CBC-PROCOS S.p.A. – Quality Control

Data Integrity: reliability, quality and competitiveness factors of API manufacturers

Laboratory assessment: case history

Pavia, November 10th , 2017

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DATA INTEGRITY IN QUALITY CONTROL LABORATORIES

From a theoretical point of view it consists in:

- **Management of the single data itself (ALCOA)**
- **Management of data (audit trails, inventory, reconcilitation)**

Very simple at first glance BUT…

From a practical point of view we need to consider

- **Available hardware systems**
- **Available software systems (including the most complex one that are… people! ☺)**

TOPICS

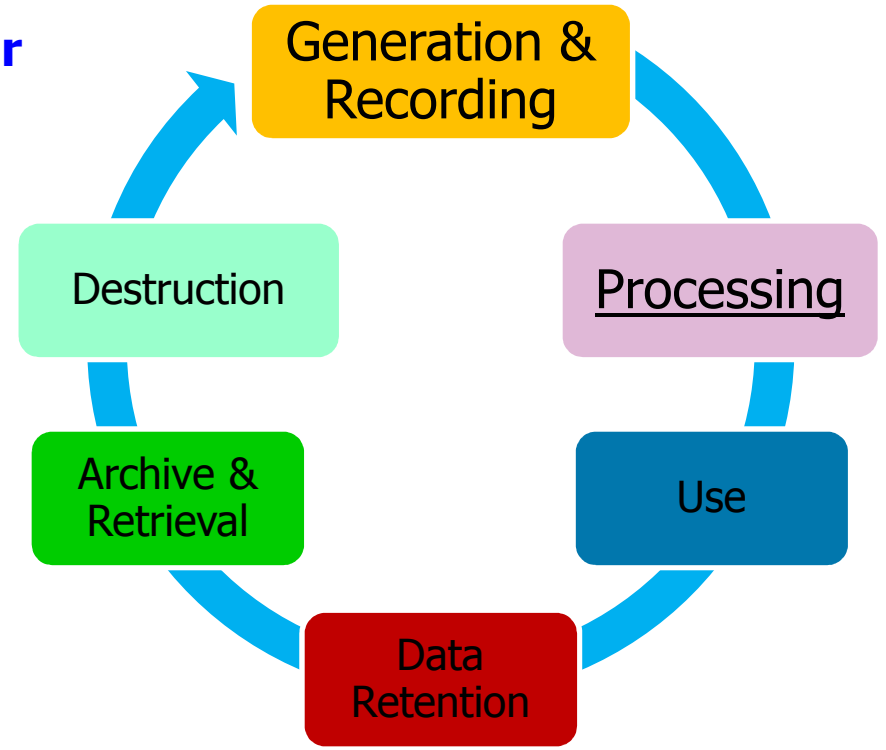
Data integrity &…

- … integration
- … hardware and software systems
- … review of data (integrity)

Conclusion

Data Integrity is the set of requirements for complete, consistent and accurate data throughout the data lifecycle

Data Lifecycle: all phases in the life of the data (including raw data) from initial generation and recording through processing (including transformation or migration), use, data retention, archive/retrieval and destruction.



PROCESSING OF CHROMATOGRAPHIC DATA

The process that, through the integration the peaks in the chromatogram (raw data) and application of a defined calculation, generates the final result.

How the chromatogram should be integrated to get the correct result?

How to perform the integration in a consistent and reproducible way?

WHY THE INTEGRATION OF CHROMATOGRAMS IS CRITICAL FROM A DATA INTEGRITY PERSPECTIVE?

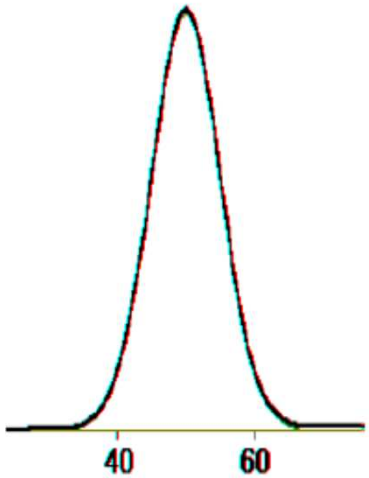
From WL 320-13-22 / Aarti drugs Ltd

Failure to maintain laboratory control records with complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays.

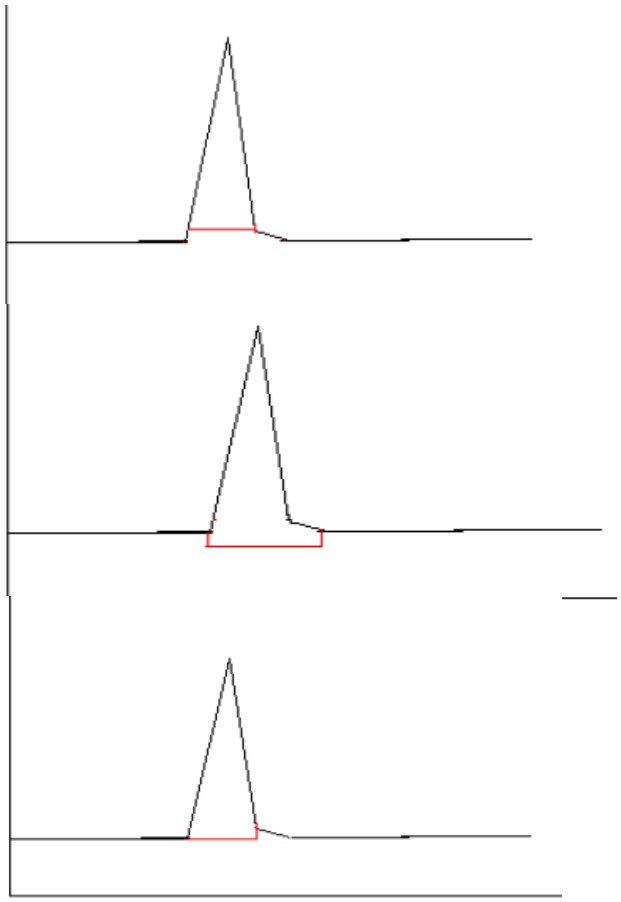
a. The inspection documented that HPLC processing methods (including integration parameters) and re-integrations are executed without a pre-defined, scientifically valid procedure. Your analytical methods are not locked to ensure that the same integration parameters are used on each analysis. A QC operator interviewed during the inspection stated that integrations are performed and re-performed until the chromatographic peaks are "good", but was unable to provide an explanation for the manner in which integration is performed. Moreover, your firm does not have a procedure for the saving of processing methods used for integration.

