

Pharmacopoeial Reference Standards

Industry view point

Antony Raj Gomes
Head- Quality Management

Presentation Overview

- ❖ *Indian Industry – an update*
- ❖ *Available guidelines*
- ❖ *Industry practices*
- ❖ *Current challenges (Technical/Practical)*
- ❖ *Few case studies*
- ❖ *Regulatory positions*
- ❖ *Future trends*
- ❖ *Conclusions*

Indian Industry – an update

- *Fastest Growing Industry at 9% rate.*
- *4th Largest in the World- volume (after USA, Europe & Japan).*
- *Value of production at \$15 billion (2007).*
- *300 Large Scale & 10,000 Small & Medium Scale Units.*
- *Exports –from almost nil in 1960 to over \$ 4.0 billion.*
- *40% of the world's API requirement is met by India.*
- *Predominant play in the Generic space.*
- *CRAMS – catching up at a rapid speed.*
- *Highest number of FDA/EDQM Approved facilities outside respective regions.*
- *India itself is poised to become a large consumer.*

Available Guidelines

- *European Pharmacopoeia – 5.12 (Reference standards)*
- *USP general chapter <11>*
- *WHO TRS [Technical report series] 885 ANNEX 3 - CRS*
- *ISO guide 30 (terms and definitions)*
- *ISO guide 31 (certificates)*
- *ISO guide 34 (competence of producers)*
- *ISO guide 35 (statistical principles for certification)*
- *USFDA - Guideline for submitting samples and analytical data for methods validation*
- *EDQM - Content of the dossier for chemical purity and microbiological quality - PA/PH/ CEP (04) 1 4R*
- *Industry SOP's*

Definitions – WHO TRS 885 ANNEX 3

- **Primary chemical reference substance** : A designated primary chemical reference substance is one that is widely acknowledged to have the appropriate qualities within a specified context, and whose value is accepted without requiring comparison to another chemical substance.
- **Secondary chemical reference substance** : A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance. The extent of characterization and testing of a secondary chemical reference substance may be less than for a primary chemical reference substance. This definition may apply *inter alia* to some substances termed "working standards".

SUPPLY CHAIN, USER POINTS & CONCERNS



Pharmacopieal Bodies



Pharmacopieal Reference standards



In-House reference standards
(API/Impurity/System suitability mix)
Fully characterized



Cost saving
Larger volumes

Secondary Standards
Compared against PRS
Periodic re-evaluation
Lot change re-evaluation

Pharmacopieal Standards

System suitability Mixtures
Impurity standards
for one time analysis

Cost saving
Larger volumes

Secondary standards
(Prepared and evaluated on
periodic basis) May not require
full charectirisation

Propagated error
Extended uncertainty

Budget constraints
Customer requests

Propagated error
Extended uncertainty
Potency /Purity issue

Transportation
Issues

Generic
manufacturer

Transportation
Issues

Generic
manufacturer



Industry Practices

❖ In-house reference standards – Drug/impurities

- Developed and characterized by R&D/Analytical R&D.
- Identity (NMR, Mass, IR, elemental, chiral, polymorph).
- Purity (chromatographic, inorganic, volatiles, complimenting
- Orthogonal techniques – Mass balance approach).
- Storage and directions for use - determined.
- Validity period assignment.

As a start up point -> The “Joel Davis Rule”, a historical rule-of thumb can be used, -- acceptable results from 3-month stability testing of a drug product at 37– 40°C can be used to project a tentative expiry date of 2 years from the date of manufacture.

Stressing for one week at 70°C would be roughly the same as 588 days at 25C. [# Pharmaceutical Stress Testing: Predicting Drug Degradation, edited by Steven W. Baertschi]

Industry Practices

- ❖ **Working standards – Drugs/impurities/performance evaluation standards**
- **QC or Analytical R&D – defined SOP's in the industry**
- **Identity (comparison with RS/IRS).**
- **Potency (Assay against RS/IRS).**
- **Storage and directions for use – strategy.**
- **Validity period assignment – stability data , direction for use are considered.**
- **Revalidation - tracking with validity of RS.**
- **Multi pharmacopoeia products – stringent storage followed.**

Current technical challenges

- Availability of validated analytical methods at start point.
- Finding suitable orthogonal, non overlapping techniques.
- Assigning the shelf life at initial time point (forced degradation – thermal stress -Arrhenius relation).
- Differences in impurity profiles and solvents between lab scale and scale up.
- Mass value differences for impurities due to inorganic and volatile residues.
- Response factor – validity – Variations among different lots (0.8 to 1.2. considered as 1.0? But not by all !!).

