Quality Assurance in Chemotherapy

Contribution of HPTLC to a hospital manufacturing unit

METHOD & RESULTS

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Quality Assurance and Pharmacotechnical-Pharmacochemical Activity

- post-production manufacturing control
  - -chemotherapy
  - -morphinic analgesic
- raw material control
- manufacturing and post-production assay
- analgesic drugs assay
- microbiological control of working places

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Chemotherapy post-production control Functionnal Unit

- p27'000 chemotherapy productions in 2002
- 100% of these productions are sampled, from which 96,3% is analysed
- 1 pharmacist, 1 technician, 1 resident medical student
- 1 HPTLC automated system, HPLC/UV systems

HPTLC Analytical system

Samplers ATS III

- 60 applications/plate
- 100 à 5000 nL
- N_2 Gas

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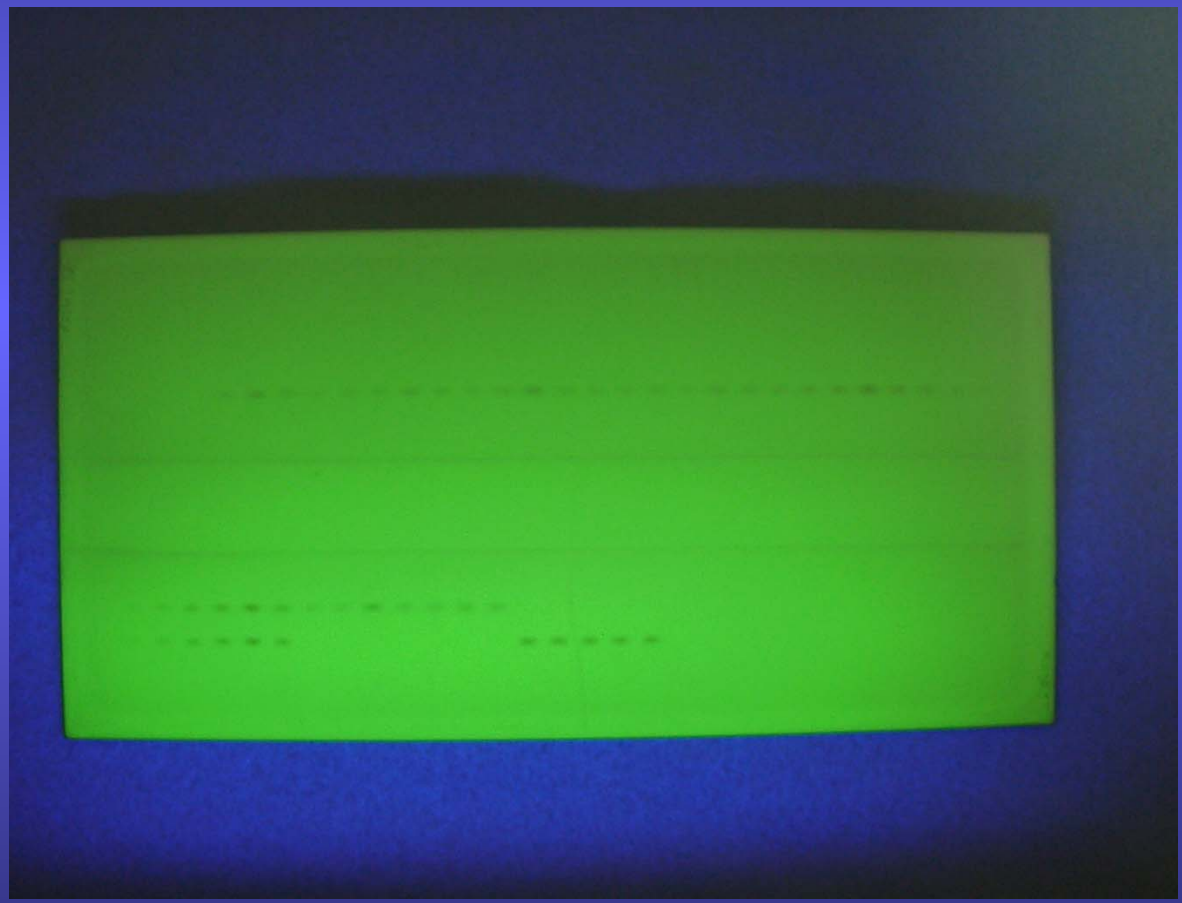
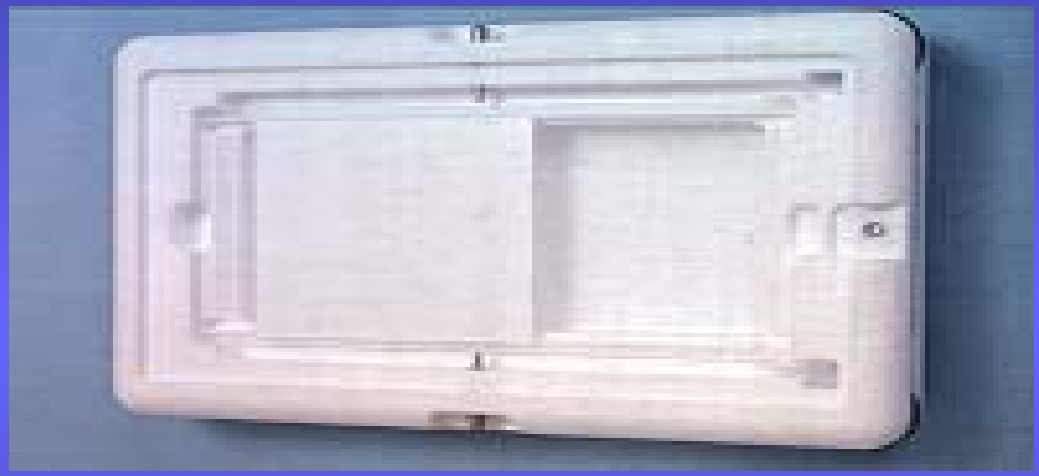
HPTLC Analytical system

