

Investigating Analyst Error in Andersen Cascade Impaction

Jay Adamson

Covance Laboratories Ltd, Otley Road, Harrogate, HG3 1PY, UK

Summary/Introduction

This poster summarises an investigation performed at Covance into the effects that analyst error may have on the outcome of Andersen Cascade Impaction (ACI) Data. The objective was to produce a “trouble shooting guide” which would show up the various errors that could potentially occur during a typical day’s analysis, and put into place measures which would significantly reduce, the chance of these errors occurring.

16 deliberate errors were identified to reflect those which were historically believed to be the cause of erroneous data but where this could not be verified after the analysis had taken place. The effects of these errors were recorded and using particle size distribution charts and data tables, displayed alongside control analysis using the same batch of MDI Product.

Experimental

The errors chosen were as follows:

1) Transposition of stages

a) Stages 1 & 2 transposed

b) Stages 3 & 4 transposed

2) Incorrect seating of collection plates

Stage 1 collection plate incorrectly seated

3) Dryness of ACI

ACI built before completely dry

Analysis performed without allowing the ACI to fully dry

4) Flow rate variation

a) Analysis performed at 15 L min⁻¹

b) Analysis performed at 40 L min⁻¹

c) Analysis performed at 0 L min⁻¹ (vacuum pump switched off)

5) Shaking and Firing variation

a) “Slow” (1-2 shakes per second) canister shaking; firing immediately

b) “Normal” (3-4 shakes per second) shaking; delay in firing

Contact was made with the throat during firing.

6) Static

ACI shaken and throat tapped to simulate rough handling of the ACI from the firing location to the place of wash down

7) Transportation of the ACI

a) Stage’s 1 and 2 washed into the same volumetric flask.

8) Washing down the ACI

(200 mL and 250 mL volumetric flasks are easily mistaken for each other)

b) No soaking of the ACI plates (which was necessary for this API) in solvent to ensure complete dissolution.

9) Incorrect glassware usage

a) Using a 250 mL rather than a 200 mL volumetric flask for collection of stage 5

b) Using a 250 mL rather than a 200 mL volumetric flask for collection of stage 4

c) Using a 250 mL rather than a 200 mL volumetric flask for collection of stage 3

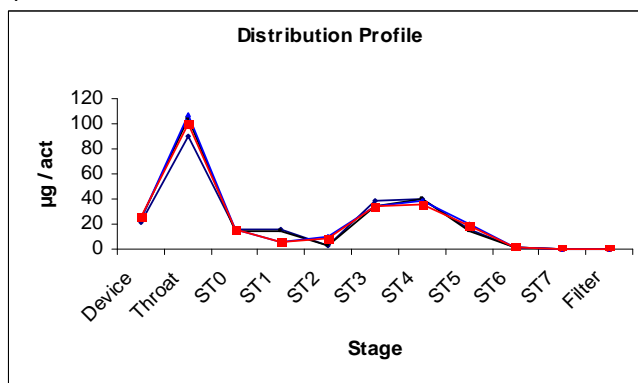
The particular batch of pMDI analysed had a label claim of 250µg per actuation delivered with HFA-134a propellant.

During all analysis both the temperature and the humidity of the air flow through the ACI was controlled to within the range of 17-23°C and 45-55%RH.

Results & Discussions

1a) Transposition of stages - Stages 1 & 2 transposed.

