

# IMS for Cleaning Verification

**The need to verify cleaning between manufacturing runs presents a special challenge to the analytical chemist. In this article, the principles of ion mobility spectrometry are described, its performance is compared to HPLC for the analysis of cleaning validation samples, and findings are presented from a study to establish the feasibility of using IMS in validating a cleaning verification method.**

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**C**leaning verification is one of the critical processes in pharmaceutical manufacturing. Equipment contamination can come from any of the materials that have been in contact with the equipment surfaces, including active pharmaceutical ingredients (APIs) from previous runs and cleaning agents. It is critical to avoid carryover of trace amounts of either active or other materials from one batch to another to avoid adulteration of the product.

For that reason, equipment used in pharmaceutical manufacturing must be cleaned before each use, and the cleaning procedure used must be in accordance with good manufacturing practices (GMPs). Before cleaning validation, cleaning verification procedures describing specific sampling and associated analytical methods are used to demonstrate the efficacy of the cleaning procedure.

Volumes of information have been written on cleaning verification in print and online, and many universities offer courses dedicated to this topic. FDA has standards (for example, 21 CFR Part 211.67) and associated guidances detailing requirements and offering interpretations for cleaning verification. Companies spend significant resources developing and validating the analytical methods required for cleaning verification. The analytical method must be specific, sensitive, accurate, and precise, and, to be cost-effective, it must be fast. Along with these requirements, the analytical method should be easy-to-use and it must be compliant with 21 CFR Part 11, FDA's regulation for electronic data collection.

After the equipment has been cleaned according to one of the company's standard operating procedures (SOPs), it is quarantined until the cleanliness is verified. This is where operational time can be lost: the slower the analysis, the longer the equipment is offline. The time involved encompasses sampling, instrument set-up, and analysis. Non-compound selective methods such as total organic carbon (TOC) have been used as well as compound selective methods such as high performance liquid chromatography (HPLC). Although TOC can be run more rapidly, the lack of selectivity for the specific active can leave questions as to whether the active or other background carbon compounds are the source of an observed signal. As a result, HPLC is currently considered the method of choice for cleaning verification.



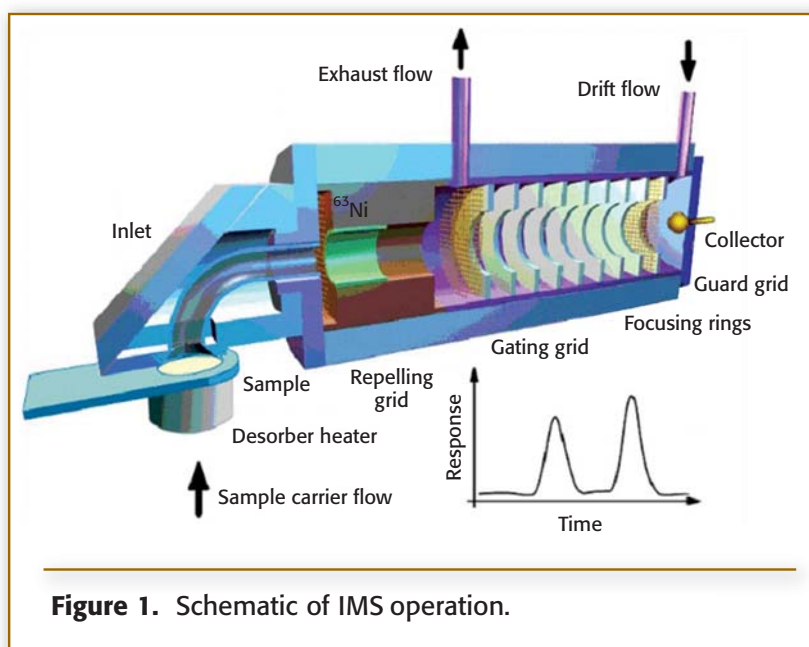
IONSCAN-LS (Smiths Detection)

## **Ion Mobility Spectrometry**

One emerging alternative to HPLC analysis is ion mobility spectrometry (IMS), which has been used in trace determination in military and security applications for more than 30 years. Cardinal Health (Somerset, NJ), a leading provider of health care industry services including pharmaceutical development and manufacturing, has just completed a comparison of IMS versus HPLC for cleaning verification testing.

Sampling techniques — either swab or rinse sampling — are similar for HPLC and IMS. HPLC instrument set-up time, which includes preparation of the mobile phase and column equilibration, takes about 2–4 h. In IMS, setup consists of warming up the instrument, which takes about 1–2 h. In the analysis, IMS is dramatically faster than HPLC.