Instruction for a correct integration should be written and established in the Quality System (e.g. reported in a SOP)

- **Baseline to Baseline (BB)**

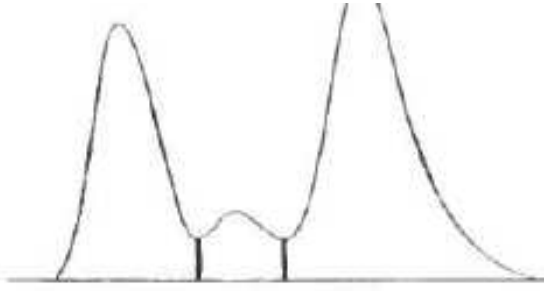


Correct integration



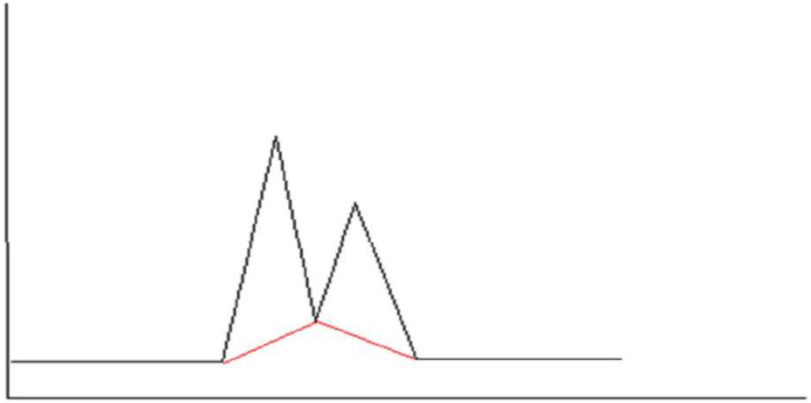
Wrong integration

- **Baseline to Valley (BV) o Valley to Baseline (VB) o Valley to Valley (VV)**



1° peak: Baseline to Valley (BV)
2° peak: Valley to Valley (VV)
3° peak: Valley to Baseline (VB)

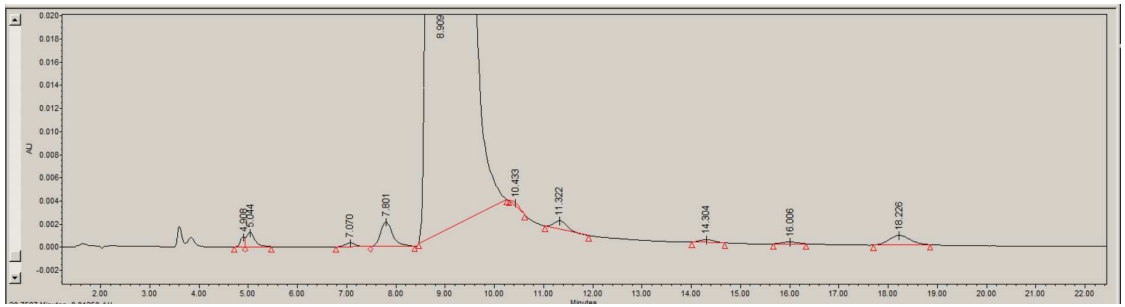
Correct integration



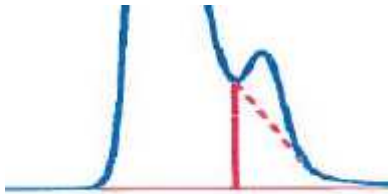
Wrong integration

➢ Tangent skim (TT)

Correct integration



Wrong integration



Wrong integration (solid line)

How to perform the integration in a consistent and reproducible manner?

use the automatic integration!

Automatic integration consist of specific sets of instruction (processing method) that are automatically applied to the chromatogram by the software

Steps

1st step: setting of integration parameters

2nd step: identification and calculation model

3rd step: saving of the final processing method

How to build an automatic processing method?

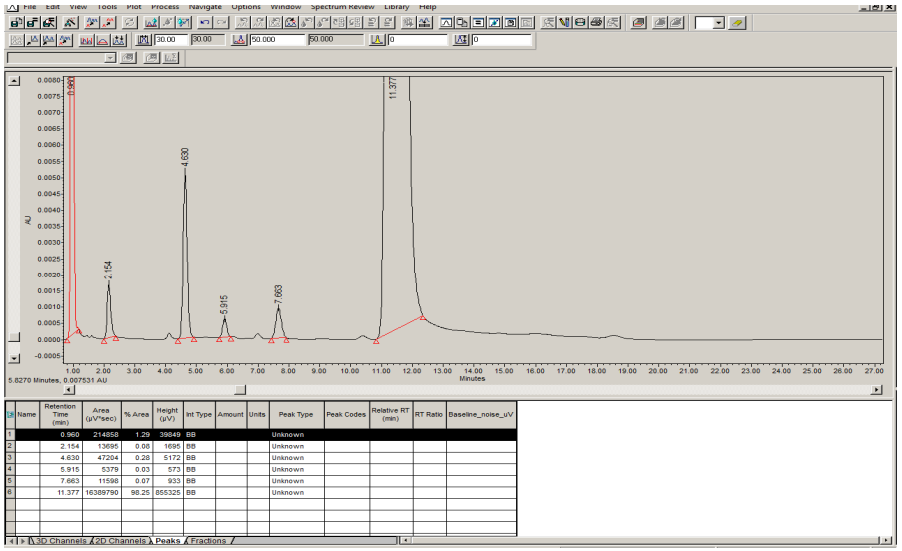
1st Step: definition of integration parameters to be automatically applied to obtain the correct integration of the sample's peaks and not attributable to the blank.

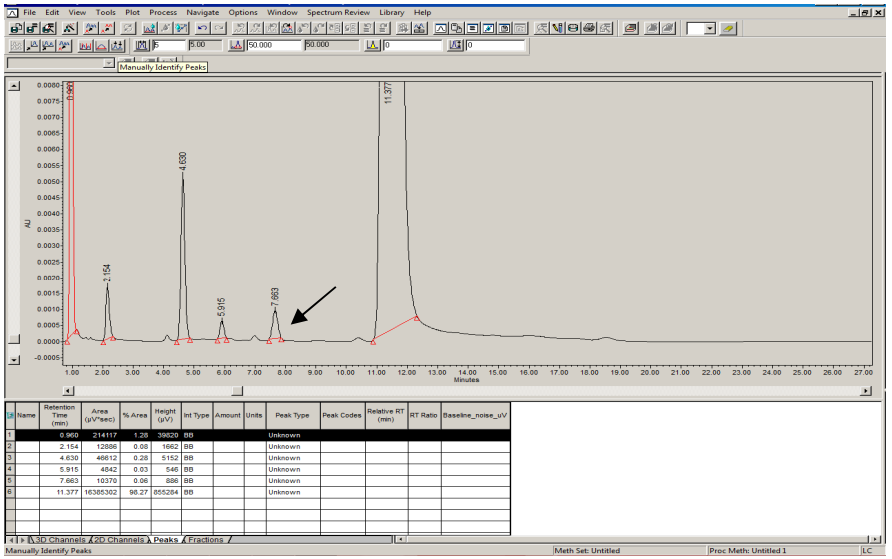
Typical parameters are (but not limited to):

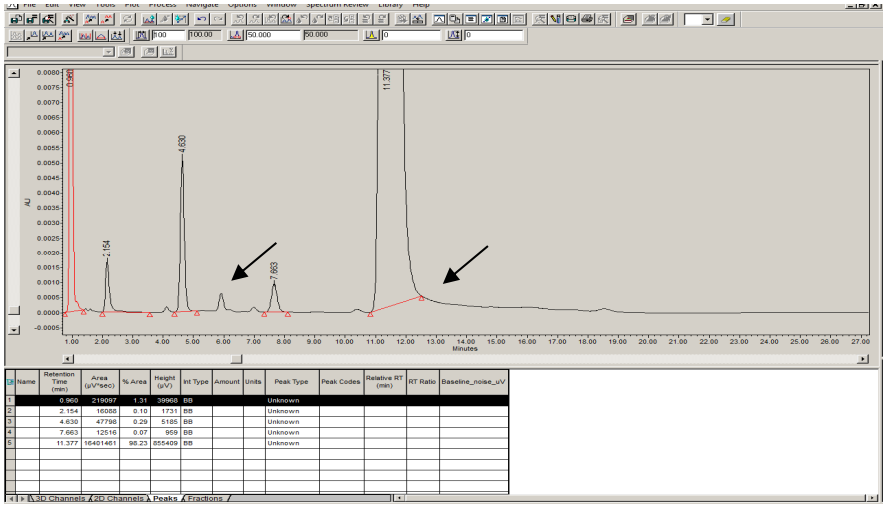
- **Peak Width**
- **Threshold**
- **Minimum Area / Minimum Height**
- **Integration on/off**

