

**ACTIVE PHARMACEUTICAL INGREDIENTS (API) SURROGATE CONTAINMENT TESTING ON ESCO
POWDERMAX™ POWDER WEIGHING BALANCE ENCLOSURE**

By: Alexander Atmadi, Yayi Nestiti | Esco Micro Pte. Ltd.

Introduction

The manufacture and production of potent and highly potent Active Pharmaceutical Ingredients (API) is becoming commonplace in pharmaceutical and biopharmaceutical industries. The active ingredient can be extremely potent even at very small quantity, and must be handled with care. In general, most parties define a potent API as one with an occupational exposure limit (OEL) at or below 10 µg/m³ (10,000 ng/m³), highly potent API as having an OEL below 1 µg/m³ (1000 ng/m³), and super potent API as having OEL approximately 30 ng/m³ or less, when measured over an 8 hours' time weighted average (TWA).

The effect of API exposure ranges from localized moderate to acute reversible systemic toxicity such as cardiac or liver toxicity caused by potent API, to severe acute irreversible carcinogenic and mutagenic effect to sub population caused by super potent API.

There are a number of factors which must be considered to control worker exposure, but one of the most important approaches to ensuring safe handling of potent and highly potent APIs is the containment equipment selection. Generally, a well-designed containment device can provide a containment performance of 50 ng/m³ and below. An example of an API containment device is a powder containment balance enclosure, such as the Esco Powdermax™ balance enclosures.

The Esco Powdermax™ containment performance was evaluated using naproxen sodium as surrogate powder. Naproxen sodium, a non-potent active pharmaceutical ingredient (API), was used because it is easy to use, safe to handle, and relatively non-toxic. The Occupational Exposure Limit (OEL) for naproxen sodium is 5000 µg /m³, which is relatively safe to handle compared to potent powder that has OEL of typically below 10 µg/m³, when measured over an 8 hours TWA.

Nevertheless, naproxen sodium is readily detectable in air at low concentrations (2 ng using HPLC), which allows the assessment of exposure on a task-oriented basis, even for brief duration works. Naproxen sodium is a crystalline API with high dustiness quotient and challenging electrostatic properties. This surrogate provides a robust challenge to operator and containment in balance enclosure. It provides a useful insight into the potential exposures and/or levels of control that are likely to be achieved at the workstation for potent APIs, where the compounds are handled in a similar fashion.

Method

The study was set up to assess potential exposure to airborne concentrations of naproxen sodium for three operators (i.e., differing skill level and physical stature) during consecutive weighing of 20x, one-gram samples of the surrogate at an electronic balance placed inside the Esco Powdermax™ Powder Weighing Balance Enclosure, operating at airflow nominal point of 0.50 m/s (100 fpm).

The containment ability of the balance enclosure to concentrations of surrogate (challenge agent) was also set up by weighing and dispensing task at the access opening of the enclosure and the surrounding environment. The study was set with the sampling locations consisted of:

- At the collar of each operator, in operator breathing zone to measure the personal exposure.
- Right side of the cabinet, at the face of the enclosure (access opening).
- Left side of the cabinet, at the face of the enclosure (access opening).
- Approximately 1.5 m (4.5 ft) in front of the workstation.
- Background samples, which consisted of pretest sample and operational background sample, placed outside the balance enclosure. They are placed above the exhaust HEPA filter of the balance enclosure. Pretest was prepared to characterize the concentration of naproxen sodium (if any) in the area immediately prior to manipulation of surrogate. Background sample was prepared to measure the concentration of naproxen sodium outside the balance enclosure during testing time.

In all, 15 air samples were collected and submitted to the laboratory for analysis as below:

| Quantity | Location & Purpose |
|----------|---|
| 3 | At the operators lab coat collar to sample the air at breathing zone |
| 3 | At left side opening of the balance enclosure, where the operators’ left arm comes in |
| 3 | At right side opening of the balance enclosure, where the operators’ right arm comes in |
| 3 | At 1.5 m (4.5 ft) in front of the balance enclosure |
| 1 | Pre-test background, above the balance enclosure’s exhaust HEPA filter |
| 1 | Operational background, above the balance enclosure’s exhaust HEPA filter |
| 1 | Unexposed collector, to check for non-exposure condition |

Table 1. Sampling cassette location

Air samples were collected on 37 mm (1.5 in) diameter glass fiber filters (GFF), 1-micron pore size glass fiber filters, connected to sampling pumps that were operated at flow rates between 3 – 4 liters per minute. Samples were analyzed for naproxen sodium at the SafeBridge Industrial Hygiene Analytical Laboratory in Mountain View, California using High-Performance Liquid Chromatography (HPLC) and fluorescence detection. The analytical data from SafeBridge laboratory is appended to this report.