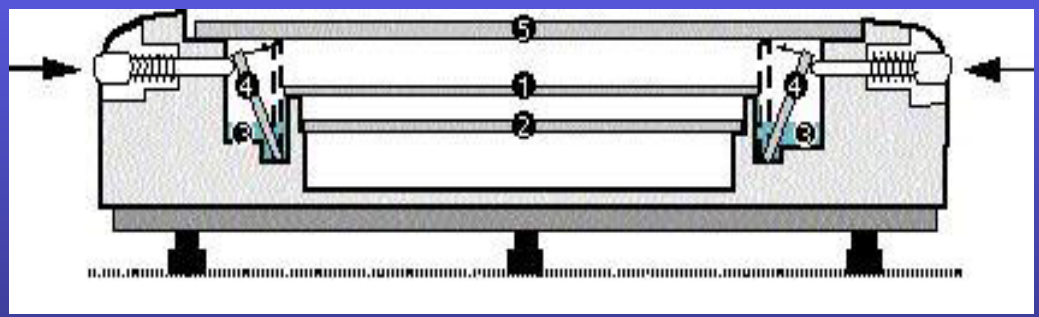


Stationary Phases

– silica Si60
– modified silica
–10 X 20 cm plate
– Ø part. 2 à 10 µm
– 200 µm layers

HPTLC Analytical system





Cuve de migration horizontale

– 4 cuves en PTFE

– mode de migration

-saturation de vapeur

-sandwich

HPTLC Analytical system

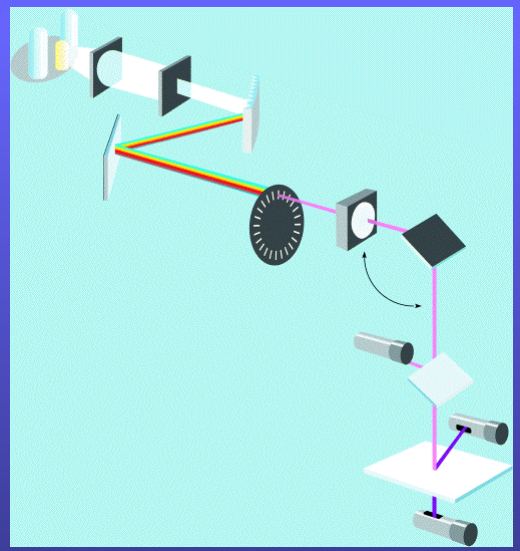
Densitomètre
(Scanner3 CAMAG)

lecture entre 190 et 800 nm

-deuterium

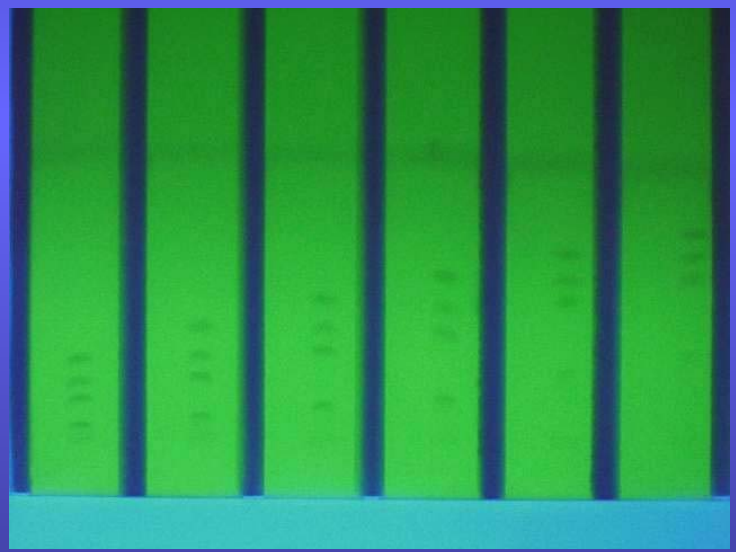
-mercure

-tungstène



Analytical method development

HPTLC-Vario ® Module



Set up

Mobile phases trials:

- Organic Solvents
- Basic and Acidic solutions, water

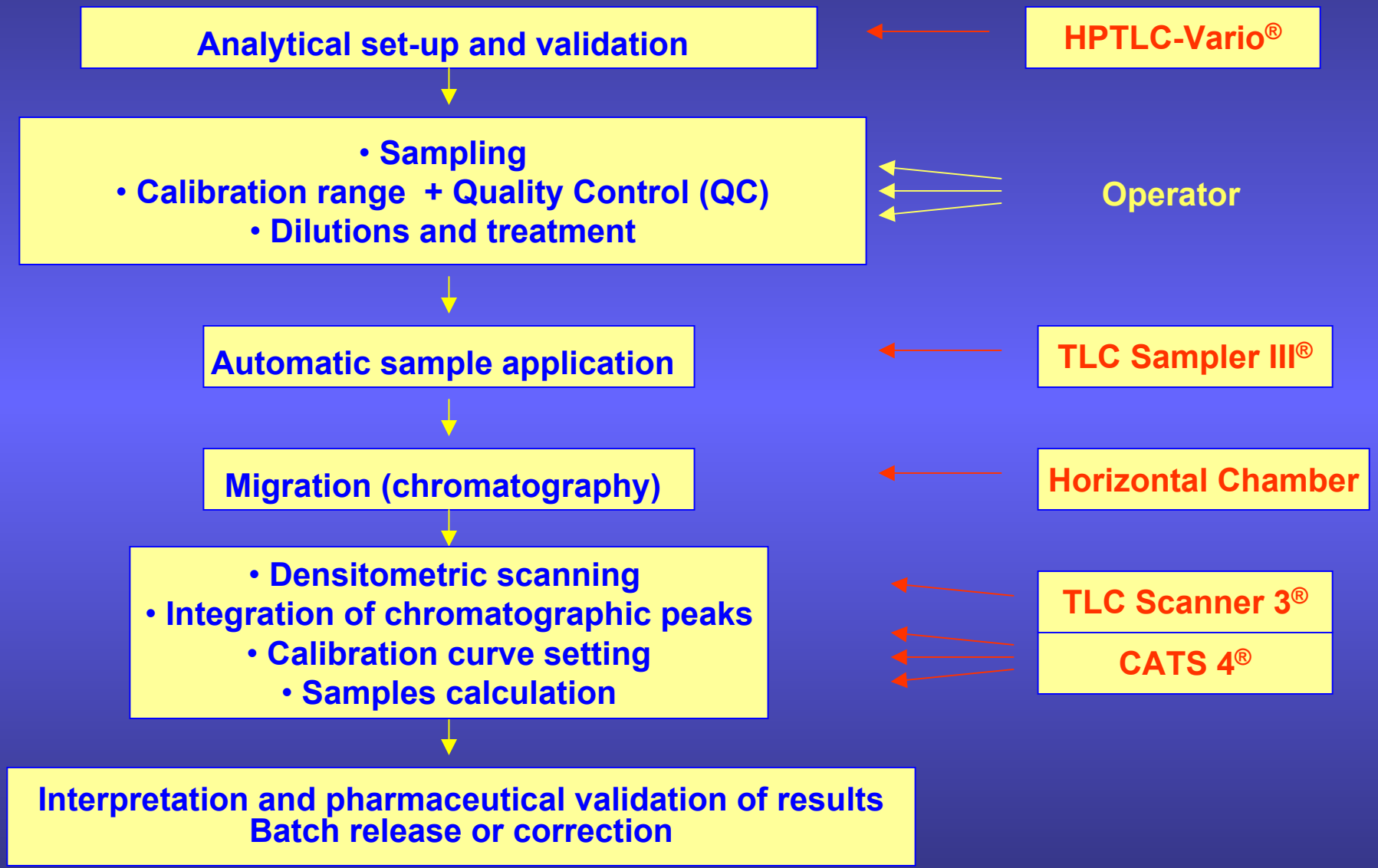
Densitometric Scanning Optimization

- Research of the UV absorbance maximum
- Compromise for two compounds

Validation

- modelisation study (Lin./Michaëlis-Menten)
- intermediate reliability study
- repetability study