Current technical challenges

- Polymorphic/ chiral standards and contamination issues with other possible forms.
- Limitations in available analytical techniques for structural confirmation and spectral match.
- Possible differences in solubility profiles leading to variation in response/recovery.
- Handling and reproducibility of residues, semi solids and liquids.
- Transportation and purity variance issues during tech transfers
- Assigning validity period for impurities – no stability data

Current practical challenges

- Handling and weighing of minute quantities in micro grams.
- Storage of reference standards at the authorized dealer point – is there a need for the user to verify??.
- Single time usage vials filled with quantities for multiple use (wastage)
- Retrieval of small quantities, liquids in ampoules
- ISO Guide 34 – 5.6.4 - responsibility of Mfg'r to ensure integrity till seal is broken – impact of this on repeated use for qualifying secondary standards.
- ISO Guide 34 – 4.7 Client feed back – how does one keep !!

Few Case Studies

❖ Compound D

Chiral analysis : 95% pure (s) – (-) α -methylbenzyl isocyanate [Chiral selective reagent] yields 1.3% of chiral impurity A. Whereas 98% purity reagent yields 0.3%. (Monograph needs strengthening)

❖ Compound S

In method B. Out of the 5 peaks that are needed to be identified using the syst.suit CRS mixture, impurity E is to be identified by its higher response related to other impurities. Though monograph simply says C18 column, it has been observed that some brands do produce lesser response for impurity E and leading to misinterpretation. (monograph strategy is not fully foolproof !!)

