70).

**Table 2:** A Company–XXX Potent Compound Category Matrix, Overall Categorization 2

| CRITERIA | Description for XXX as of July 11, 2008 | Category 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Human Dose mg/day | Clinical studies ongoing - currently > 40 mg/day | > 500 | 50 – 500 | **5 – 50** | < 5 |
| Severity of acute effects | Low grade 1/2 rash - Low | **Low** | Low to Moderate | Moderate to High | High |
| Rat 14/28d NOAEL (mg/kg) | MTD 200 mg/kg, NOAEL <50 mg/kg | > 500 | 50 – 500 | **5 – 50** | 5 – 0.5 |
| Rat 90d NOAEL (mg/kg) | | > 200 | 20 – 200 | 2 – 20 | 2 – .02 |
| Onset of acute oral toxicity | Rat 300 mg/kg | > 500 mg/kg | **50 – 500 mg/kg** | 5 – 50 mg/kg | < 5 mg/kg |
| Onset of warning symptoms | Delayed rash | Immediately / Minutes – Hours | Immediately / Hour | **Delayed** | Indeterminate |
| Medically treatable | Yes | **Yes** | Yes | Yes | Indeterminate |
| Need for medical intervention | Not required | **Not required** | Not required | Maybe required | Maybe required |
| Reversibility | Yes | **Yes** | Yes | May not | May not |
| Acute Toxicity | Moderately | Slightly | **Moderately** | Highly | Extremely |
| Sensitization | Not expected | **Not expected** | Mild | Moderate | Strong |
| Likelihood of chronic effects | Unlikely | **Unlikely** | Unlikely | Possible | Probable |
| Severity of chronic effects | Slight | None | **Slight** | Moderate | Severe |
| Mutagenicity – in vitro | Bacterial Reverse Mutation - Neg<br>Mouse Lymphoma - Neg<br>Mammalian Micronucleus - Neg | **None** | Equivocal | Single Test | Multiple Test |
| Occupational Exposure Limits (OEL) – $\mu g/m^3$ | Range 10 – 1,000 | 500 – 5,000 | **10 – 1,000** | 1 – 100 | < 1 |
| Default OEL – $\mu g/m^3$ | Suggested 100 $\mu g/m^3$ | 500 | **100** | 10 | 1 |
| Carcinogen | Negative | **Negative** | Equivocal | Group 3 & 4 | Group 1 & 2 |

**NOAEL** – No Observed Adverse Effect Level
**MTD** – Maximum Tolerated Dose
**OEL** – Occupational Exposure Limit

The highlighted fields in Table 2 are the parameter fits for the compound being evaluated. There is scattering among the categories, as expected. Our system uses a preponderance of values and expert judgment — not one simple value — to determine the category. Once all of the available data is inputted, the categorizing team uses the method of action, examination of similar drugs and matrix data to determine the appropriate categorization. The matrix serves as documentation of the categorization decision. Corporate management has agreed that the data present on the matrix, although confidential, is appropriate to share with CMOs. The matrix is reviewed and updated after every clinical trial. In addition, upon request from the CMO, EH&S shares the company's potent compound control program and will answer questions that the CMO's safety representative may pose.

Thus the use of the category matrix allows for the following:

1. Collection, presentation and organization of relevant data
2. Comparison of relevant data to reference values
3. Visualization of the over-all scatter plot
4. Discussion of the importance and answer for each parameter evaluated
5. Documentation of the categorization decision
6. A format that may be updated when additional data is acquired
7. Transmission of risk information to internal and external scientists, collaborators and contract manufacturers
8. Establishment of data points that can and should be shared with partners that executed a confidentiality agreement

Although we are indebted to SafeBridge[4,5] for their leadership in the areas of control banding and Occupational Exposure Limit (OEL) development, we chose not to default to a conservative band but rather to create a system that best fits the API to a band based on limited but guiding data, drug analogy, and expert review. This approach sets an OEL to monitor against and — since most manufacturers have done surrogate sampling — to determine exposure potential. This method empowers CMOs to measure and determine for themselves the level of containment that is appropriate for the API based on our matrix and their judgment.

We have found that use of the matrix helps clarify and speed up collection and dissemination of relevant risk communication and hazard evaluation information. It is our hope that by sharing the methodology we developed, we will help to facilitate a consensus on what data should be collected and provided to CMOs that are producing APIs in an early drug discovery environment. ■

**References**


1 B.D. Naumann et al., "Performance-Based Exposure control Limits for Pharmaceutical Active Ingredients", *AIHA Journal,* January 1996, pp. 33-42

2 SafeBridge Consultants, Inc., *Occupational Health Toxicity / Potency Categorization and Handling Practices* – SafeBridge, Fifth Revision – January 2002, pp.12

3 Association of the British Pharmaceutical industry, *Guidance on Setting In-house Occupational Exposure Limits for Airborne therapeutic Substances and their Intermediates* – ABPI Publication, October 1995

4 C.D. Money, *European Experiences in the Development of Approaches for the Successful Control of Workplace Health Risk,* Ann.occup. Hyg., Vol. 47, No 7, pp 533 – 540, 2003

5 SafeBridge Consultants, Inc., *Important elements in evaluating contract manufacturing organizations,* Chemistry Today, Vol. 25 nr 2, pp 56-60, 2007