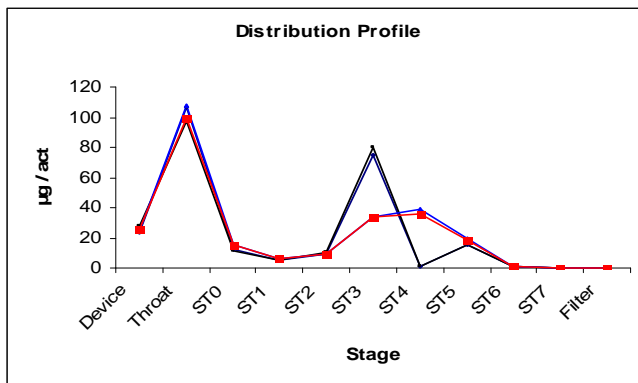
Stage	Experimental		Control	
	Can 1	Can 2	Can 1	Can 2
Device	22.1	25.0	24.9	25.8
Throat	90.7	104.9	107.2	99.5
ST0	16.0	14.2	15.4	15.6
ST1	15.4	14.2	6.2	6.0
ST2	3.3	3.1	9.3	9.0
ST3	38.1	34.3	34.3	34.0
ST4	39.8	39.5	38.5	36.2
ST5	16.2	14.4	19.5	18.7
ST6	1.1	1.1	1.3	1.3
ST7	0.2	0.2	0.3	0.3
Filter	0.1	0.1	0.2	0.2
Total	243.0	251.0	257.1	246.6
FPM	94.1	88.2	92.3	88.9



Increased level of drug deposited on stage 1 with a decreased level of drug deposited on stage 2. The remainder of the profile is typical. FPM comparable, total deposition comparable.

1b) Transposition of stages - Stages 3 & 4 transposed.

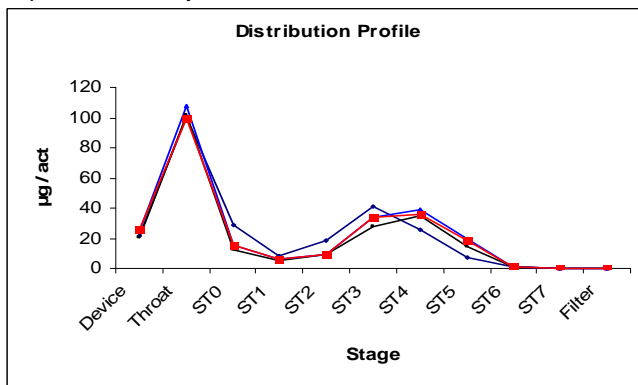
Stage	Experimental		Control	
	Can 1	Can 2	Can 1	Can 2
Device	23.5	27.7	24.9	25.8
Throat	106.9	97.3	107.2	99.5
ST0	12.6	11.3	15.4	15.6
ST1	5.5	5.4	6.2	6.0
ST2	9.2	10.4	9.3	9.0
ST3	74.4	80.2	34.3	34.0
ST4	0.9	1.3	38.5	36.2
ST5	15.8	15.3	19.5	18.7
ST6	1.1	1.1	1.3	1.3
ST7	0.3	0.2	0.3	0.3
Filter	0.1	0.1	0.2	0.2
Total	250.3	250.3	257.1	246.6
FPM	91.1	96.8	92.3	88.9



Largely increased level of API deposited on stage 3 and virtually no API (in comparison) deposited on stage 4. The remainder of the profile is largely typical. FPM comparable, total deposition comparable.

2) Incorrect Seating of Plates - Stage 1 collection plate incorrectly seated.

Stage	Experimental		Control	
	Can 1	Can 2	Can 1	Can 2
Device	21.8	20.6	24.9	25.8
Throat	100.6	101.5	107.2	99.5
ST0	28.3	11.8	15.4	15.6
ST1	7.8	5.0	6.2	6.0
ST2	18.6	9.1	9.3	9.0
ST3	40.6	27.4	34.3	34.0
ST4	26.0	34.6	38.5	36.2
ST5	6.8	14.8	19.5	18.7
ST6	1.0	1.1	1.3	1.3
ST7	0.5	0.2	0.3	0.3
Filter	0.2	0.1	0.2	0.2
Total	250.3	250.3	257.1	246.6
FPM	91.1	96.8	92.3	88.9