Few Case Studies

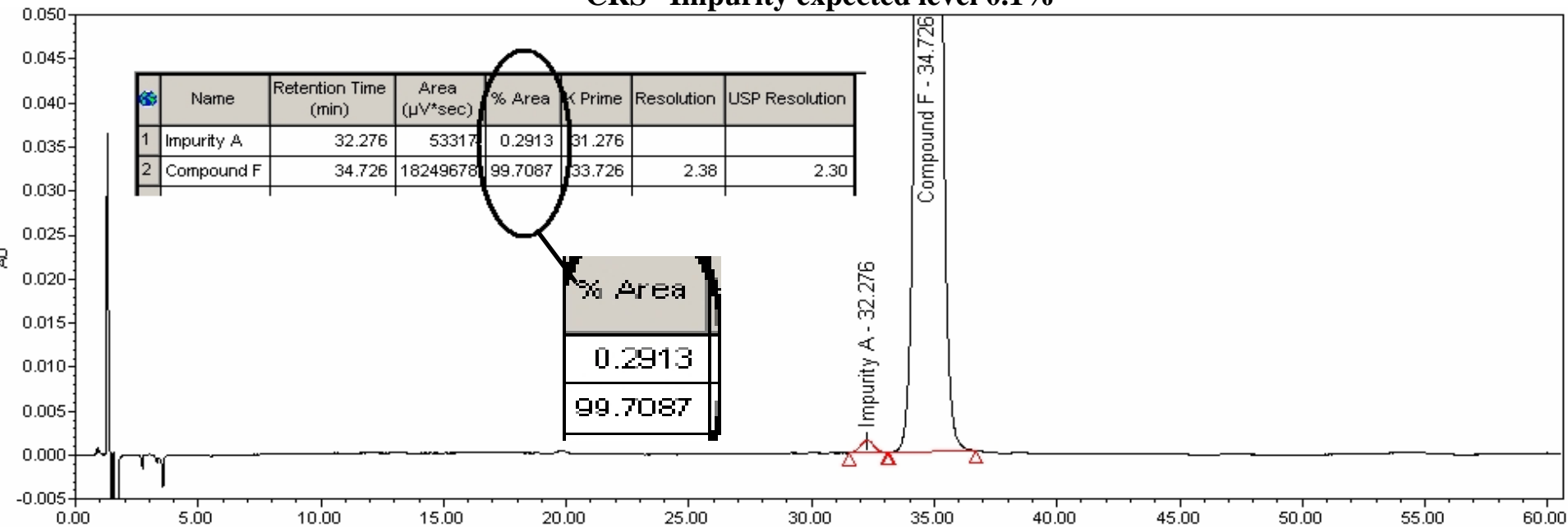
❖ Compound F

The sys.suit reference material spiked with known qty of impurity and sample analysis is in reference to this. It was observed that sample analysis showed less impurity. Investigation revealed that while preparing sys.suit ref.mat, laboratory has spiked qty of impurity without accounting for the amount of impurity already present in the drug.

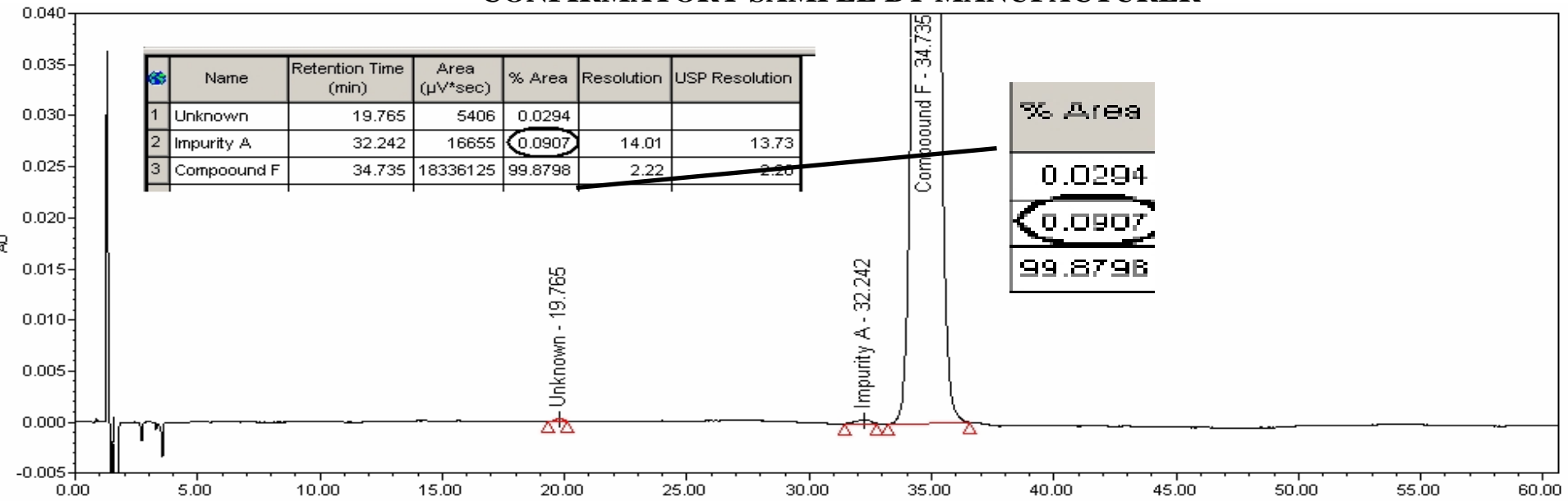
- protocol inadequacy
- test design – not captured critical aspects
- approval process - gaps