➢ Peak Width: it is the width of peak at half height

Decreasing values



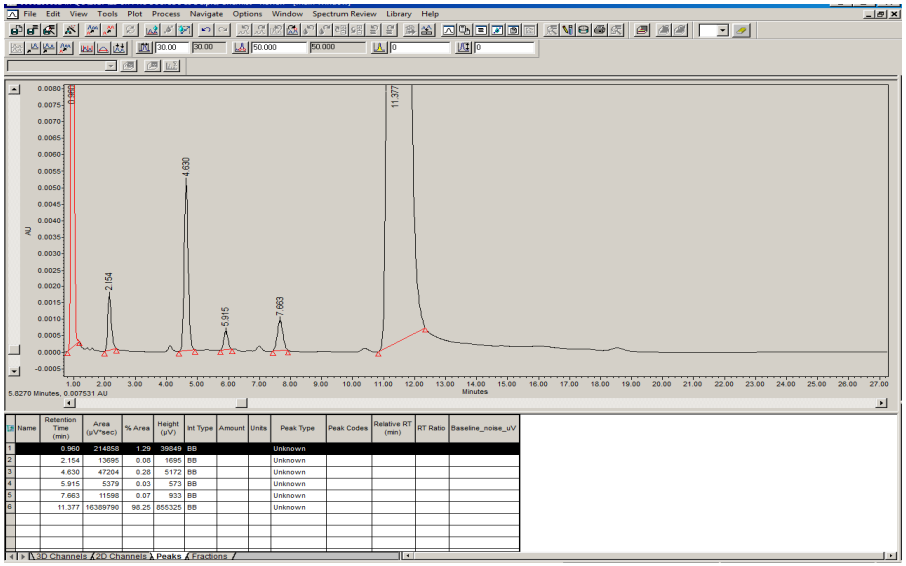


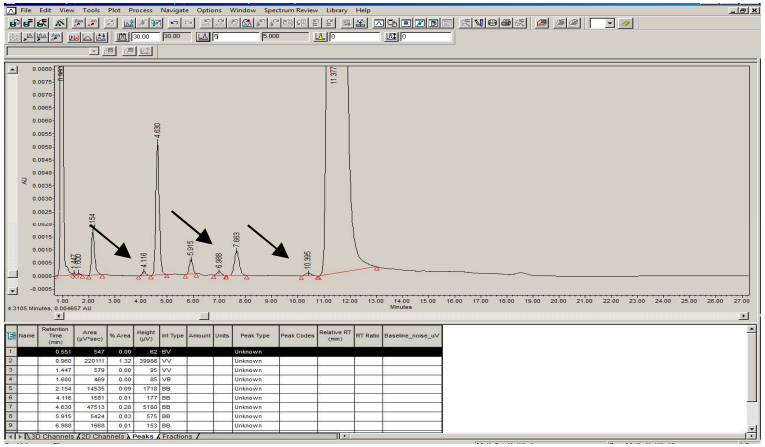


Increasing values

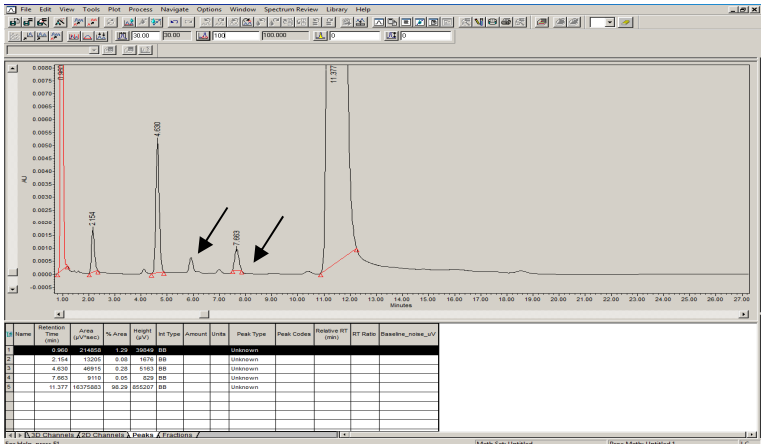
- **Threshold: math algorithm used by the CDS to distinguish the beginning and end of the chromatographic peak from the base line by detecting the slope variation of the base line.**

