

Designing and Testing Containment Devices Used on High Potency Active Pharmaceutical Ingredients



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Background:

Flow Sciences is a company that designs, tests and manufactures all sorts of laboratory containment devices.

In the ongoing search for new therapeutic treatments, pharmaceutical companies are developing a new class of active ingredients known as High Potency Active Pharmaceutical Ingredients (HPAPI's). As the name suggests, these compounds are highly potent, requiring "solid dilution" into therapeutic doses. It is therefore critical to maintain very minimal exposure to such ingredients during compounding and other operations. Commonly associated with oncology and cardiology drugs, an 'explosion' of HPAPI's is predicted over the next 5 years due to the high levels of research currently being conducted in this area. ¹

Unlike better-known typical reactive chemicals, these Pharmaceutical Ingredients *are designed* to be biologically active. Since, by definition, they are all high potency, HPAPI's can harm researchers with adverse symptoms at *very small* exposure levels! The blood thinner Warfarin, for example, shares its chemical roots with rat poison! ²

CMOs (contract manufacturing organizations) are the key stakeholders in this market as a good proportion of HPAPI manufacturing and compounding is understandably outsourced due to stringent manufacturing protocols and safety requirements. During our research, we identified 96 CMOs (with over 130 production facilities worldwide) that are focused in this area; *approximately 40% of these facilities are dedicated to manufacturing of both HPAPI's and cytotoxic drugs.*

A Containment Testing Program Geared for HPAIP's

In 2011, Flow Sciences, Inc. was tasked by a major pharmaceutical company with designing and constructing a hybrid isolator for the protection of its employees during tablet crushing operations. The design of the isolator included a bag in / bag out (BIBO) annex and a main enclosure.

After design and construction of the isolator, it was factory tested using a variety of recognized testing methods, including flow visualization, tracer gas testing, and surrogate powder testing. In each of these tests the detectable level for the agents used was far below the client's exposure standards, and often below quantitative levels of detection.³ Examples of such devices are shown below.



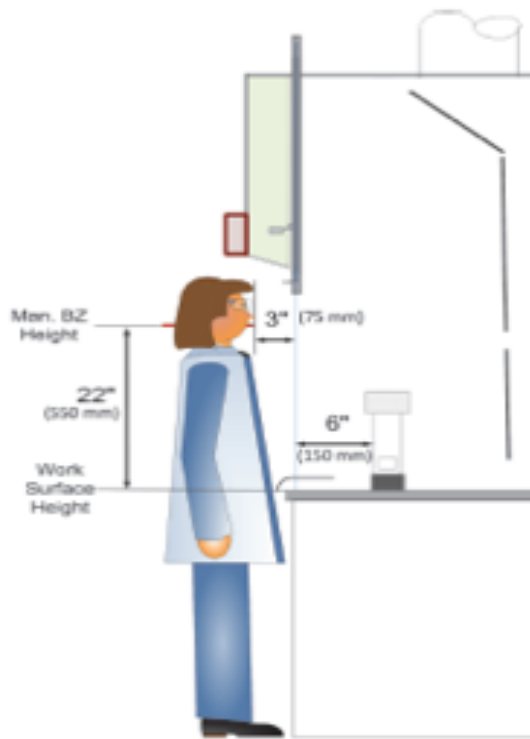
Hybrid Isolator (Plastic w/filter housing)
filter housing)

Hybrid Isolator (Stainless Steel w/

To test such devices for *effective containment* of the materials used within them, FSI uses a series of specific tests detailed below:

1) ASHRAE 110-2016 test 4

In the ASHRAE test, the presence of sulfur hexafluoride, a tracer gas, is monitored in various locations around the containment device. The gas is released at a flow rate of 4L per minute inside the fume hood using a mushroom-shaped diffuser and a factory acceptance level of 0.05 ppm in the mannequin breathing zone is set as the maximum acceptable level (AIHA Z9.5). Results of this test found that the concentrations of sulfur hexafluoride outside of the hybrid isolator is usually far below this level.



Mannequin and ejector depicted in ASHRAE 110 arrayed about a fume hood

2) Human as Mannequin (HAM) test 5

A modified HAM test (Human as Mannequin) uses ASHRAE 110 equipment in the vicinity of manipulated small lab objects on the containment device's work top. Development of this test was commissioned by Lawrence Berkeley National Laboratory. Results of this test must show the concentrations of sulfur hexafluoride outside of the hybrid isolator at or below the test equipment's level of detection (0.050 ppm).



HAM Test on Unit Similar to Hybrid Isolator and Standard Fume Hood Respectively

3) Surrogate Powder Test 6

For this study, naproxen sodium tablets are used to generate the surrogate powder. Two operations are performed – tablet crushing within the isolator and a procedure where powder is transferred. Air samples are collected from 12 locations around the isolator (Figure 2). The location of the detectors is designed to represent areas frequently occupied by workers, including operator breathing spaces and other areas, such as joints, where leakage can be experienced. The samples are collected on PTFE sample media, and the analysis for tracer powder performed by a third party. A factory acceptance level of 2 ng/m³ is used. In our tests, sodium naproxen has always been found to be below this level.

Figure 2. Locations of detectors for sampling of surrogate powder testing.

4) Other Tests at the Customer's Discretion:

Many pharma labs have specific applications, operations, or logistics challenges requiring special test arrangements. For these situations, Flow Sciences individualizes custom procedures which may include any or all of the following:

- a) Incorporating actual devices used by the CMO into our factory containment tests. (Grinders, shakers, etc.)
- b) Building MDF aerodynamic models of equipment to simulate air flow challenges inside the containment area.
- c) We have even coordinated overseas shipments to shipping locations Stateside where equipment is tested before shipment.