Compound F

CRS Impurity expected level 0.1%



CONFIRMATORY SAMPLE BY MANUFACTURER



Few Case Studies

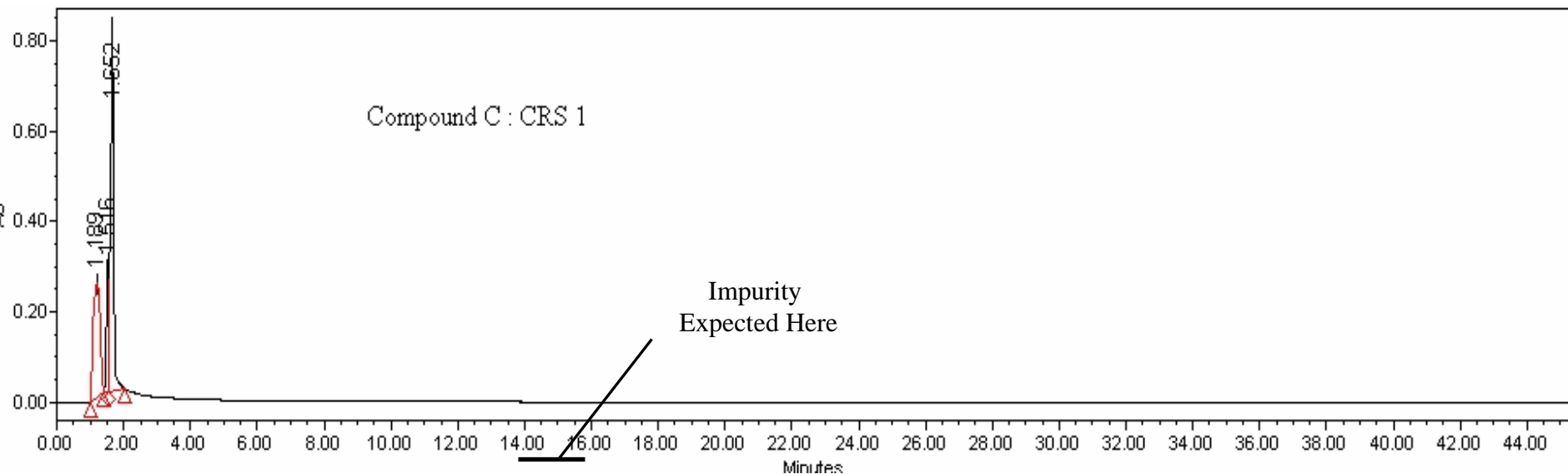
❖ Impurity – G of Compound T

The Ref Std supplied by one of the pharmacopoeia was meant for TLC id test and when the same was used for in-house drug product test for impurity, the retention time wasn't the same as expected. Other pharmacopoeia standard yielded correct retention time.

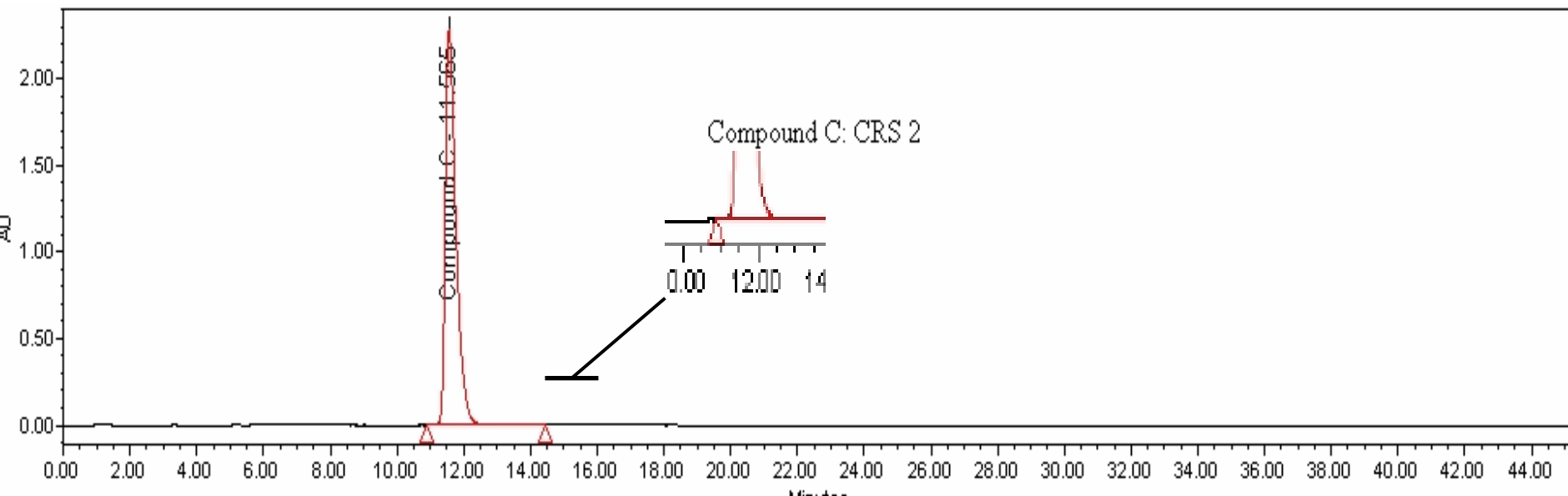
- may be a case of mislabeling
- possible case of approval based on R_f in TLC
- possible gap in lot approval process
- may be a case of degradation