HPTLC Analytical flow chart



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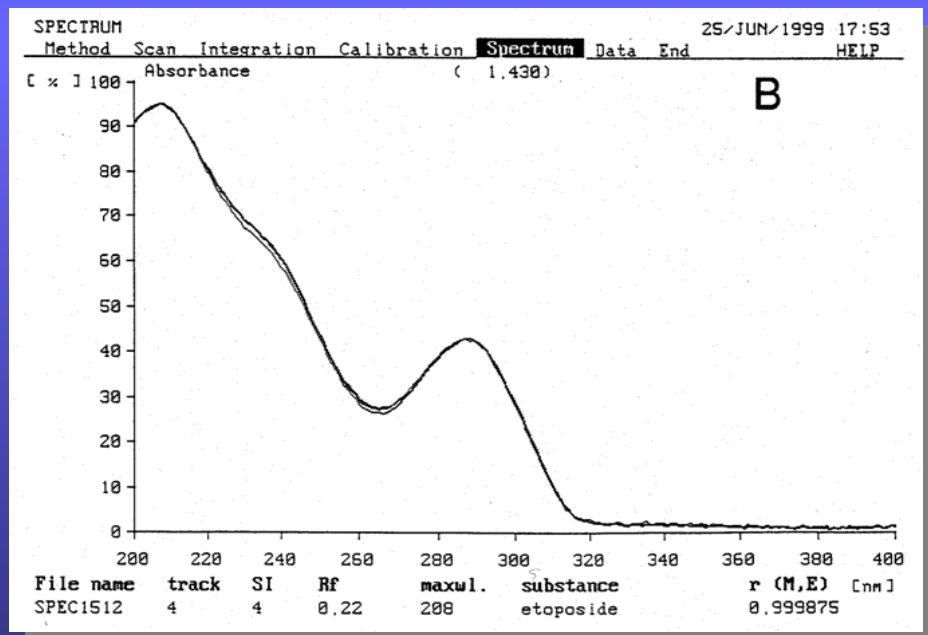
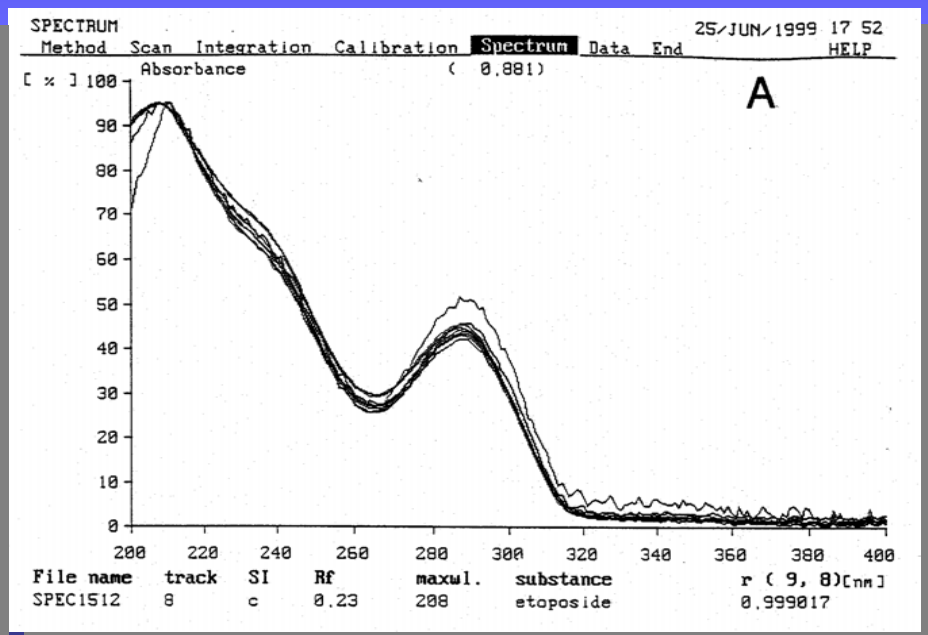
HPTLC Qualitative analysis

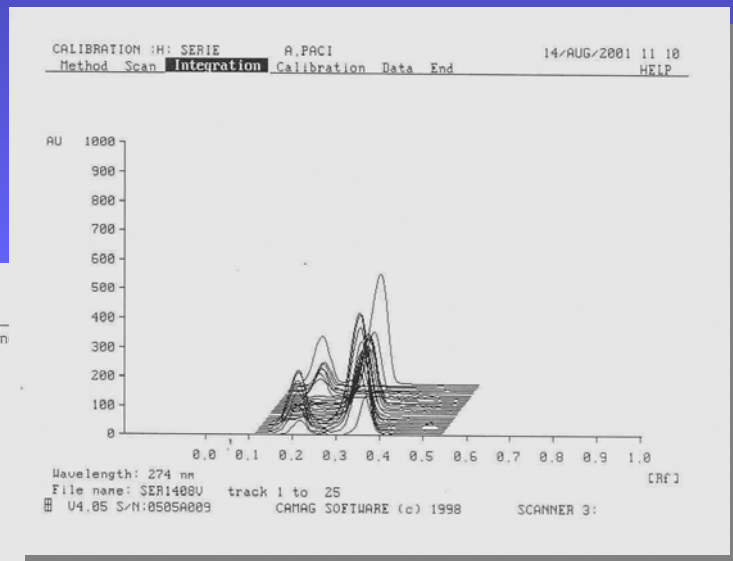
- **Identification : correlation factor calculation between sample and a reference molecule, for identity proving**
- **Purity criteria with UV spectra**
- **spectrum and absorption *maxima determination***