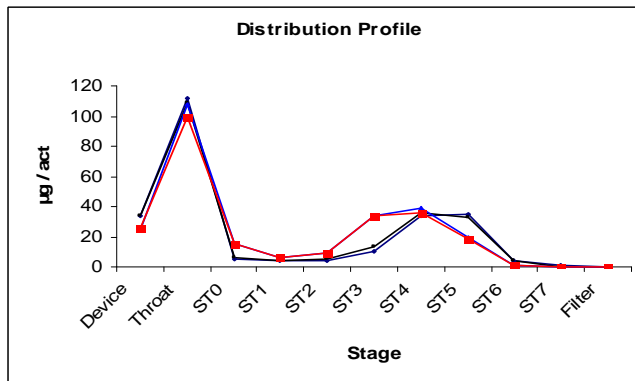


Distribution noted to be erratic, with incomparable profiles between cans 1 & 2, possibly due to air flow disruption throughout the ACI. FPM comparable, total deposition comparable.

3) Dryness of ACI — ACI built before completely dry - 2 cans analysed prior to allowing the ACI to fully dry. No comparable deference noted. Level of solvent on the internal surface of the impactor not known. It is possible that the impactor had dried sufficiently to prevent non-typical deposition of API. FPM comparable, total deposition comparable.

4a) Flow rate variation - 2 cans analysed at 15 L min⁻¹.

Stage	Experimental		Control	
	Can 1	Can 2	Can 1	Can 2
Device	34.1	34.2	24.9	25.8
Throat	112.2	108.9	107.2	99.5
ST0	5.3	6.1	15.4	15.6
ST1	3.9	4.1	6.2	6.0
ST2	3.8	5.2	9.3	9.0
ST3	10.5	13.1	34.3	34.0
ST4	33.5	35.4	38.5	36.2
ST5	34.7	33.1	19.5	18.7
ST6	4.6	4.3	1.3	1.3
ST7	0.7	0.5	0.3	0.3
Filter	0.1	0.1	0.2	0.2
Total	243.4	245.0	257.1	246.6
FPM	78.7	81.6	92.3	88.9



Higher device deposition. The profile has shifted such that more API is deposited in stages 4, 5 & 6 with lower deposition in stage 3. FPM decreased, total deposition comparable.

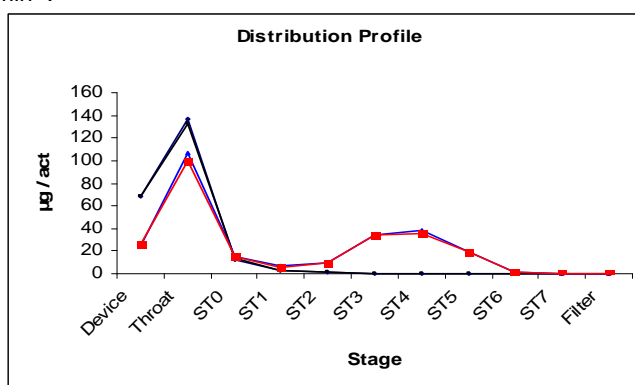
4b) Flow rate variation - 2 cans analysed at 40 L min⁻¹.

Lower device deposition. The profile has shifted such that more API is deposited in the higher part of the ACI,

thus reversing that of 4a) above, with lower deposition in stage's 4 and 5. FPM decreased, total deposition comparable.

4c) Flow rate variation - 2 cans analysed at 0 L min⁻¹.

Stage	Experimental		Control	
	Can 1	Can 2	Can 1	Can 2
Device	67.7	68.4	24.9	25.8
Throat	136.5	132.7	107.2	99.5
ST0	12.6	13.3	15.4	15.6
ST1	3.0	2.8	6.2	6.0
ST2	0.8	0.7	9.3	9.0
ST3	0.1	0.1	34.3	34.0
ST4	0.1	0.1	38.5	36.2
ST5	0.0	0.0	19.5	18.7
ST6	0.0	0.0	1.3	1.3
ST7	0.0	0.0	0.3	0.3
Filter	0.0	0.0	0.2	0.2
Total	220.8	218.1	257.1	246.6
FPM	0.2	0.2	92.3	88.9



Increased level of API in the device & throat, rapidly decreasing to almost no API after stage 1. FPM reduced, total deposition reduced.