Decreasing values



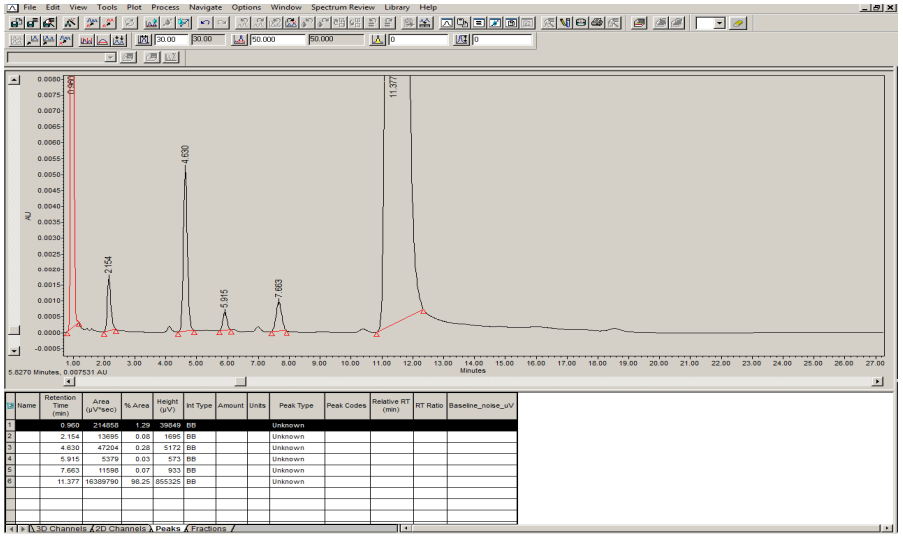


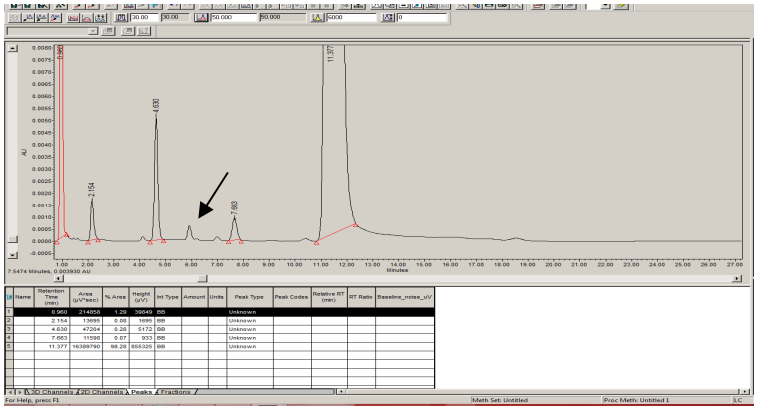
Increasing values



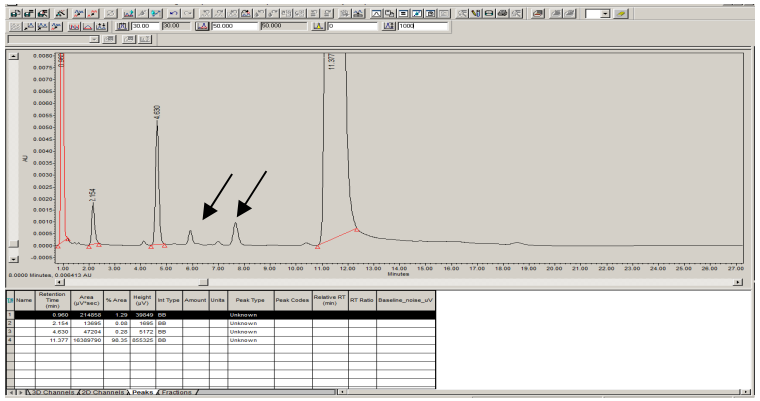
- **Minimum Area / Minimum Height: minimum value of area or height usually defined at method validation stage (LOD, LOQ) to discriminate signals attributable to the baseline noise**

Area

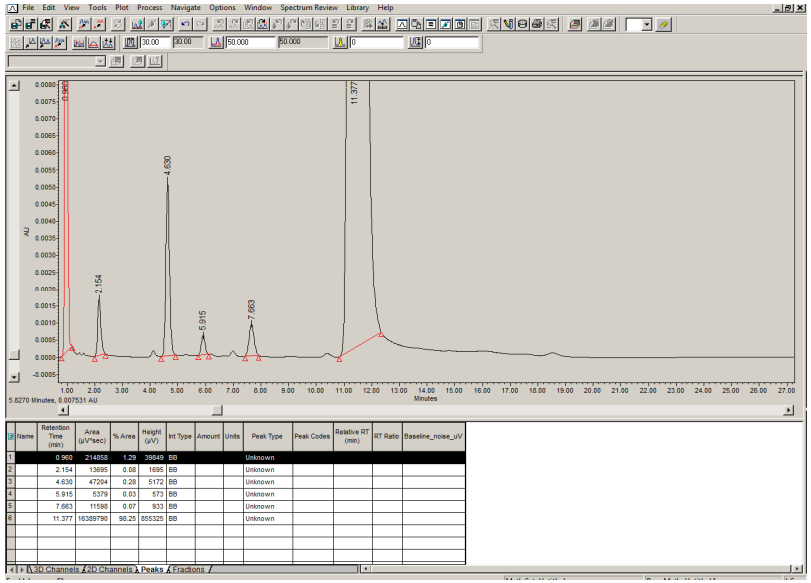


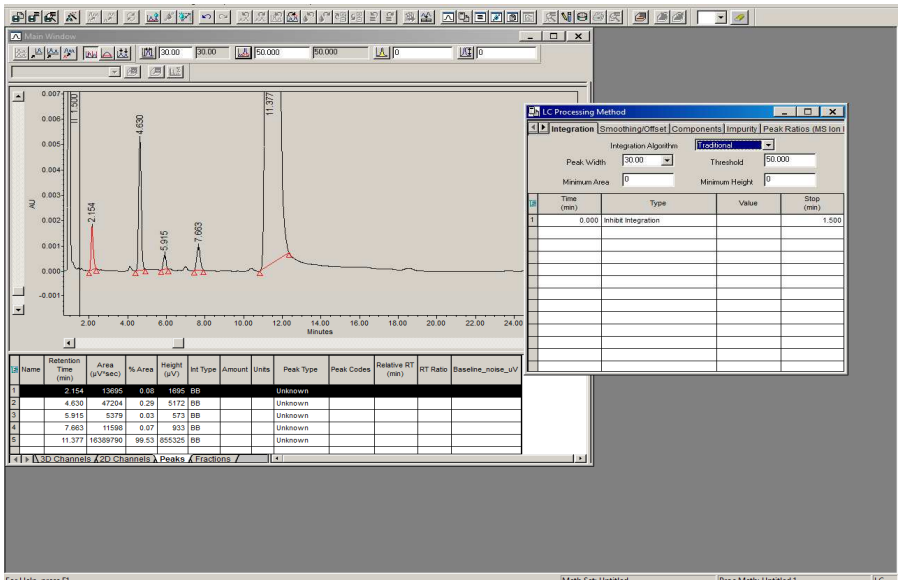


Height

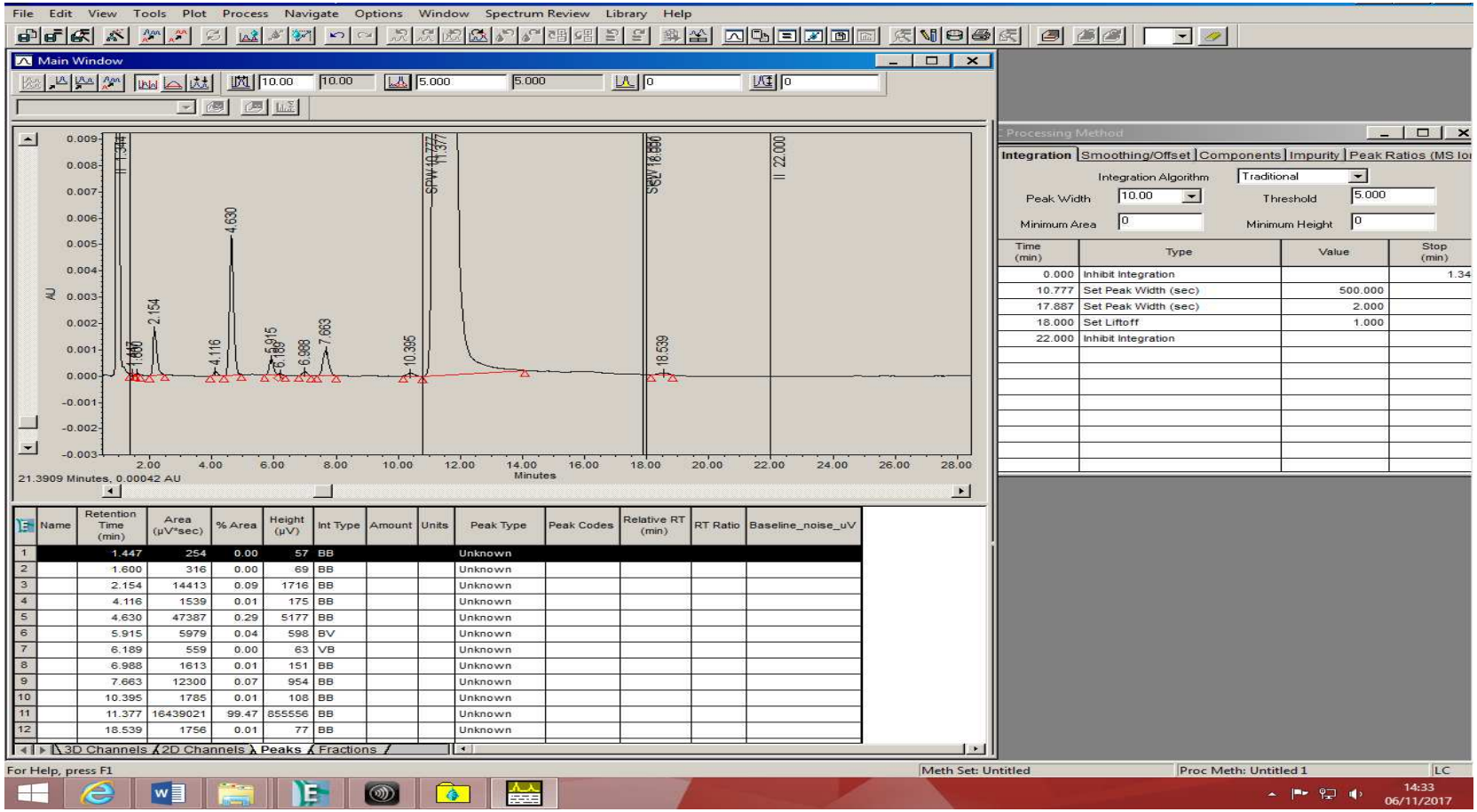


- **Integration on/off: event that permanently inhibits the integration in part of the chromatograms**