RT of Impurity G (Actual RT/RRT as per monograph : RT12 / RRT 0.9)

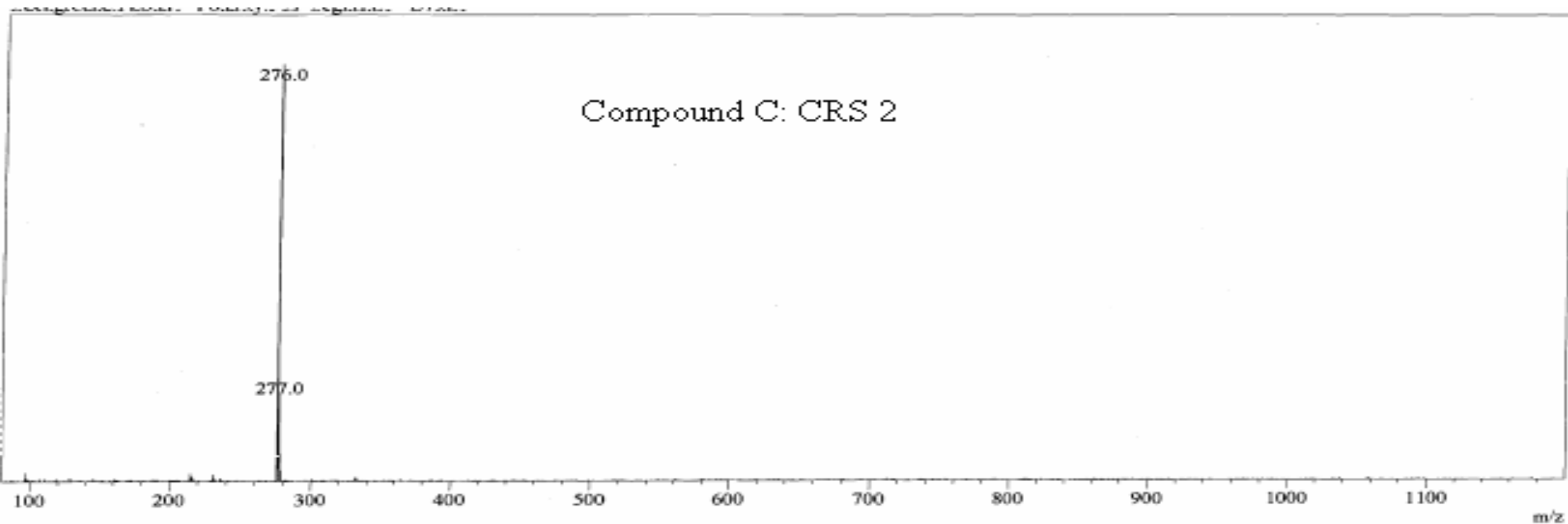
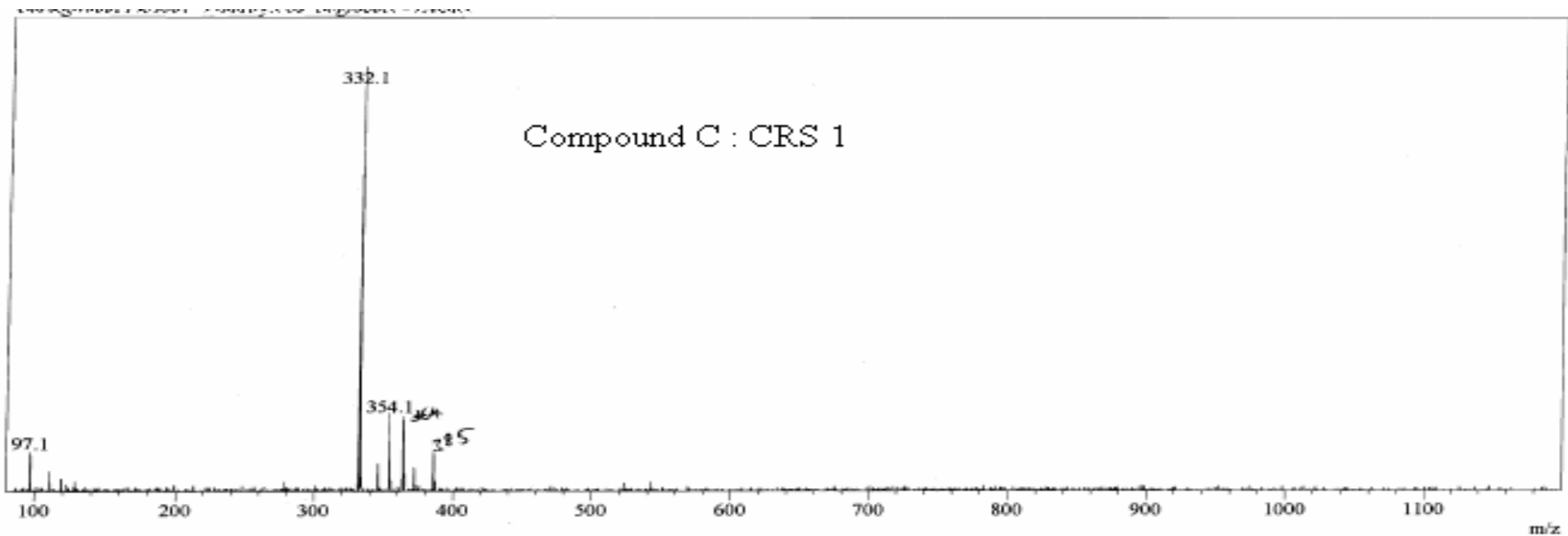
RS by one Pharmacopoeia