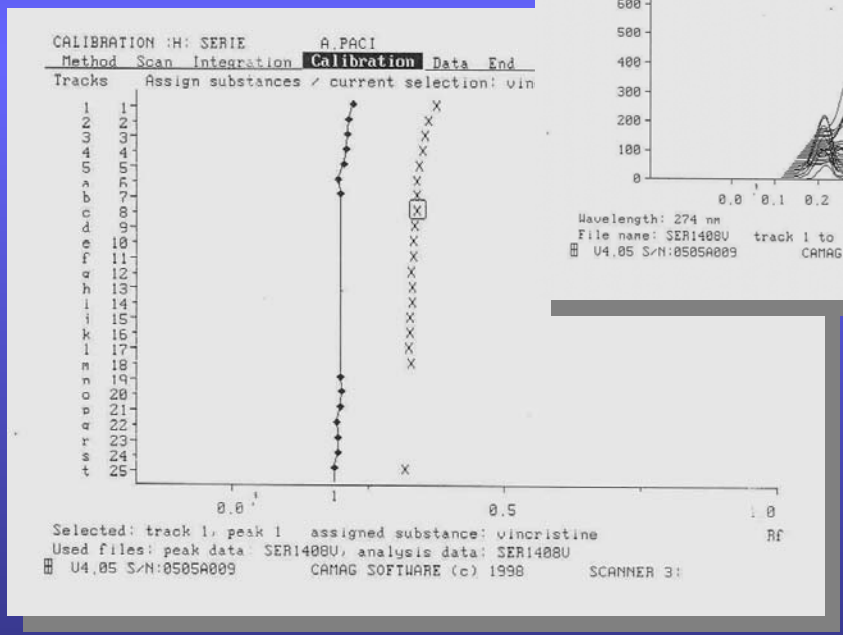


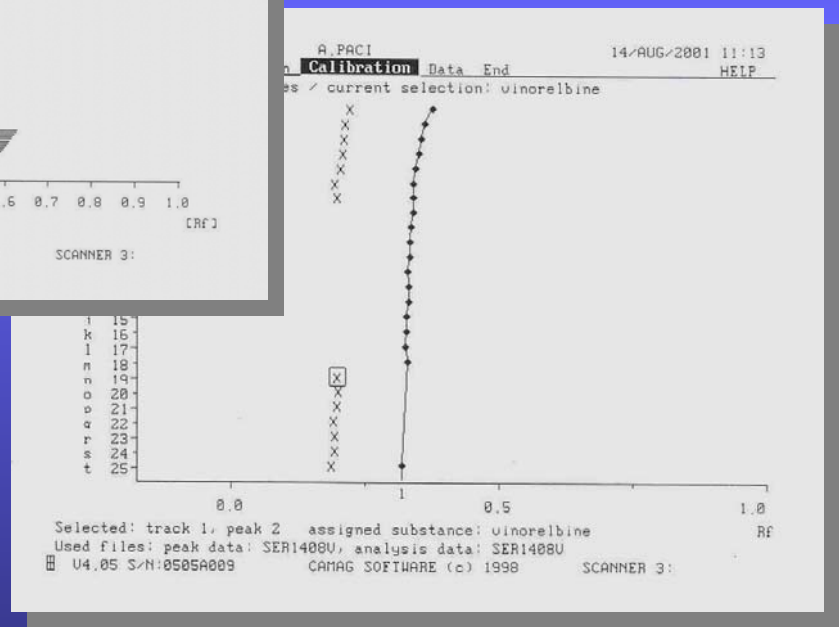


HPTLC Qualitative analysis

Rf checking







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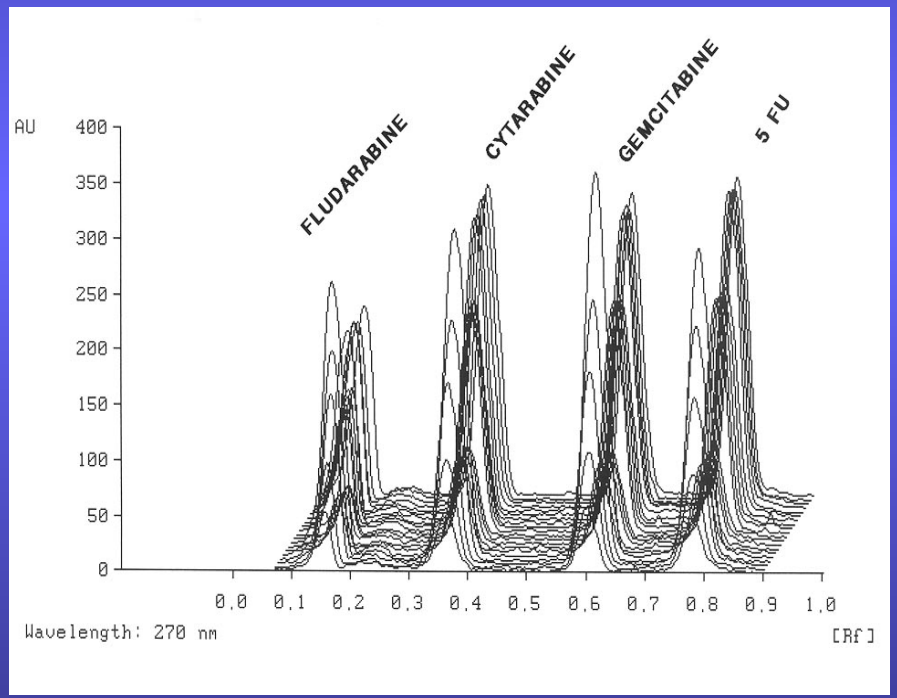
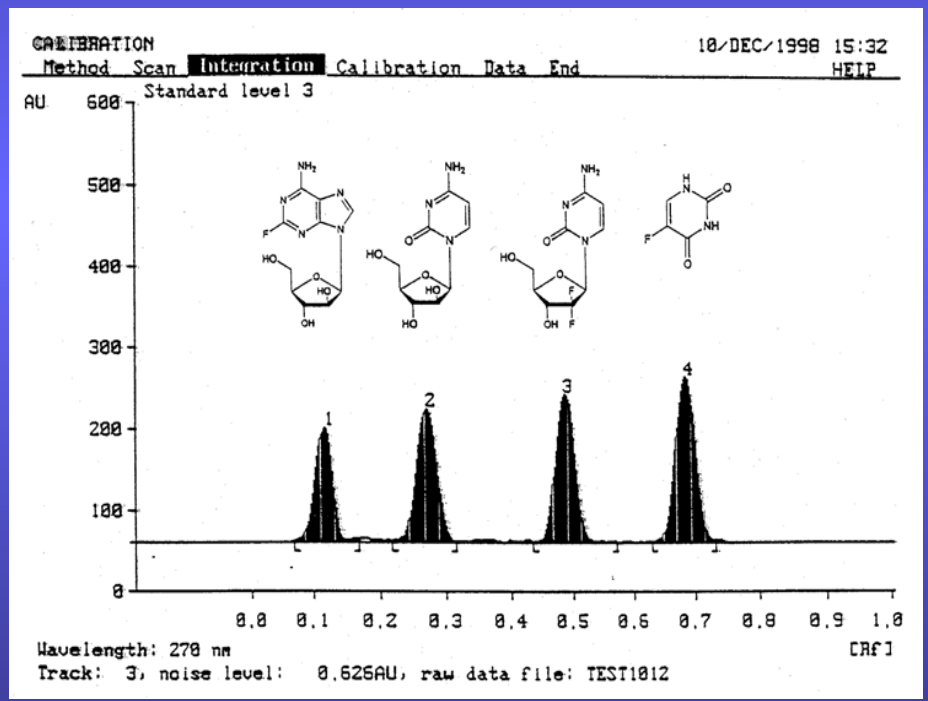
HPTLC Quantitative analysis