Description of the Weighing and Dispensing Task

Naproxen Sodium (NS) was dispensed and weighed twenty times by each operator, each weighing 1 gram ($\pm 5\%$), using spatula, into a sealable plastic vials. This weighing was done in three rounds with three different operators. In Round 1 (operator 1) and round 2 (operator 2), operators dispensed surrogate out of a 50-g source (bulk) container. In Round 3, operator 3 dispensed surrogate with a combination of a source containers, about 5 g from initial source of 50 g bulk container and about 15 g from a new 25 g bulk container, summarized below:

| Round / Operator | 1 | 2 | 3 |
|---|---|--|---|
| Background | Microbiologist | Mechanical engineer | Marketing executive |
| Gender | Female | Male | Male |
| Physical stature | Small | Medium | Big |
| Powder weighing skill | Basic Skill | Very limited | None |
| Active hand | Right | Right | Right |
| Put empty vials at | Right side of work tray | Right side of work tray | Right side of work tray |
| Take NS powder from | 50 g bulk container | 50 g bulk container | 50 & 25 g bulk container |
| Transfer NS to vials at | Right side of work tray | Right side of work tray | Right side of work tray |
| Put NS filled vials at | Left side outside cabinet, after each weighing | Left side of work tray, until all 20 vials are filled, then took them out to left side outside cabinet | Left side outside cabinet, after each weighing |
| Weight recording | On notepad outside cabinet, after each weighing | On notepad inside cabinet, after each weighing | On notepad outside cabinet, after each weighing |
| Spillage during work | Small | Moderate | Heavy |
| Routine work surface wiping with moistened cloth, to remove NS | Yes | Yes | No |
| Right hand accidentally came close to cassette at operator's collar | No | No | Yes |

Table 2. Operator background and technique

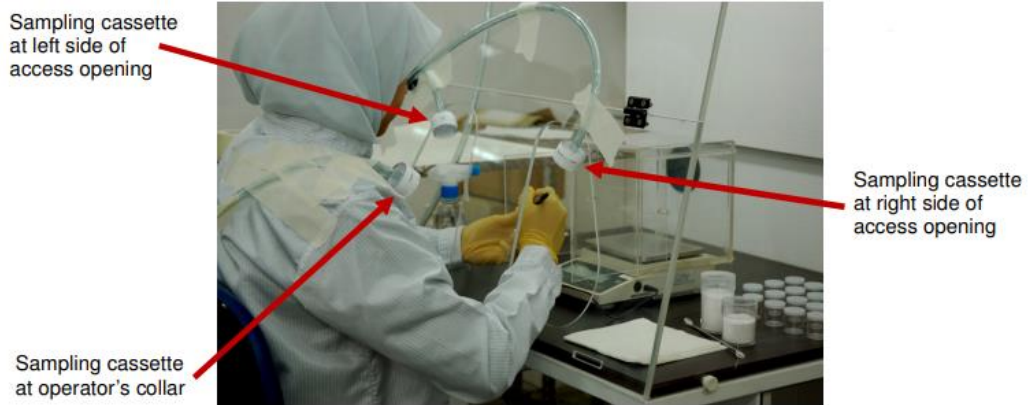


Figure 1. Operator 1 (Yayi Nestiti) and Sampling Cassette Placement



Figure 2. Operator 2 (Alexander Atmadi)

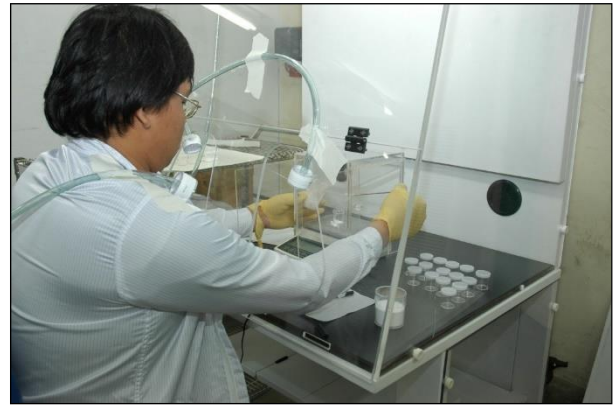


Figure 3. Operator 3 (Leonard Indrayanto)