RS by other Pharmacopoeia



LC Mass spectra comparison of impurity G



Few Case Studies

❖ Compound M

The monograph specified melting range was not met by a new supplier material. When the RS was tested, that too failed!!. Investigation revealed that the monograph limits were set based on natural extracts having lower purity compared to the new source and the RS, that are derived synthetically – hence high pure and higher melting (RS evaluation did not consider relevancy of certain monograph test)

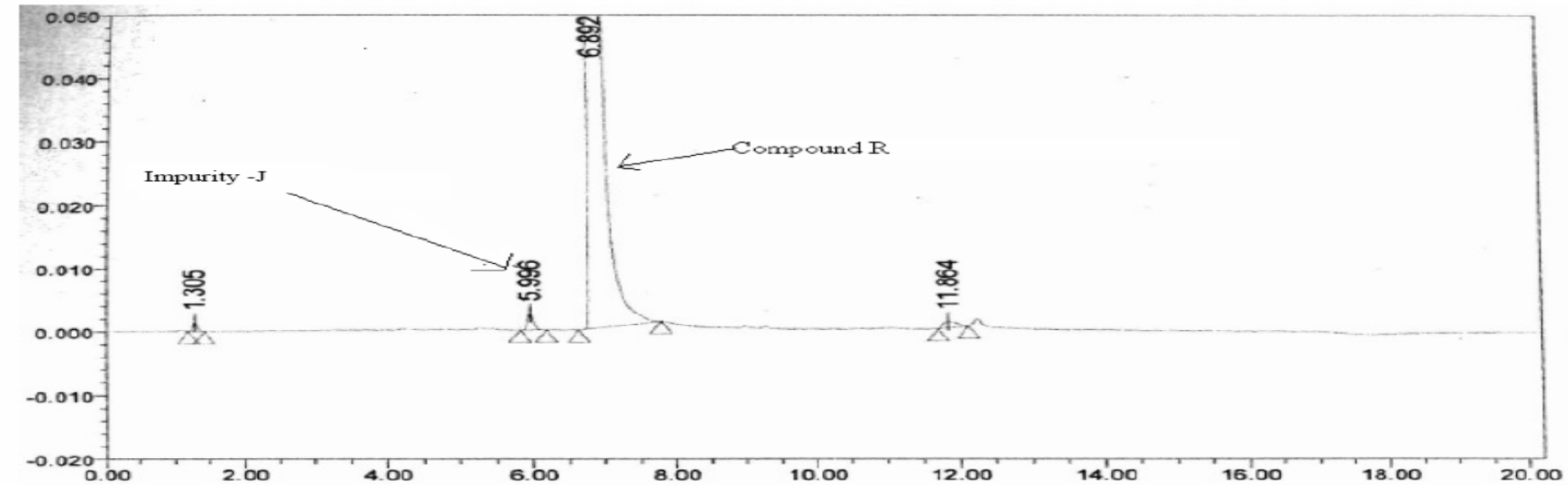