Cytotoxics identification and assay





Exemple with the nucleotidic 4-bases

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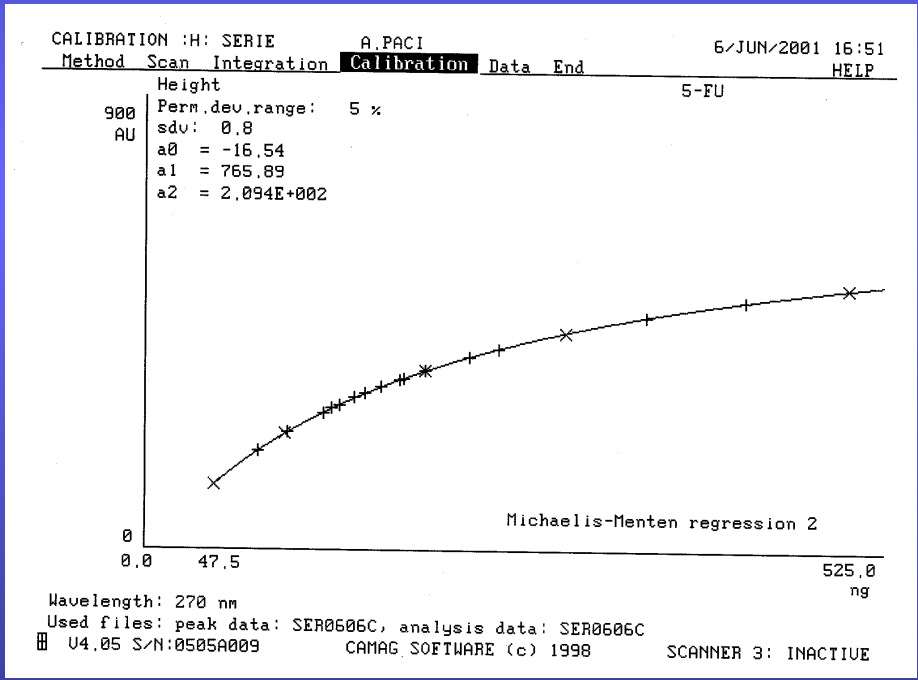
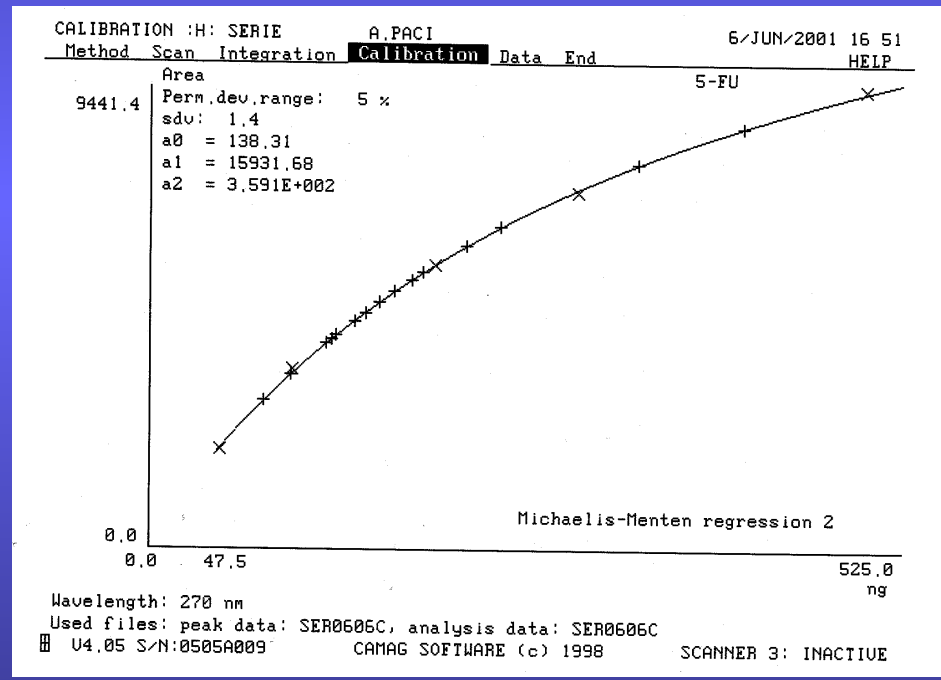
HPTLC Quantitative analysis