5a) Shaking and Firing variation - 2 cans analysed after "slow" shaking; firing immediately.

No significant variation in profile seen. The slower shaking technique was most likely to have been sufficient enough to provide adequate mixing of the suspension.

5b) Shaking and Firing variation - 2 cans analysed after "normal" shaking; delay in firing.

Higher deposition seen throughout the ACI, particularly the Throat and stages 2, 3 & 4. FPM increased, total deposition increased.

6) Static - 2 cans analysed after contact was made with the throat during firing.

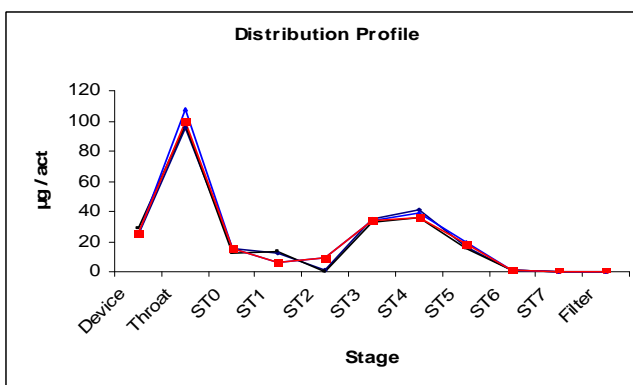
Little difference is seen. Slight variation in FPM, probably due to canister to canister variations, total deposition comparable. Level of static not quantifiable.

7) Transportation of the ACI - 2 cans analysed and the ACI shaken and throat tapped to simulate rough handling of the ACI from the firing location to the place of wash down.

Profiles comparable, no significant difference noted. FPM comparable, total deposition comparable.

8a) Washing down the ACI - 2 cans analysed and stage's 1 and 2 washed into the same volumetric flask, followed by the rewashing of stage 2 into the correct flask.

Stage	Experimental		Control	
	Can 1	Can 2	Can 1	Can 2
Device	24.4	28.8	24.9	25.8
Throat	95.2	97.8	107.2	99.5
ST0	15.2	12.6	15.4	15.6
ST1	12.3	13.7	6.2	6.0
ST2	0.7	0.4	9.3	9.0
ST3	34.6	33.0	34.3	34.0
ST4	40.7	35.8	38.5	36.2
ST5	16.0	15.2	19.5	18.7
ST6	1.4	1.4	1.3	1.3
ST7	0.2	0.3	0.3	0.3
Filter	0.2	0.3	0.2	0.2
Total	240.9	239.3	257.1	246.6
FPM	91.3	84.0	92.3	88.9



High deposition seen in stage 1 followed by little API present in stage 2.

8b) Washing down the ACI - 2 cans analysed without soaking the ACI plates (which was necessary for this API) in solvent to ensure complete dissolution.

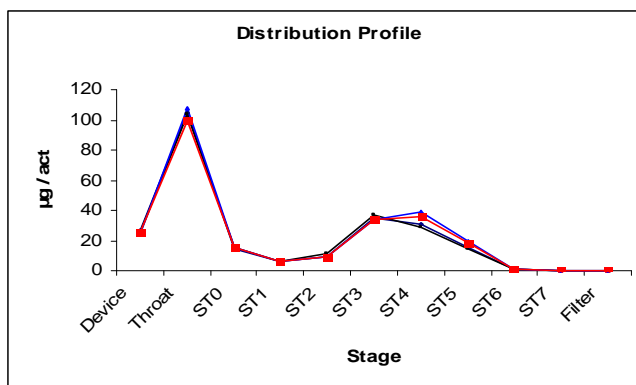
Slight variation in stage 0 deposition otherwise no significant difference noted. FPM comparable, total deposition comparable.