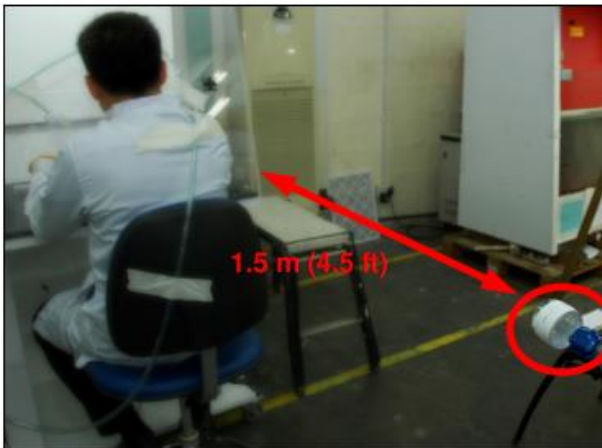


Figure 4. Sampling Cassette at 1.5 m (4.5 ft) in front of cabinet

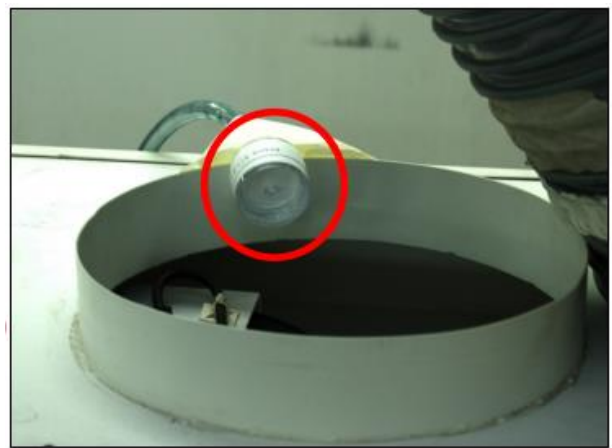


Figure 5. Sampling Cassette for pre-test & background

Table 3. Summary of Test Results

| Round | Sample ID | Sample Description | Period (minutes) | Concentration (ng/m ³) |
|-----------------|----------------------|---|------------------|------------------------------------|
| Pre-test | Pre-test | Background | 230 | <8.70 |
| 1,2,3 | Background 1,2,3 | Background | 492 | 19.0 |
| 1 | Operator 1: lab coat | Taped on Operator 1 lab coat | 120 | 26.3 |
| 1 | Operator 1: left | Left side of access opening | 112 | 25.8 |
| 1 | Operator 1: right | Right side of access opening | 112 | <17.9 |
| 1 | Operator 1: 4-5 feet | Area, 1.5m (4.5') in front of workstation | 115 | 20.3 |
| 2 | Operator 2: lab coat | Taped on Operator 2 lab coat | 148 | 270 |
| 2 | Operator 2: left | Left side of access opening | 139 | 21.4 |
| 2 | Operator 2: right | Right side of access opening | 138 | 58.2 |
| 2 | Operator 2: 4-5 feet | Area, 1.5m (4.5') in front of workstation | 142 | 20.2 |
| 3 | Operator 3: lab coat | Taped on Operator 3 lab coat | 88 | 2.47 x 10 ³ |
| 3 | Operator 3: left | Left side of access opening | 83 | 81.1 |
| 3 | Operator 3: right | Right side of access opening | 82 | 119 |
| 3 | Operator 3: 4-5 feet | Area, 1.5m (4.5') in front of workstation | 84 | 32.4 |
| NA ¹ | Blank Control | Blank Control | NA | BQL ² |

Notes:

¹NA : not applicable

²BQL: below quantization limit for analyses method

Analysis

The tasks were conducted to evaluate the containment ability of the cabinet of weighing and dispensing powder operation inside the cabinet, performed with three different operators with different skills and physical stature. Due to the un-availability of skilled personnel for powder weighing process, two non-related operators were chosen.

Round 1

Operator 1 is a microbiologist, female, with basic skill in powder weighing, small in physical stature, right handed. Operator 1 was the first of three operators who opened a full 50-gram API container. Operator 1 was observed to commit a minor spillage, but the naproxen sodium exposure is still low in all areas.

Exposure outcome over 34 minutes:

- Personal exposure: 26.3 ng/m³
- Area exposure (left side of access opening): 25.8 ng/m³
- Area exposure (right side of access opening): <17.9 ng/m³
- Area exposure (1.5 m (4.5 ft) in front of the workstation): 20.3 ng/m³

The highest exposure concentration is 26.3 ng/m³, which is in range of a well-made containment device, which has the containment performance of 50 ng/m³ and below.

Round 2

Operator 2 is a mechanical engineer, with very limited skill in powder weighing, average in physical stature, right handed. Operator 2 observed spilling moderate amounts of surrogate onto work surface in accomplishing the task. Note that operator 2 chose to record the sample weights onto a notepad which put inside the cabinet, increasing possible risk factor of exposure for operator.

