Agenzia Italiana del Farmaco

AIFA

Case Study of Fraud
An Italian Experience and Following Actions

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The Beginning

- BE Application
- 2 studies
- During the assessment, some doubts were raised
- An Inspection was requested by the AIFA Office for Marketing Authorization

The 1st Inspection

- The inspection was announced just one week before, without mentioning the studies
- 5 days inspection

The 1st Inspection: Critical Findings

- Analysis of unknown samples were backdated (to 1 year back)
- Long Term Stability was not performed
- HPLC software without audit trail system
- Lack of source documents / lack of traceability (weighing of standards, stock solution preparation, preparation of calibration samples and QC samples…logbook…)
- Lack of temperature logs
- Lack of freezer logs
- …

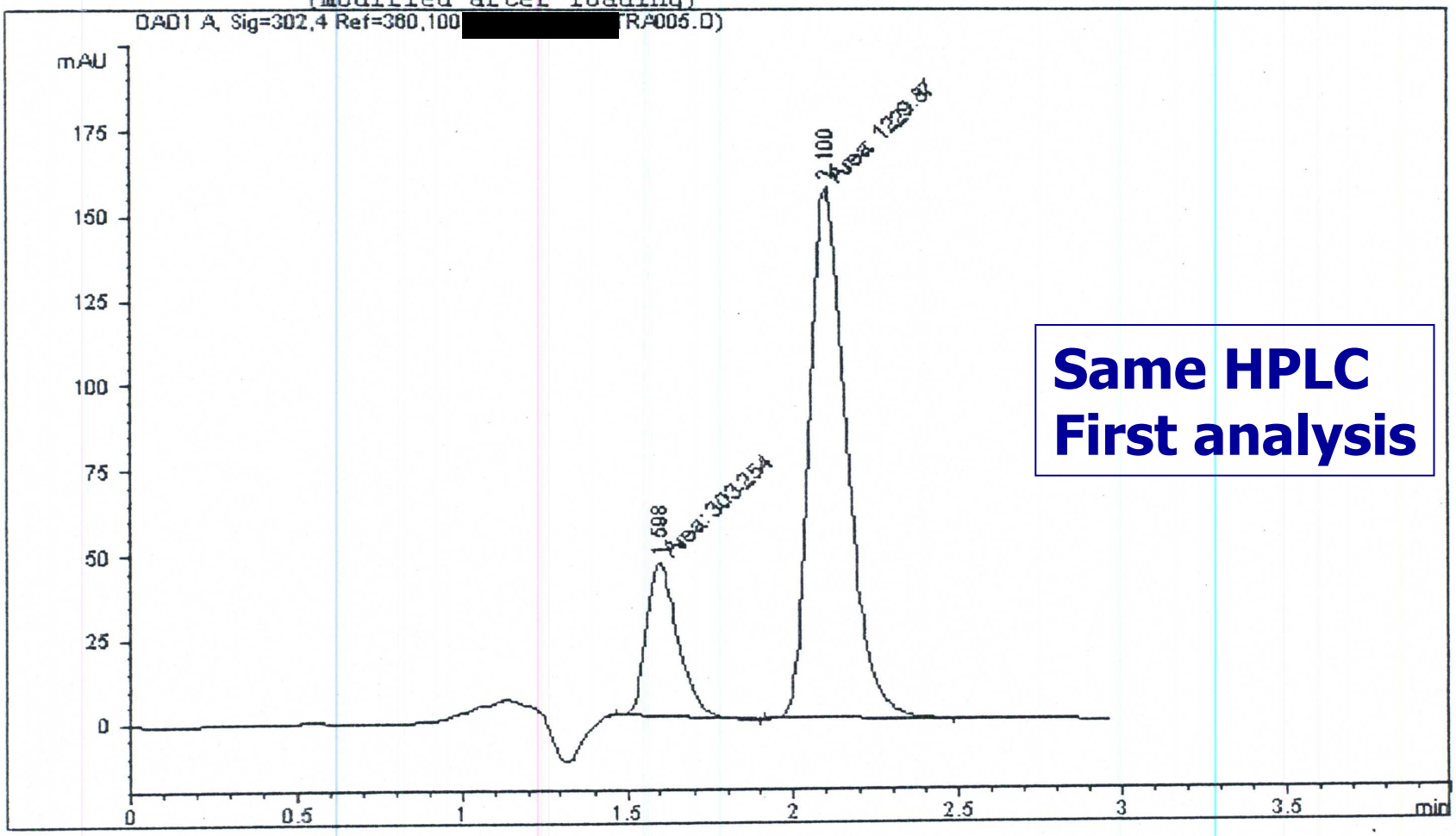
Data File C:\HPCHEM\1\DATA[redacted]NTRA005.D Sample Name: 200 ng/ml