The Rendering of Our Products into Separate Disciplines

So testing our equipment to scrupulously contain HPAPI's is important. As you might imagine, the high standards and *diverse applications* of these pharma customers lead to an overwhelming number of different containment products whose containment must be evaluated.

The need for hybrid isolators, bulk powder isolators, stainless steel press enclosures, sieve enclosures, balance enclosures, nitrogen enclosures, etc. has required Flow Sciences to devise a method of showcasing our design diversity without becoming confusing to customers. We have therefore operationally designated several respective markets and developed an “e-Access” for each market.

For instance, we have just published an electronic booklet for the Contract Manufacturer, detailing containment technologies developed for this industry. ⁷



Web address: www.flowsciences.com/contract-manufacturing-contract-research-solutions-booklet/

Below, please find a table of all the electronic booklets and “apps” currently developed for various scientific disciplines with whom Flow Sciences deals with on a daily basis:

#	Research Focus	“e Booklet” or “app” Title	e-Access
1	C o n t r a c t Manufacturing	Contract Manufacturing	flowsciences.com/contract-manufacturing-contract-research-solutions-booklet/
2	Chemistry R&D or QC	Chemical Fume Hoods	flowsciences.com/solutions/containment-enclosures/fume-hoods/
3	Complete Isolation	Contained Env. Systems	flowsciences.com/solutions/containment-enclosures/contained-environmental-systems/
4	S e m i C o m p l e t e Isolation	Contained Env. Systems	flowsciences.com/solutions/containment-enclosures/contained-environmental-systems/

5	Automation/Robotic Aps	Lab Automation/Robotic	flowsciences.com/solutions/containment-enclosures/lab-automationrobotic-equipment/
6	Very Unique Needs	Taskmatch	flowsciences.com/taskmatch/

Item number six on the table is for applications either totally unique or not easily fitting into one of the previous categories. This sixth category is diverse. Many researchers who believe their unique application will require an unwieldy custom design may unexpectedly find a product match here.

Category six is an “App” that uses key words to find matching products from most of the products we have ever made. There are over 200 enclosure types represented in this reference, which may be found by clicking on a category or by typing in a word or phrase.

The screenshot shows the Taskmatch website interface. On the left, there is an 'Application Search' section with a search bar labeled 'Search for products'. Below it are 'Product Categories' including: Benchtop / Scale Up, Chemical Workstations, Contained Environmental Systems, Contract Manufacturing / Research, Fume Hoods, Glovebox Workstations, Lab Automation / Robotic Equipment, Nanotechnology, Necropsy Workstations, Pathology / Anatomy Workstations, Pilot Plant / Manufacturing, Specialty Hoods, and Steel Manufacturing. There is also a 'Filter by Width' section with options: 2' and Less (16), 2' Wide (63), 4' Wide (90), 5' Wide (57), 6' Wide (66), 7' Wide (25), 8' Wide (32), and 9' and Above (14). The main content area features the Taskmatch logo at the top, a 'Default sorting' dropdown, and 'Showing 1-16 of 252 results'. Below this is a grid of six product images with labels: '2 Position Draft Shield Enclosure', 'Acid Bath Hood', 'Acrylite Chemical Resistant HEPA/Carbon Enclosure', 'ADC Glovebox Workstation', 'Additive Manufacturing Enclosure', and 'All Clear Acrylic Enclosure'.

Webpage matching categories or keywords with FSI containment device: www.flowsciences.com/taskmatch/

We highly recommend customers contact us directly for guidance before choosing the best Flow Sciences product for your application. Remember, anything we ship, will have been completely tested and the tests will be part of the deliverable package!

Contact Information for Companies Carrying Flow Sciences Equipment:

#	Country	Company Name	City	Phone	email
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1	India	Dyna Filters	Pune	(+91) – 9370144760	info@dynafilters.com
2	China	Flow Sciences China	Beijing	+86-10-60789687	flowsciences.com.cn
3	Korea	GF Tech	Seoul	02-2662-7417	http://gftec.co.kr/shop/goods/goods_list.php?&category=032
4	Taiwan	Chuan Hua Precision	New Taipei City	02-2698-1222	chuanhua.com.tw
5	Jordan	Taawon	Amman	962 6 46 54 704	info@taawon.me

Summary

In the ongoing search for new therapeutic treatments, pharmaceutical companies are developing High Potency Active Pharmaceutical Ingredients (HPAPI's) into completed products. For worker safety, it is critical to maintain very minimal exposure to such ingredients during compounding and other operations.

Flow Sciences designs such products and then rigorously tests them in our test facility to document their effectiveness and containment. We have experience in producing over two hundred different varieties of containment devices to achieve this purpose. Research labs, CMO's, and government testing agencies who use such products may use either field or factory-based customer advocates or online "e access" resources on our website to find a match between their application and the appropriate FSI containment product.

Footnotes:

- 1) <https://www.giiresearch.com/report/root310060-hpapis-cytotoxic-drugs-manufacturing-market.html>
- 2) <https://en.wikipedia.org/wiki/4-Hydroxycoumarins>
- 3) Flow Sciences can share test results with any interested party.
- 4) ASHRAE 110-2016, ASHRAE Standard Project Committee 110 Cognizant TC: 9.10, Laboratory Systems SPLS
- 5) "Human as Mannequin" (HAM) Test Methodology, ECT, Inc. & Lawrence Berkeley National Laboratory (LBNL), 2005
- 6) <http://www.flowsciences.com/solutions/services/>
- 7) <http://www.flowsciences.com/contract-manufacturing-contract-research-solutions-booklet/>