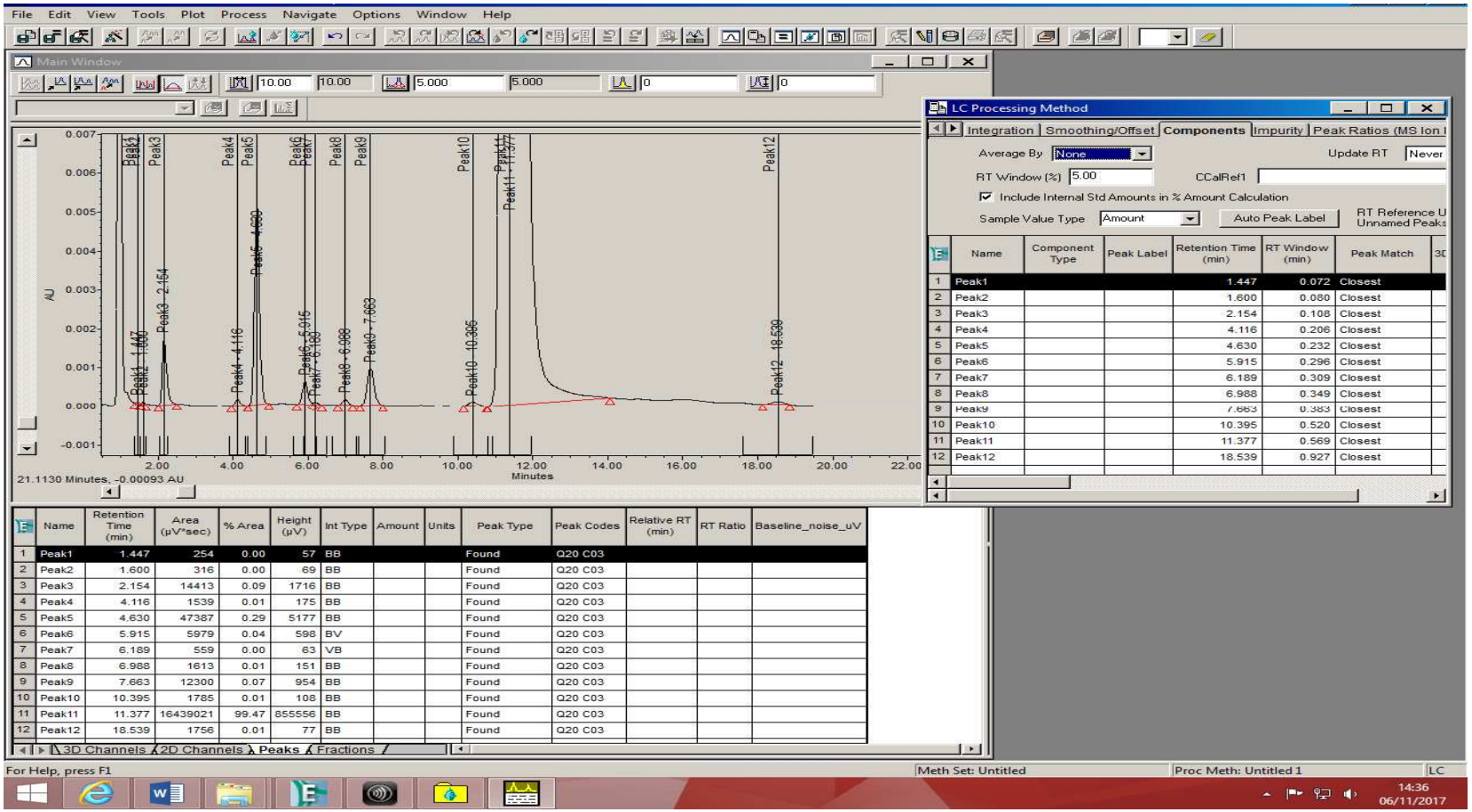




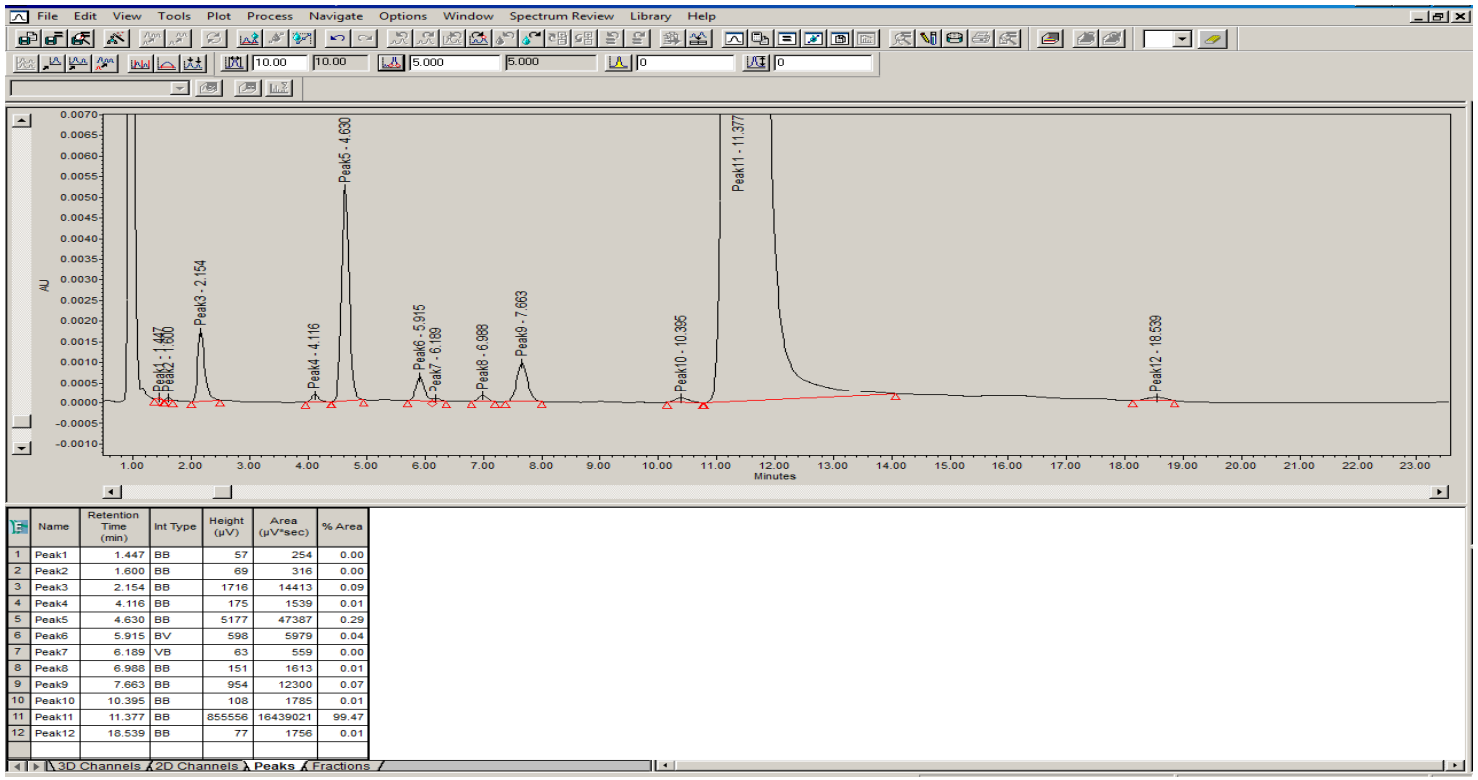
➢ Final chromatograms after the definition of the suitable integration parameters