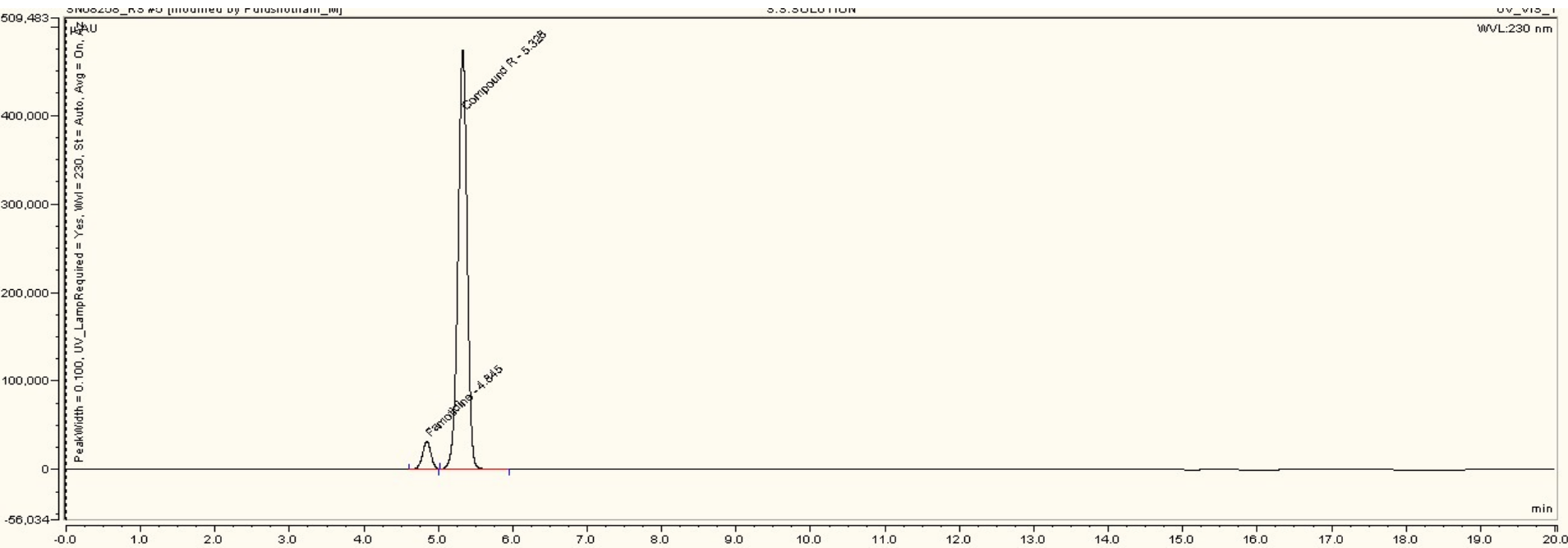
- missed co-relation between monograph & RS
- protocol design
- cant avoid industry using RS as a test conformance tool

Few Case Studies

❖ Compound R

The monograph requires impurity J for syst.suit of HPLC. Being extremely expensive and scarcely available, Famotidine was chosen as an alternate as it elutes at the same RT as that of impurity j. Laboratory smartly used for its in-house method for product monograph

- ✓ Save efforts on isolation of impurity
- ✓ Cost saving
- ✓ Ensures availability