IMS operation is shown in Figure 1. IMS operates at ambient pressure and uses air as the carrier gas. The analyte is deposited on a PTFE substrate either manually or by using an autosampler. It then is vaporized by thermal desorption and the resultant vapors are swept in through the inlet by the carrier gas and ionized. The product ions are gated into the drift tube and accelerated by an electric field to the detector. Drift times depend upon the size, shape, and mass of the analyte



**Figure 1.** Schematic of IMS operation.

**Table I. IMS vs. HPLC**

	HPLC	IMS
Sample cycle time	600–4500 s	30–60 s
Sample preparation time	Same	Same
Cost per sample	High	Low
Method development	Slow	Fast—able to run many samples very quickly
Waste solvents	Mobile phase	None
Direct swab analysis	No	Under development

and range from about 3 to 50 ms. The specificity of the IMS is based upon the movement of the ions. The characteristic speed at which an ion moves under the influence of an electric field, that is, its ion mobility, is a distinct thumbprint that identifies the original substance.

The IMS instrument can be set to detect either positive or negative ions.

The result of the analysis is displayed on a plasmagram, which is plot of peak intensity (in digital units) versus drift

time; the plasmagram usually includes a peak for the calibrant, a substance used by the instrument for internal calibration and displayed as a reference point. The plasmagram can be output in two or three dimensions. The third dimension represents analysis time. In the 3-D view, each segment (a group of scans averaged together for increased precision) within an analysis can be seen on a single graph (see Figure 2).

Using high performance injection

(HPI), the range of compounds that can be analyzed by IMS is expanded through the use of hot or cold injection, split flow, large volume injection, and temperature and flow staging. In the present study, the unique IMS parameters that were optimized were temperature and carrier flow for hot HPI injection. With an autosampler, IMS affords an easy-to-operate analysis system that accommodates a broad range of samples and is specific, accurate, and fast.

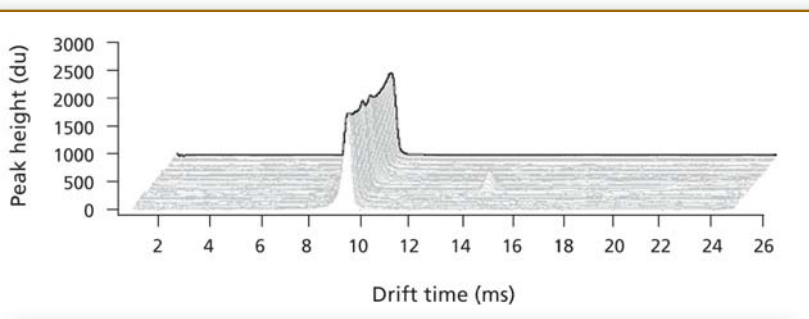
### IMS vs. HPLC

IMS is ideally suited for use in cleaning verification and, in a head-to-head comparison with HPLC, it offers many advantages. Any problems associated with columns, such as poor packing or column fatigue, are non-existent in IMS. Similarly, the cost of column materials and eluting solvents are eliminated with IMS.

Both HPLC and IMS are specific and accurate methods, but IMS generally is much faster. The major savings in time and associated costs gained by using IMS are in the speed of method development and analysis. Method development is an iterative process involving running a sample, checking results, modifying parameters, then running and checking results, and so on, to optimize the method. Because samples are run quickly and analysis results obtained within seconds, IMS parameters can be modified quickly and optimization reached faster than in the slower HPLC method. After method development and optimization, timesavings are obtained in the analyses a company runs in the ongoing monitoring of their cleaning methods. Table I presents a comparison of the two methods.

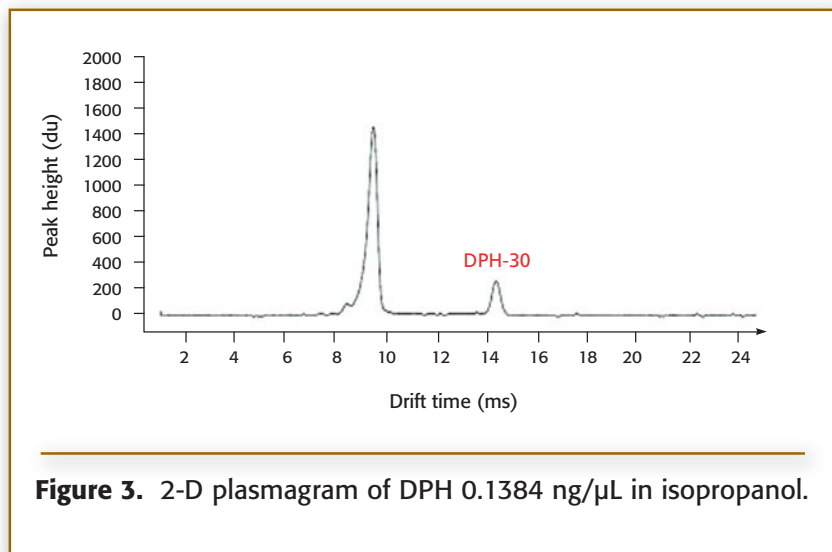
### Experimental

Cardinal Health evaluated IMS with the IONSCAN-LS (Smiths Detection) for use in cleaning verification with a protocol used to determine residual Diphenhydramine HCL (DPH) on stainless steel surfaces using a swab technique. This protocol was developed for HPLC analysis and contained requirements for specificity (non-interference from swabs, solvents, excipients, etc.), precision, linearity, limit of detection/limit of



**Figure 2.** 3-D plasmagram of DPH 0.1384 ng/μL in isopropanol.

Table II. Accuracy results				
Action Level (%)	%RSD Obtained	% RSD Required	% Recovery Obtained	% Recovery Required
75	3.1	≤ 15	102.1	> 70
100	3.0	≤ 15	98.5	> 70
125	3.4	≤ 15	95.0	> 70



excipients, swabs, or solvents; the requirement is ≤ 5%.