Cytotoxics identification and assay





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HPTLC Routine analysis

- Anthracyclines : Daunorubicine, Doxorubicine, Epirubicine, Idarubicine
- Anti-metabolites : 5-Fluorouracile, Gemcitabine, Cytarabine, Fludarabine, Methotrexate
- Epipodophyllotoxine : Etoposide
- Taxanes : Paclitaxel, Docetaxel
- Camptothécine : Irinotecan
- Vinca-alcaloïdes : Vincristine, Vinorelbine, Vinblastine, Vindésine
- Oxazaphosphorines : Cyclophosphamide, Ifosfamide
- Platinium derivatives: Cisplatine, Carboplatine
- Others : Melphalan, Mitoxantrone, Busulfan
- Opioïdes : Morphine, Pethidine

HPLC Routine analysis

- Cytotoxics : Oxaliplatine (5 %Glucose)

  ThioTEPA, Dacarbazine, Carmustine et Fotémustine

- Opioïdes : Fentanyl, Sufentanil

HPTLC Method data

(table of some content of the method development results)

Molecule	wv in nm	staining	LOQ in ng/spot (1st std)	HRf	mobile phase composition
Fludarabine	270	no	100	15	CH3OH/H2O/CH3COOC2H5 (60:60:300)
Cytarabine	270	no	50	28	CH3OH/H2O/CH3COOC2H5 (60:60:300)
Gemcitabine	270	no	50	49	CH3OH/H2O/CH3COOC2H5 (60:60:300)
Fluorouracil	270	no	50	69	CH3OH/H2O/CH3COOC2H5 (60:60:300)
Etoposide	290	no	100	20	CH3OH/CH2CL2/(C2H5)2O (2:45:53)
Cisplatin	485	*para*-nitrosodimethylalanine	50	90	CH3COCH3/H2O (90:10)
Methotrexate	370	no	20	65	HCL(0.001N)/CHCL3/CH3OH (16:34:50)

HPTLC advantages and limits

Advantages :

- Analysis of numerous samples (2x25/plate) → Cost
- Analysis of samples simultaneously → Stability study
- Speed set-up + automatisation → Emergency & cost
- Qualitative et quantitative analysis → Conformity

Limits :

- Repetability (5 à 10 %) → Technician's experience
- Matrix (Glucose 5 %) → Dilution/sensitivity
- Staining repetability → Quantification ± 10%
- Low sensitivity but adaptated to manufacturing concentration

Non-conformity studies on the 1er semestre 2003

1er sem. 2003	FAB.	%CQ	1ère analyse			2ème analyse			CONFORMITES		
			Total	C	A Vérifier	Non Conf.	C	Non Vérif*	CONF	NC	NV
4-EPI	360	93	336	317	19	2	333	1	99,1%	0,6%	0,3%
5-FU	3289	76	2484	2348	136	25	2455	4	98,8%	1,0%	0,2%
ARA-C	658	66	437	410	27	13	423	1	96,8%	3,0%	0,2%
CBDCA	614	51	316	298	18	4	311	1	98,4%	1,3%	0,3%
CDDP	1680	69	1155	1058	97	18	1135	2	98,3%	1,6%	0,2%
CPM	660	85	564	507	57	18	541	5	95,9%	3,2%	0,9%
CPT11	88	91	80	79	1	1	79	0	98,8%	1,3%	0,0%
DFDC	187	107	200	194	6	1	199	0	99,5%	0,5%	0,0%
DNR	42	102	43	42	1	0	43	0	100,0%	0,0%	0,0%
DXR	726	90	657	594	63	24	628	5	95,6%	3,7%	0,8%
FDR	22	191	42	41	1	1	41	0	97,6%	2,4%	0,0%
IDA	20	90	18	18	0	0	18	0	100,0%	0,0%	0,0%
IFM	1094	78	852	802	50	10	842	0	98,8%	1,2%	0,0%
LOHP	232	106	246	213	33	11	235	0	95,5%	4,5%	0,0%
MPH	56	113	63	48	15	2	61	0	96,8%	3,2%	0,0%
MTX	407	90	365	317	48	33	332	0	91,0%	9,0%	0,0%
NVT	32	116	37	37	0	0	37	0	100,0%	0,0%	0,0%
TXL	152	88	133	121	12	4	129	0	97,0%	3,0%	0,0%
TXT	46	117	54	50	4	1	53	0	98,1%	1,9%	0,0%
VCR	284	64	183	162	21	7	175	1	95,6%	3,8%	0,5%
VDS	34	85	29	28	1	0	29	0	100,0%	0,0%	0,0%
VLB	90	93	84	72	12	3	81	0	96,4%	3,6%	0,0%
VNB	176	85	149	134	15	1	148	0	99,3%	0,7%	0,0%
VP16	1384	89	1229	1185	44	8	1213	8	98,7%	0,7%	0,7%
DTIC	98	67	66	51	15	0	66	0	100,0%	0,0%	0,0%
TTP	43	37	16	16	0	0	16	0	100,0%	0,0%	0,0%
BCNU	18	0	0	0	0	0	0	0	#DIV/0!	#DIV/0!	#DIV/0!
FTM	16	0	0	0	0	0	0	0	#DIV/0!	#DIV/0!	#DIV/0!
TOTAL	12474	79	9838	9142	696	187	9623	28	97,8%	1,9%	0,3%
				92,9%	7,1%						