Exposure outcome over 42 minutes:

- Personal exposure: 270 ng/m³
- Area exposure (left side of access opening): 21.4 ng/m³
- Area exposure (right side of access opening): 58.2 ng/m³
- Area exposure (1.5 m (4.5 ft) in front of the workstation): 20.2 ng/m³

The highest exposure concentration is 270 ng/m³, which is still a reasonably safe figure to work with highly potent API, that has OEL of below 1000 ng/m³.

Round 3

Operator 3 is marketing executive, with no skill in powder weighing, large physical stature, right handed. Operator 3 observed spilling much amounts of surrogate onto work surface. Note that the operator 3 was the quickest to complete the shortened task of weighing/dispensing only. Note also that operator 3 performed no post-activity cleaning of interior work surfaces of the balance enclosure. Operator 3 was a simulation for a worst operation condition in the cabinet.

Exposure outcome over 25 minutes:

- Personal exposure: 2470 ng/m³
- Area exposure (left side of access opening): 81.1 ng/m³
- Area exposure (right side of access opening): 119 ng/m³
- Area exposure (1.5 m (4.5 ft) in front of the workstation): 32.4 ng/m³

The highest exposure concentration is 2470 ng/m³ (2.47 µg/m³), which is still a reasonably safe figure to work with potent API, that has OEL of below 10,000 ng/m³, although this exposure would be too much for highly potent API that has OEL of below 1000 ng/m³.

Conclusion

The Esco Powdermax™ Powder Weighing Balance Enclosure, operating at 0.50 m/s (100 fpm) average inflow, has shown its capability as a containment of surrogate API (naproxen sodium) for a challenge of repetitive weighing of 20 x 1-gram quantities of API, where the operator exercises different weighing skill.

In a typical case scenario, when Powdermax™ is used by a someone that has some powder weighing skill, the exposure level was found to be 26.3 ng/m³, which is the typical well-made containment device, which generally has the containment performance of 50 ng/m³ and below. This containment performance is well below the threshold of highly potent API, that has OEL of below 1000 ng/m³, and even also below the threshold of super potent API that has OEL below 30 ng/m³.

In a worst case scenario, when Powdermax™ is used by a someone with a large build that has no skill / experience in powder weighing, the exposure level was found to be 2740 ng/m³, which is well below the threshold of potent API, that has OEL of below 10,000 ng/m³. This indicates that the Powdermax™ can be used to handle a wide range of potent API, as long at the OEL of that API is safely above this exposure level.

This study concludes that Esco Powdermax™ balance enclosures can be used to handle a wide range of highly potent API, and the weighing is done by an operator that has some basic skill in powder weighing.

References

Allan W. Ader, Justin J. Mason, John P. Farris. "Important Elements in Evaluating Contract Manufacturing Organizations in the Handling of "Potent" Active Pharmaceutical Ingredients and Products." Chemistry Today • Vol 25 nr 2 (March/April 2007): 56-60.

J. Nguyen, T. Brying. Concentration of Naproxen Sodium on Samples Collected at Esco Micro Pte Ltd Singapore. Data Report. Mountain View, CA, USA: Safebridge Consultants Inc., 2009.

John P. Farris, Allan W. Ader, Robert H. Ku. "History, Implementation and Evolution of the Pharmaceutical Hazard Categorization and Control System." Chemistry Today • Vol 24 nr 2 (March/April 2006): 5-10.

Martin W. Axon, John P. Farris, Justin Mason. "Handling Highly Potent Active Pharmaceutical Ingredients." Chemistry Today • vol 26 n 2 (March-April 2008): 57-61.

Safebridge Consultants, Inc. "Industrial Hygiene Sampling." Potent Compound Training Course (2002): 1-2.

Compound: Naproxen Sodium
Data Report: SB1068
Date: 03/19/09

Issued to: Yayi Nestiti
ESCO Micro Pte. Ltd
21 Changi Street 1
Singapore 486777

DATA REPORT

**CONCENTRATIONS OF NAPROXEN SODIUM ON SAMPLES COLLECTED AT
ESCO MICRO PTE LTD, SINGAPORE**

Distribution List:

Y. Nestiti, ESCO Micro Pte. Ltd
T. Bryning, SafeBridge
J. Nguyen, SafeBridge
File Copy, SafeBridge

ISSUED BY **SafeBridge Consultants, Inc.**
Analytical Laboratory
1924 Old Middlefield Way
Mountain View, CA 94043-2503
Phone: (650) 961-4820
Fax: (650) 623 0096