Injection Date : 11/09/2006 16.29.47
Sample Name : 200 ng/ml
Acq. Operator : .

Acq. Method : C:\HPCHEM\1\METHODS[redacted]
Last changed : 11/09/2006 16.29.20 by .
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS[redacted]
Last changed : 11/09/2006 16.48.27 by .
(modified after loading)

Seq. Line : 6
Location : Vial 36
Inj : 1
Inj Volume : 10 µl

INTRA DAY
VECCHIA
VALIDAZIONE



Same HPLC
First analysis

CRONOLOGICA DELLA VECCHIA VALIDAZIONE

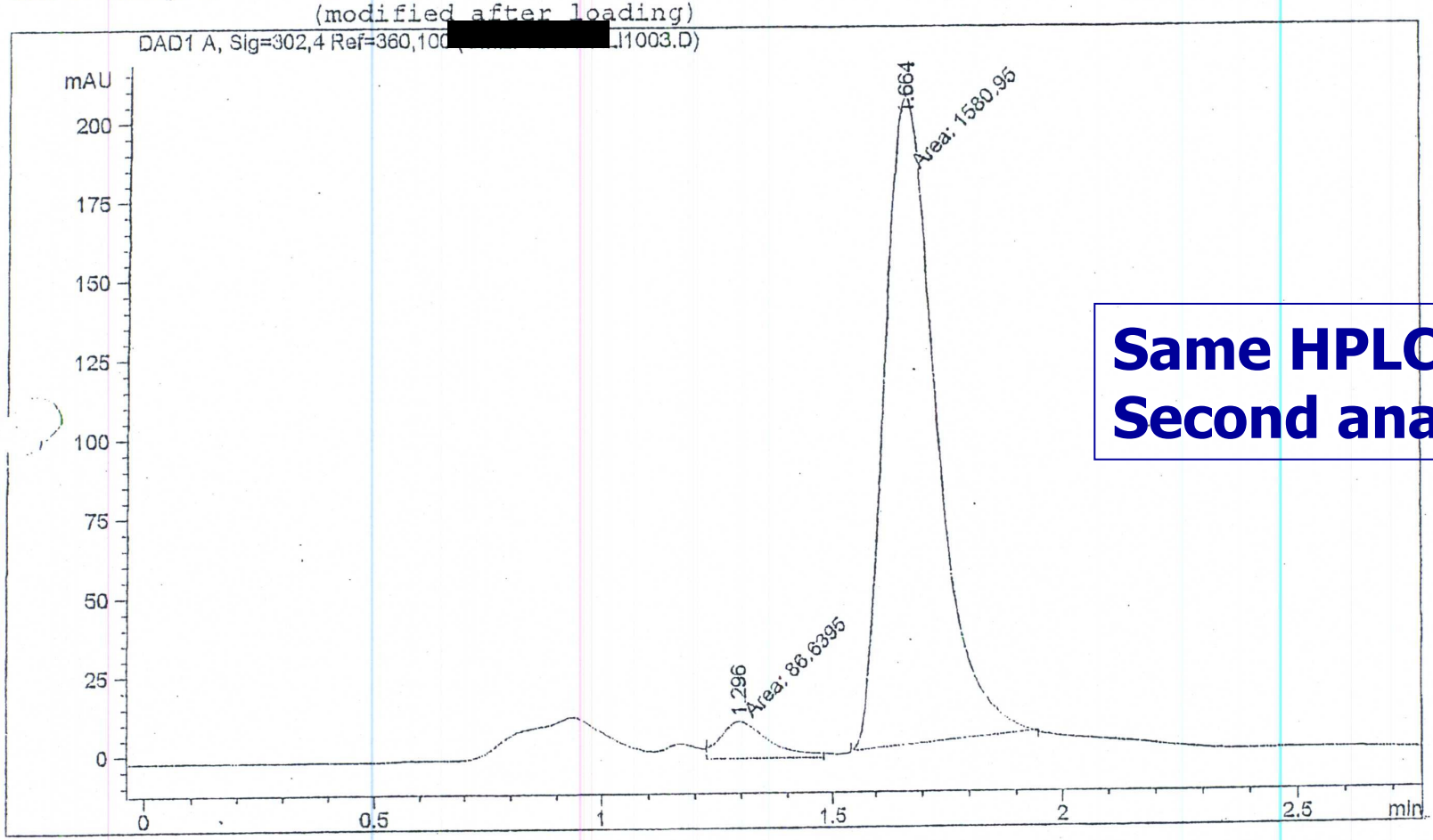
ata File C:\HPCHEM\1\DATA[redacted]ALI1003.D Sample Name: cal 50 ng/ml