Prod T	12960		Dégradés	25	0,3%
Prod ND	486	3,8%	Etiquetage	0	0,0%
Prod D	12474	96,3%	Tube vide	8	0,1%

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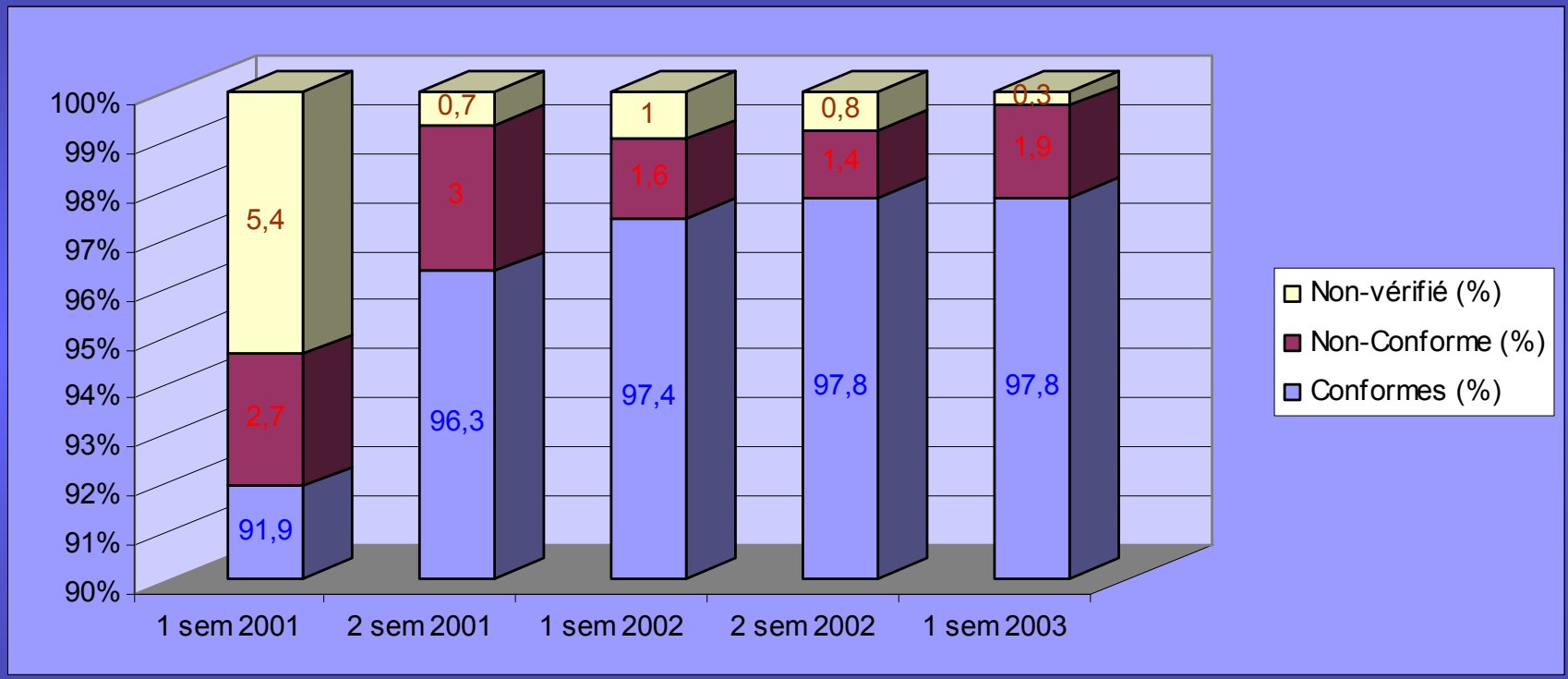
Non-conformity studies on the 1er semestre 2003



IMPACT

Validation of manufacturing process :

- Mixture homogeneity → MTX, TXL et TXT
- Validation of the waste → QAS for Manufacturing FU

Employees motivation :

- Follow up daily, monthly, semesterly
- Education of permanent and non-permanent teams
- Errors fighting (despite QAS)
- Target definition

Some figures as conclusion

- Time (sampling – pharmaceutical validation) : 1 à 2 heures
- 1 500 to 2 000 analysis/month
- 29 cytotoxics et 4 analgesics opioïdes assayed in routine
- 76 % of the manufacturing are analysed

- Non-conformity analysis of the chimiotherapies
  - 1er semester 2003 : 12 960 manufacturings
    - 9 838 analysis (76 %)
    - 97,8 % conforms
    - 1,9 % non-conforms
    - 0,3 % non verified (degradation, …)

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In the 'Departement de Pharmacie Clinique' of the 'Institut Gustave Roussy', HPTLC is giving these impressive results… and is also helping to save the life of young people fighting against cancer !

Thank you for listening.

October 17, 2003