Regulatory Views

❖ EDQM

- ❖ Content of the dossier for chemical purity and microbiological quality - PA/PH/ CEP (04) 1 4R - February 2007
- When in-house standards/working standards, non-official or official standards other than the appropriate Ph. Eur. CRS are employed, they have to be suitably described (in terms of identification, purity, assay, etc) and their establishment has to be demonstrated. If other standards are used instead of their respective Ph. Eur. CRS an appropriate comparison to the Ph. Eur. CRS is required.
- ❖ The TOP TEN deficiencies found in CEP applications (PA/PH/Exp. CEP/T (06) 35 - April to July 2006).
- Placed at Top 8 (3.2.S.5): Characterization of the reference standard (29% of the dossiers) not in comparison with the Ph.Eur CRS.

Regulatory Views

❖ FDA

- **QbR Frequently Asked Questions - 2.3.S.5 Reference Standards [Released June 2007]**
- **How were the primary reference standards certified?**
- **For non-compendial, in-house reference standards, what type of qualification data is recommended? Will a COA be sufficient?**
- **COA should be included in Module 3, along with details of its preparation, qualification and characterization. This should be summarized in the QOS.**
- **It is expected that these reference standards be of the highest possible purity fully characterised**

Regulatory Views

❖ Health Canada [GMP Q and A on Health Canada Site]

Q. What is the Inspectorate's position on the use of secondary reference standards and what are the conditions for the use of secondary reference standards?

A. While the Inspectorate recommends the use of the official standards for the analysis of compendia articles, the use of a secondary RS is acceptable if each lot's suitability is determined prior to use by comparison against the current official reference standard and each lot is re-qualified periodically in accordance with a written protocol. The protocol should clearly address the receipt, storage, handling and use of primary reference standards, the purification of secondary standards, and their qualification against official reference standards.

Regulatory Views

❖ Health Canada [GMP Q and A on Health Canada Site]

- Q. Is it acceptable to use a third party lab's available pharmacopoeial reference standard to qualify an establishment's secondary standard?**
- A. This practice is acceptable providing the contract testing lab has an Establishment License (EL) and has been audited by the client to demonstrate its capability to qualify the secondary standard (ie. the official standard and the proper equipment is available on the tester's premises, the method used has been validated, etc.). Transfer of the standard between the sites should be under controlled conditions.**

Future Trends

- ❖ **Certified Reference Materials (USP) – the usage of metrology.**
- ❖ **Multi method monograph (USP initiative)- strategy for suitability /specific impurity markers (labeled for the test??).**
- ❖ **Industry and regulatory understanding of assigned uncertainty in case of CRM's – revision of general chapter, internal SOP's , regulatory guidelines ?!!**
- ❖ **Performance verification standards – tests and technique.**
- ❖ **Closer interlinking of monograph instructions and RS design (especially syst.suit applications).**
- ❖ **Polymorphic impurity standards.**
- ❖ **Genotoxic impurity standards.**

Future Trends

- ❖ Improved analytical capabilities for assigning true potency
- ❖ Harmonization among USP / EP / BP / JP on common molecules (storage and direction for use at least)
- ❖ Orthogonal testing for potency confirmation.
- ❖ Defining scientific storage conditions – lesser temperatures may not be better in all cases.
- ❖ Cold chain integrity proof – data loggers -for critical items ??!
- ❖ Standards beyond monographs
- ❖ Elution order based identification RS mixtures – monograph strategy for column selectivity ?!
- ❖ Enhanced industry participation on collaborative testing ?!

Conclusions

- ❖ RS characterization gets more and more complex due to various elements – need to look for analytical solutions beyond monograph
- ❖ Secondary standard – though an economical option - not always provide the same assurance of a primary standard- Appropriate evaluation measures to be in-built in the process
- ❖ Next level of compliance – stability based validity for impurities, cold chain adherence at all time for critical items, etc
- ❖ Industry needs guidelines that reflect solutions for current challenges and provides insight on future possibilities.
- ❖ Harmonization – at least to an extent that is beneficial to the industry
- ❖ Greater industry participation !!



Thank You !

antonyrg@shasun.com
antonyrajgomes@rediffmail.com

Phone : +91 9600989166