2nd step: definition of the retention time range for the identification and of the quantification method for each analyte in the sample



3rd step: saving of the final processing method and its application to standards and samples to calculate the results. From now on the processing method is managed under audit trail and is permanently associated to the result

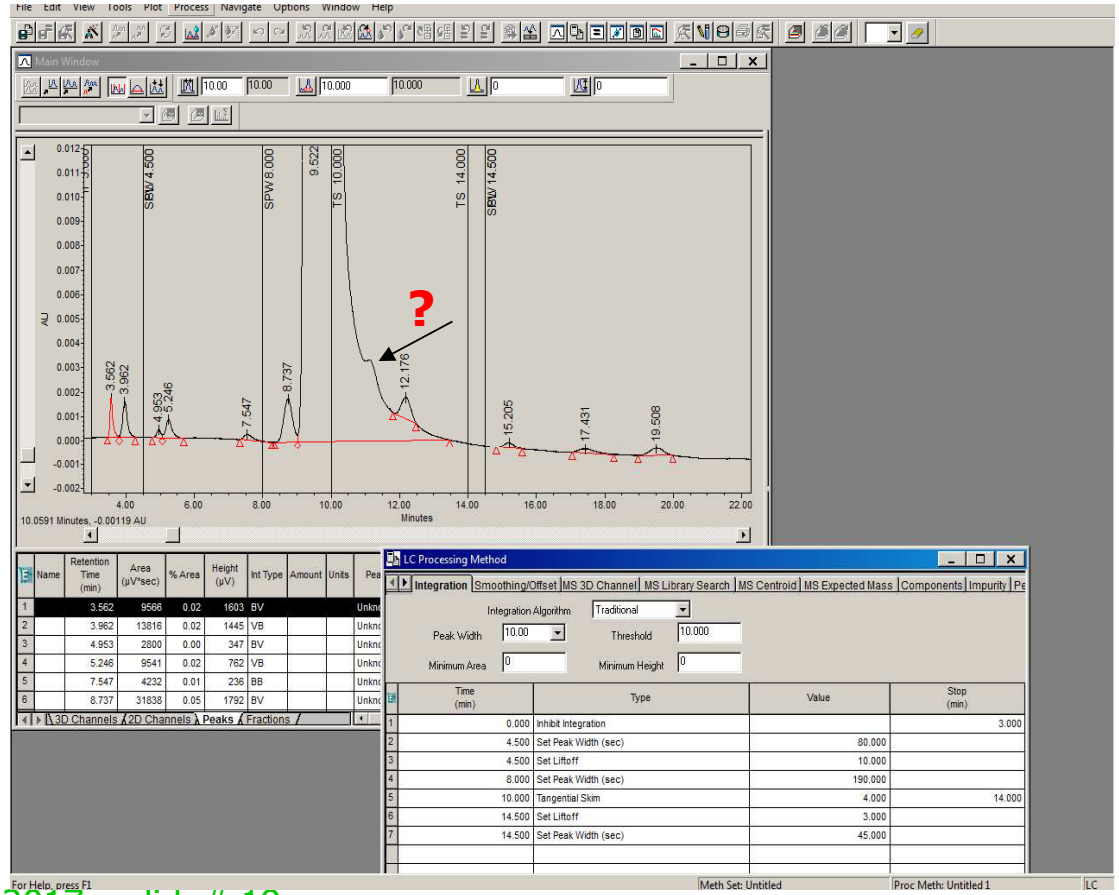


	Name	Retention Time (min)	Int Type	Height (µV)	Area (µV*sec)	% Area
1	Peak1	1.447	BB	57	254	0.00
2	Peak2	1.600	BB	69	316	0.00
3	Peak3	2.154	BB	1716	14413	0.09
4	Peak4	4.116	BB	175	1539	0.01
5	Peak5	4.630	BB	5177	47387	0.29
6	Peak6	5.915	BV	598	5979	0.04
7	Peak7	6.189	VB	63	559	0.00
8	Peak8	6.988	BB	151	1613	0.01
9	Peak9	7.663	BB	954	12300	0.07
10	Peak10	10.395	BB	108	1785	0.01
11	Peak11	11.377	BB	855556	16439021	99.47
12	Peak12	18.539	BB	77	1756	0.01