- A precision of 1.8% was obtained for six replicate injections at the action level; the requirement is ≤ 5%.
- Linearity results are shown in Figure 4. An  $R^2$  of 0.9955 was obtained; the requirement is ≥ 0.98. All samples were analyzed within the linear range established.
- The LOD was 0.00898 ng. The LOQ was 0.0224 ng and the relative standard deviation (RSD) obtained for LOQ was 8.3%; the requirement is ≤ 10%.
- The accuracy test was conducted at 75%, 100%, and 150% of the action level. The results obtained are shown in Table II.
- Test samples were evaluated after

## BECAUSE SAMPLES ARE RUN QUICKLY AND ANALYSIS RESULTS OBTAINED WITHIN SECONDS, IMS PARAMETERS CAN BE MODIFIED QUICKLY AND OPTIMIZATION REACHED FASTER THAN IN HPLC.

quantitation (LOD/LOQ), accuracy, and stability (comparison of samples aged 48 h to fresh samples). Additionally, the protocol requires the preparation and analysis of mock samples, that is, sam-

ples of known DPH concentration.

Figure 3 shows a typical plasmagram obtained for DPH. The following results were obtained:

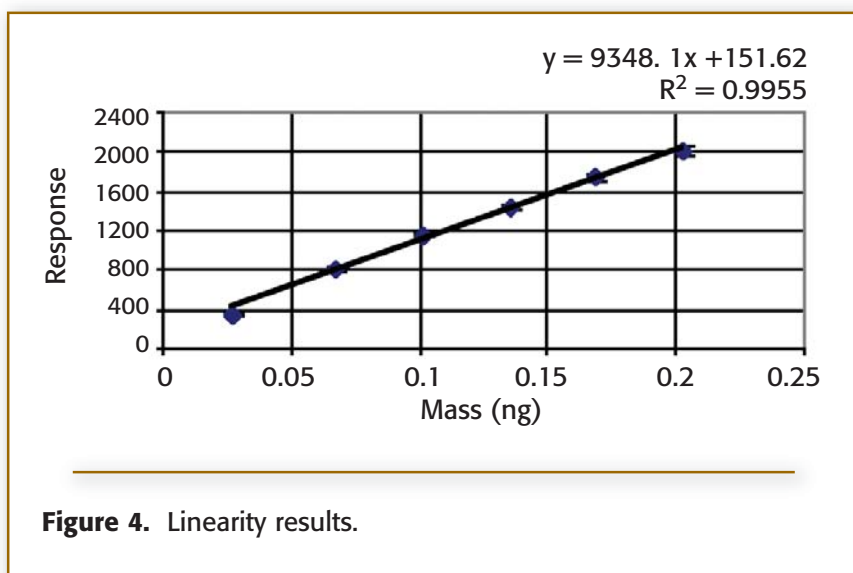
- No interference was seen from

48 h and compared to fresh samples. The standard and swab samples assayed at 99.3 and 100%, respectively, of the fresh sample; the requirement is 95–105%.

Twenty mock samples were prepared and analyzed at 75%, 100%, and 125% of the action level. The results of the analysis of the mock samples ranged from 93.4% to 105% of the expected value; the requirement is from 90 to 110%.

Blanks were run periodically throughout the analysis, including during runs of mock samples. The result of these blanks showed that the method exhibited no carry-over even at the highest concentration tested.

The results obtained using IMS met all requirements of the protocol; the results obtained using HPLC similarly met the requirements. The distinguishing factors of IMS vs. HPLC that make IMS a good candidate for cleaning verification testing



**Table III. DPH study results**

	HPLC	IMS
Consumables	Mobile phase: Potassium phosphate pH 2.5 and acetonitrile (70:30), flow rate 1.2 mL/min 1.2 L eluting solution	None
Equipment setup	Prepare mobile phase: 60 min Establish mobile phase flow and column equilibration: 180 min Total: 240 min	Warm up (from standby): 45 min Total: 45 min
Analysis/sample time	9 min	1 min
Analysis/total for all analyses associated with method validation	882 min (~17-3/4 h)	162 min (~2-3/4 h)

are: costs associated with consumables, instrument setup time, and, most dramatically, analysis throughput. These are summarized in Table III.

### Summary

IMS offers an ultrafast alternative to HPLC for the validation of cleaning verification methods as demonstrated by a study conducted recently by Cardinal Health. In this study using IMS with HPI injection, IMS exceeded all validation requirements for specificity, precision, linearity, LOQ/LOD, accuracy, and stability. Using IMS, the sample analysis portion of the method validation was done in just under 2-3/4 h vs. 17-3/4 h for HPLC, making it a significantly better choice than HPLC.

### References

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