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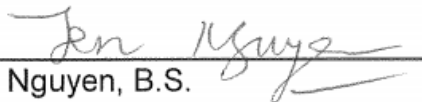
Compound: Naproxen Sodium
Data Report: SB1068
Date: 03/19/09

DATA REPORT

SUMMARY INFORMATION:

1. Samples received: 03/02/09
2. Total number of samples received: 15
3. Number of samples analyzed: 15
4. Conditions of samples upon arrival: Ambient
5. Storage conditions prior to analysis: Refrigerated at ~ 20 °C
6. Date range for sample extraction: 03/13/09
7. Method used for quantification: HPLC-FL
8. Quantitation Limit of the method: 2 ng of Naproxen Sodium per sample

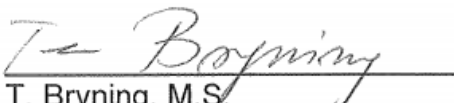
Report prepared by:



J. Nguyen, B.S.
Chemist III

03/19/09
Date

Report checked by:



T. Bryning, M.S.
Principal Chemist

3/20/09
Date

SAMPLE RESULTS FROM INDUSTRIAL HYGIENE MONITORING

Sampling Location: *Esco Micro Pte. Ltd
 Sample Collected by: Yayi Nestiti
 Analytical Chemist: J. Nguyen
 Analysis Date: 03/13/09 & 03/17/09
 Data Report Number: SB1068
 Notebook Reference: SB2009-1, pp 074 - 082

| DATE SAMPLED* | SAMPLING DEVICE* | SAMPLE ID* | ANALYTE* | AMOUNT OF ANALYTE # (ng/cassette) | AIR VOLUME (L)* | CONC.OF ANALYTE (ng/m ³) | ANALYTICAL METHOD | COMMENTS |
|---------------|------------------|------------------------------|-----------------|-----------------------------------|-----------------|--------------------------------------|----------------------|----------|
| 01/25/09 | ¹ GFF | Pre-test Background operator | Naproxen Sodium | ² BQL | 230 | <8.70 | HPLC-FL ⁴ | |
| 01/25/09 | GFF | 1,2,3 | Naproxen Sodium | 9.35 | 492 | 19.0 | HPLC-FL | |
| 01/25/09 | GFF | Operator 1-left | Naproxen Sodium | 2.89 | 112 | 25.8 | HPLC-FL | |
| 01/25/09 | GFF | Operator 1-right | Naproxen Sodium | BQL | 112 | <17.9 | HPLC-FL | |
| 01/25/09 | GFF | Operator 1-labcoat | Naproxen Sodium | 3.16 | 120 | 26.3 | HPLC-FL | |
| 01/25/09 | GFF | Operator 1- 4-5 feet | Naproxen Sodium | 2.33 | 115 | 20.3 | HPLC-FL | |
| 01/25/09 | GFF | Operator 2-left | Naproxen Sodium | 2.98 | 139 | 21.4 | HPLC-FL | |
| 01/25/09 | GFF | Operator 2-right | Naproxen Sodium | 8.03 | 138 | 58.2 | HPLC-FL | |
| 01/25/09 | GFF | Operator 2-labcoat | Naproxen Sodium | 40.0 | 148 | 270 | HPLC-FL | |
| 01/25/09 | GFF | Operator 2- 4-5 feet | Naproxen Sodium | 2.87 | 142 | 20.2 | HPLC-FL | |
| 01/25/09 | GFF | Operator 3-left | Naproxen Sodium | 6.73 | 83 | 81.1 | HPLC-FL | |
| 01/25/09 | GFF | Operator 3-right | Naproxen Sodium | 9.75 | 82 | 119 | HPLC-FL | |
| 01/25/09 | GFF | Operator 3-labcoat | Naproxen Sodium | 217 | 88 | 2.47 x 10 ³ | HPLC-FL | |
| 01/25/09 | GFF | Operator 3- 4-5 feet | Naproxen Sodium | 2.72 | 84 | 32.4 | HPLC-FL | |
| 01/25/09 | GFF | Field Blank | Naproxen Sodium | BQL | ³ NA | NA | HPLC-FL | |

¹GFF- Glass Fiber Filter, 1 µm pore size, 37 mm in Polystyrene cassette
²BQL-Below quantitation limit. Quantitation limit of method for Naproxen Sodium is 2.00 ng/sample
³NA- Not Applicable
⁴HPLC-FL - SBM023
 *information provided by client
 # Data not corrected for blank. Amount found on blank QC was BQL
 Results relate only to the items tested