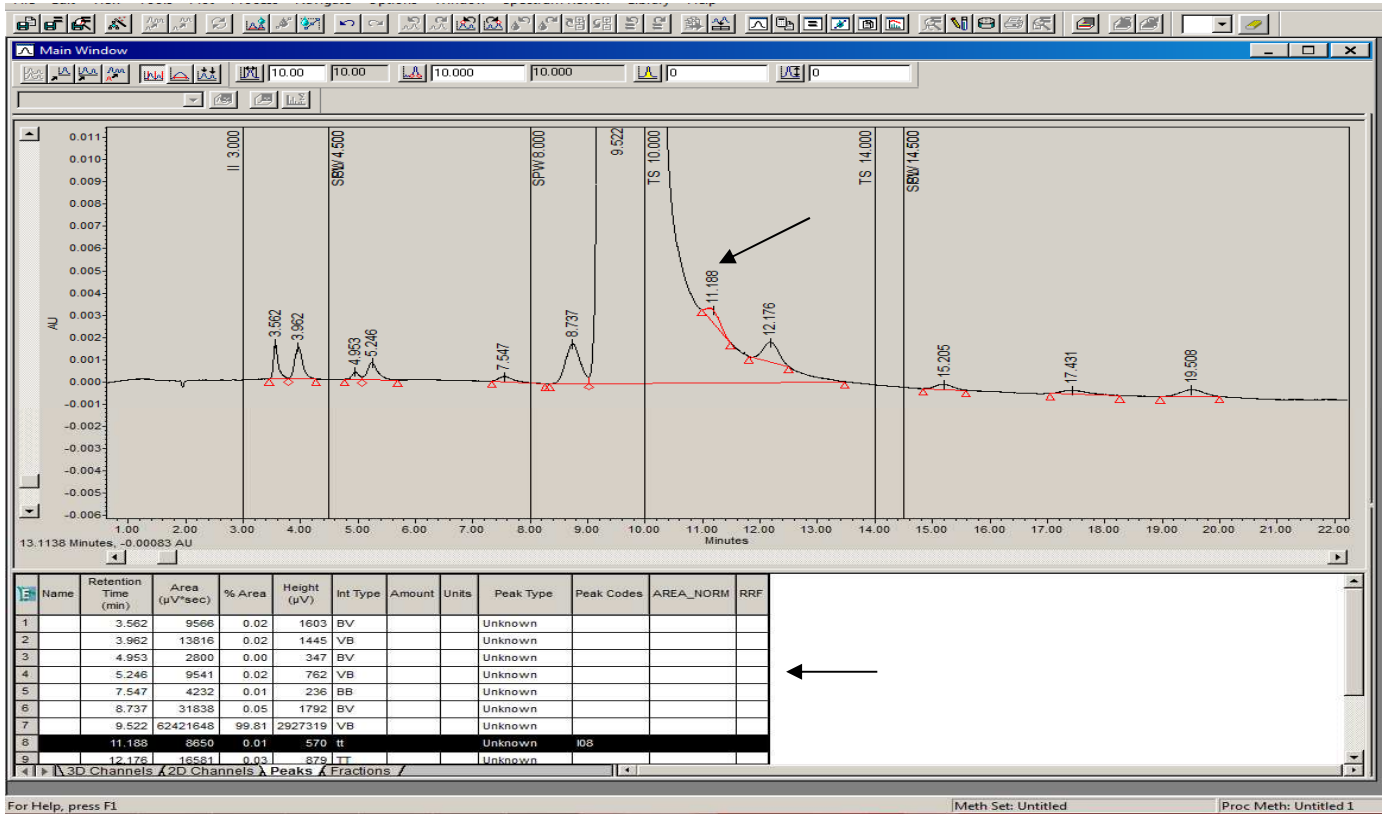
3D Channels 2D Channels Peaks Fractions

This is the best scenario…

But how to proceed when suitable integration parameters cannot be defined for all the peaks in the sample?



If the required integration cannot be obtained automatically, it is allowed respecting well defined requirements (SOP) to manually modify the integration only for the peak for which automatic integration is not achievable (manual integration).



	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes	AREA_NORM	RRF
1		3.562	9566	0.02	1603	BV			Unknown			
2		3.962	13816	0.02	1445	VB			Unknown			
3		4.953	2800	0.00	347	BV			Unknown			
4		5.246	9541	0.02	762	VB			Unknown			
5		7.547	4232	0.01	236	BB			Unknown			
6		8.737	31838	0.05	1792	BV			Unknown			
7		9.522	62421648	99.81	2927319	VB			Unknown			
8		11.188	8650	0.01	570	tt			Unknown	I08		
9		12.176	16581	0.03	879	TT			Unknown			

Manual Integration

Typical chromatographic issues that can make not feasible the automatic integration are:

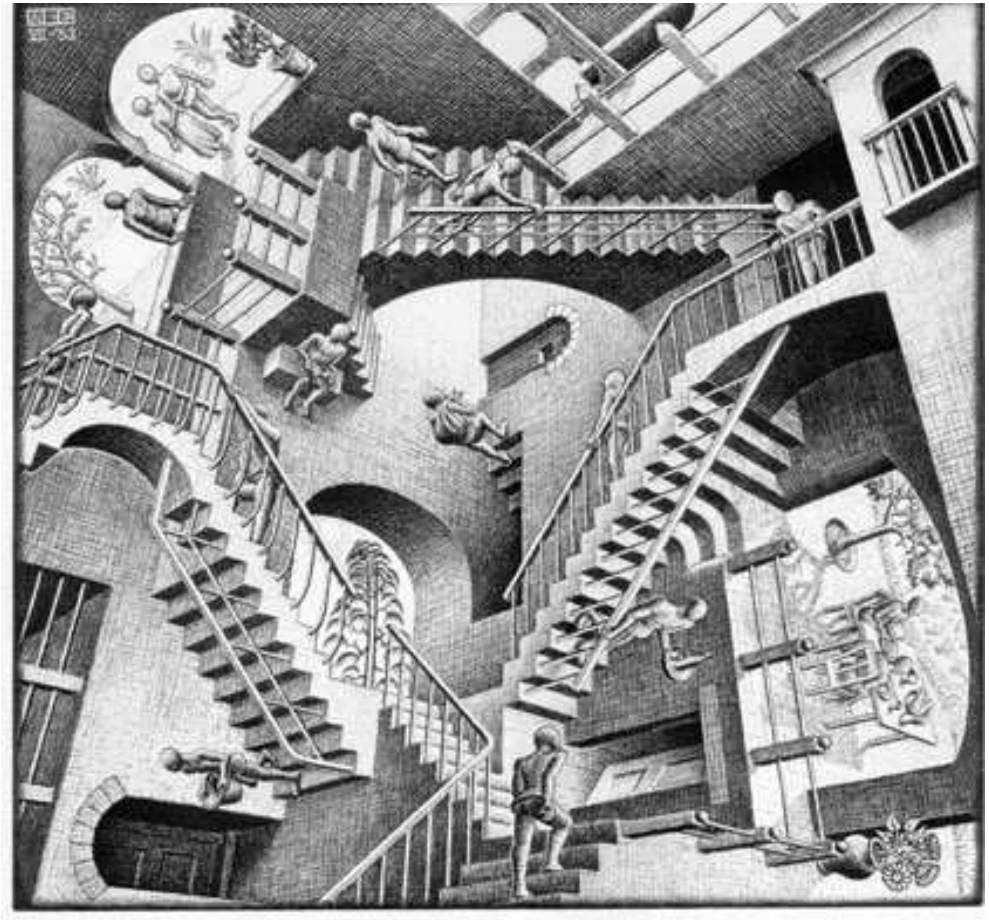
- **The peak is not integrable due to the low response**
- **Wrong identification of peaks due to the a very close elution (similar Retention Times)**
- **Baseline noise**
- **Partial coelution of peaks**
- **Peaks that elute on the tail of the main component**
- **Splitted peaks (ex diastereoisomers)**
- **Different tailing or fronting of the peaks**
- **Complex chromatographic profiles**

Requirements for Manual Integration

Manual changes to automatic integration must:

- be scientifically justified to demonstrate the non intentional manipulation of the automatic integration aimed to get the product in specifications
- be authorized
- be recorded by the CDS
- comply with the rules of integration
- be fully reviewed before the batch release