Injection Date : 11/09/2006 16.29.38
Sample Name : cal 50 ng/ml
Operator :

Acq. Method : C:\HPCHEM\1\METHODS[redacted]
Last changed : 11/09/2006 16.28.23
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\STABOME1.M
Last changed : 12/09/2006 18.46.24
(modified after loading)

Seq. Line : 4
Location : Vial 4
Inj : 1
Inj Volume : 10 µl

CROMATOGRAMMA DELLA VALIDAZIONE RIPETUTA (NUOVA VALIDAZIONE)



Same HPLC
Second analysis

The 1st Inspection: Outcome

- Analysis backdated = Public Prosecutor
- MA = not granted
- Warning on the Lab!!!!

    1. Problems about other studies performed by the Lab (2004 – 2009)
    2. Problems about future studies

For Future Studies

Activities of the Lab have been stopped until suitable corrective actions would be implemented

1. Other Studies

The Italian Inspectorate was requested to inspect all studies of this Lab related to MA (granted or submitted)

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Type of Inspections

- Study Specific Inspection: strong results but time consuming…
- System Inspection: it is difficult to check system in the past; it is difficult to apply the results of system inspection on single studies in order to take regulatory decisions…

Inspection on Key (strong) Points – System inspection on specific studies

Key point to verify	Study xxx	Study yyy	Study zzz
Analysis backdated			
Monitoring on lab activities			
Audit on lab activities			
Software audit Trail			
Compliance with Guideline FDA on Method Validation			
Source documents on validation			
Source documents on unknown samples			
Long term stability demonstrated			
Temperature records & Freezer Logs			
Authorised manufacturer of IMP			
E-records of chromatograms			

Etc…

Inspection on Key (strong) Points – System inspection on specific studies

Key point to verify	Study xxx	Study yyy	Study zzz
Analysis backdated	NO	NO	NO
Monitoring on lab activities	NO	NO	NO
Audit on lab activities	NO	NO	NO
Software audit Trail	NO	NO	NO
Compliance with Guideline FDA on Method Validation	NO	YES	YES
Source documents on validation	NO	Incomplete	YES
Source documents on unknown samples	NO	Incomplete	YES
Long term stability demonstrated	NO	YES	YES
Temperature records & Freezer Logs	NO	Incomplete	YES
Authorised manufacturer of IMP	NO	YES	YES
E-records of chromatograms	NO	YES	YES

Inspection on Key (strong) Points – System inspection on specific studies

- Strong Points
  - Many studies could be inspected in a short time
  - Inspection conclusions can be used for regulatory decisions
- Weak Points
  - It works just in case of glaring critical findings
  - It allows to distinguish just situations like YES/NO
  - In case of uncertain feedback, a study specific inspection is required

THANK YOU