9a) Incorrect glassware usage - 2 cans analysed whilst using a 250 mL rather than a 200 mL volumetric flask for collection of stage 3

Slight reduction (approx 20%) in API content of stage 3. FPM slightly lower, total deposition comparable.

9b) Incorrect glassware usage - 2 cans analysed whilst using a 250 mL rather than a 200 mL volumetric flask for collection of stage 4.

	Experimental		Control	
Stage	Can 1	Can 2	Can 1	Can 2
Device	26.9	26.0	24.9	25.8
Throat	104.7	103.1	107.2	99.5
ST0	14.4	15.5	15.4	15.6
ST1	6.0	5.8	6.2	6.0
ST2	9.0	11.4	9.3	9.0
ST3	34.5	37.3	34.3	34.0
ST4	30.8	28.6	38.5	36.2
ST5	15.3	14.3	19.5	18.7
ST6	1.3	1.2	1.3	1.3
ST7	0.3	0.3	0.3	0.3
Filter	0.1	0.1	0.2	0.2
Total	243.3	243.6	257.1	246.6
FPM	80.6	80.2	92.3	88.9



Slight reduction (approx 20%, equivalent to the increase in flask volume) in API content of stage 4. FPM slightly lower, total deposition slightly lower.

9c) Incorrect glassware usage - 2 cans analysed whilst using a 250 mL rather than a 200 mL volumetric flask for collection of stage 5.

Slight reduction (approx 20%, equivalent to the increase in flask volume) in API content of stage 5. FPM lower, total deposition lower. Lower stage 3 believed to be due to canister to canister variations.

Conclusions

Of the 16 deliberate errors made, 11 produced data that gave evidence of analytical deviations. The remainder produced data typical of the MDI product used for the investigation and hence are potentially undetectable.

Detectable Errors

- 1a) & b) Transposition of stages
- 2) Incorrect seating of plates
- 4a), b) & c) Flow rate variations
- 5b) Shaking and Firing variation (firing delay)
- 8a) Washing down of the ACI (washing error)
- 9a), b) & c) Incorrect glassware (stage's 3, 4 & 5)

Undetectable Errors

- 3) Dryness of ACI
- 5a) Shaking and Firing variation (slow shake)
- 6) Static
- 7) Transportation of ACI
- 8b) Washing down the ACI (no soak)

The investigation has shown that 5 of the 11 factors may be eradicated by putting simple checks in place. These checks are intended to be performed prior to beginning analysis.

These factors are as follows:

- | | |
|----------------------------------|-----------------------------------|
| 1a) & b) Transposition of stages | 4a), b) & c) Flow rate variations |
|----------------------------------|-----------------------------------|

The following verification steps are now required as part of our Standard Operating Procedures:

- Verification of the position of the stages by a second analyst prior to firing. This identifies if an analyst has incorrectly assembled the ACI by transposition of any of the stages. It does not ensure that collection plates are correctly seated.
- Verification of the flow rate through the ACI by a second analyst prior to firing. This ensures that the correct flow rate is being applied but the analyst should also be aware of any changes that need to be made to adjust the flow rate i.e. if large adjustments to the flow are required for differing stacks then this can be indicative of seal failure or flow path blockage.

Verification of volumetric glassware is already required as per company/dept SOP. The need for this verification procedure was identified during previous LIR trend analysis. Glassware is verified by a second analyst on the day of preparation prior to analysing the sample solutions. This highlights any errors made prior to data generation and hence removes the need for investigation at a later date.

For the additional 5 undetectable factors it is necessary to highlight these areas during training. These points are covered in our department SOP for ACI to be used in conjunction with the department training module for ACI analysis. Although for this investigation they have shown to be potentially undetectable, it is not acceptable to disregard these during day to day analysis. Each analyst should be aware of the impact that these factors may potentially have and that they must take great care in order to prevent errors occurring.

Acknowledgments

Gail Braz (Covance Labs) - This poster is based entirely on the investigation performed by Gail, formally of Covance Labs Ltd, for her BSc final year dissertation.