COMPLEXITY OF THE DATA MANAGEMENT

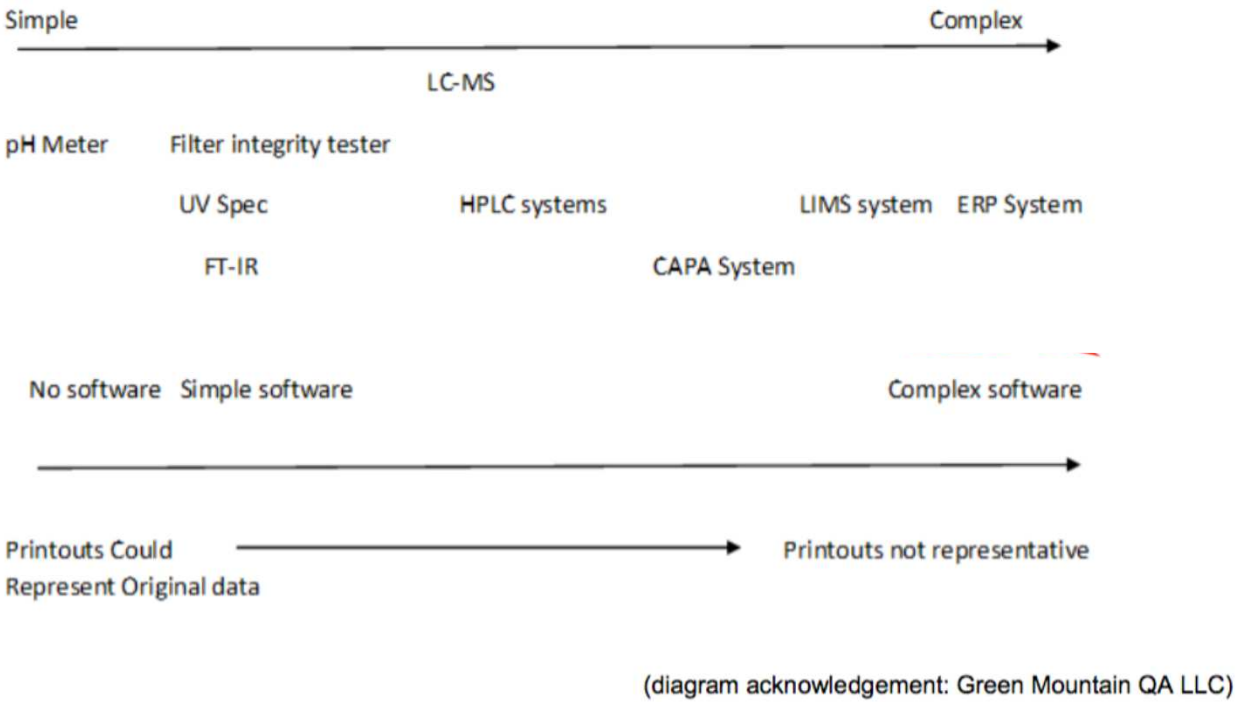


M. C. Escher
Casa di scale – Relatività, 1953

AN EXAMPLE OF COMPLEXITY: HARDWARE SYSTEMS

How many equipments are available in the QC lab?

Figure 1: Diagram to illustrate the spectrum of simple machine (left) to complex computerised system (right), and relevance of printouts as 'original data'



(diagram acknowledgement: Green Mountain QA LLC)

AN EXAMPLE OF COMPLEXITY: HARDWARE SYSTEMS

Every time a new equipment is introduced in the laboratory two different installation options should be considered:

- **Systems «network based» (client-server approach)**
- **Stand-alone systems**

How to manage the backup and restore in case of stand-alone systems? How to guarantee the functionality of a network based system in case of network failure?

Due to multi disciplinary requirements also the IT department should be aware and full trained on data integrity and on the good management of GMP critical data. A strong linkage between functions is required to fulfill regulatory expectation

AN EXAMPLE OF COMPLEXITY: CLOCK

From WL 320-16-19 / Chongqing Lummy Pharmaceutical Co., Ltd.

Failure to prevent unauthorized access or changes to data and failure to provide adequate controls to prevent manipulation and omission of data.

Our investigator's review of the audit trail for the residual solvent stability testing indicated that an analyst manipulated your computerized gas chromatography (GC) system to falsify residual solvent stability results for multiple batches of (b)(4) API distributed to the U.S.

For example, on March 4, 2016, your analyst set the GC personal computer (PC) clock back to make it appear as if testing had been done seven months earlier – on August 3, 2015. The analyst then performed five different injections to produce falsified results …

How to guarantee the timing in the QC lab?

Certificated server syncronize the clientes on the network bases system

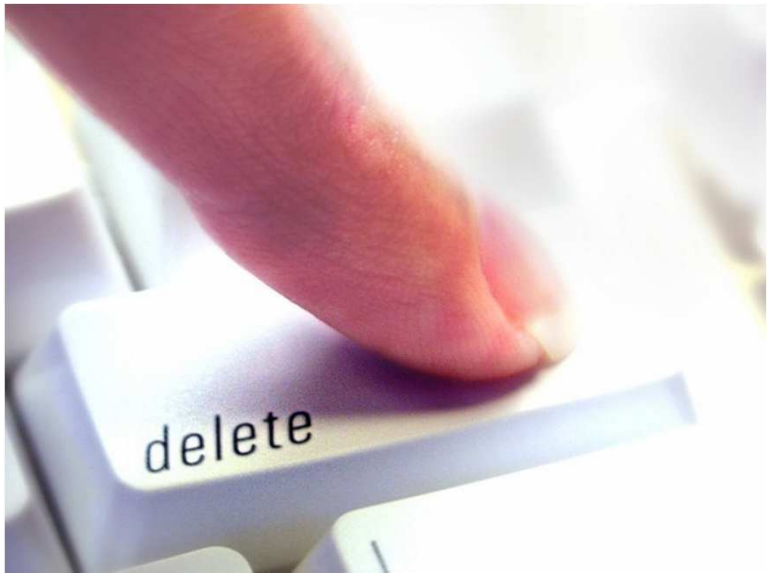
On stand-alone systems blocked access to the system clock and to time zones modification

AN EXAMPLE OF COMPLEXITY: SOFTWARE SYSTEMS

Are all the software equivalent from data integrity point of view?

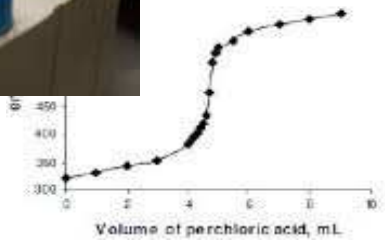
Also considering only the storage of the data

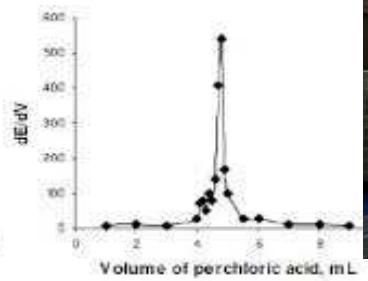
- Software that store the data on a database
- Software that store the data as single files (Windows based)



AN EXAMPLE OF COMPLEXITY: SOFTWARE SYSTEMS

Are all the suppliers aware of Data integrity topics?





Traditional CQ tecniques are more familiar with data integrity requirements

BUT

MANY DIFFICULTIES with equipments mainly dedicated to R&D purposes

Furthermore: in many cases an audit trail is present but…

… doesn't trace all the information…

… the information are present but it's difficult to find out where are stored…

REVISION OF THE AUDIT TRAIL DURING THE REVISION OF THE DATA RELATED TO EACH BATCH

Performed both on paper and on electronic data

Revision of the data: raw data, integration, calculation…

Reconciliation of analysis performed: how many analysis are expected on the batch? How many analysis have been performed?

Have the data been «altered» in some way? It seems a bad word but… have a mistyping in a description an high criticity level?

How many results have been generated from the raw data?

Average time: about 1,5 hours for each batch

Meaning that… in some cases (e.g. IR analysis) the time for the revision of the analysis and for the relevant audit trail is larger then the time spent for the analysis ifself

CONCLUSION

IMPACT ON QUALITY CONTROL LABORATORY ACTIVITIES

Huge effort to find out the best solution available to guarantee the data integrity

from the market

Cost for the purchasing of new softwares or new versions of existing software

Cost of resources to be dedicated

from a procedural point of view

Skills (especially good knowledge of softwares) required to all the personnel not only in QC lab but also in QA, IT…

Training to increment the consciousness of operators and supervisors

More complex data flows required (in terms of approval, revision, data storage)

Considering that

THANK YOU FOR THE ATTENTION!