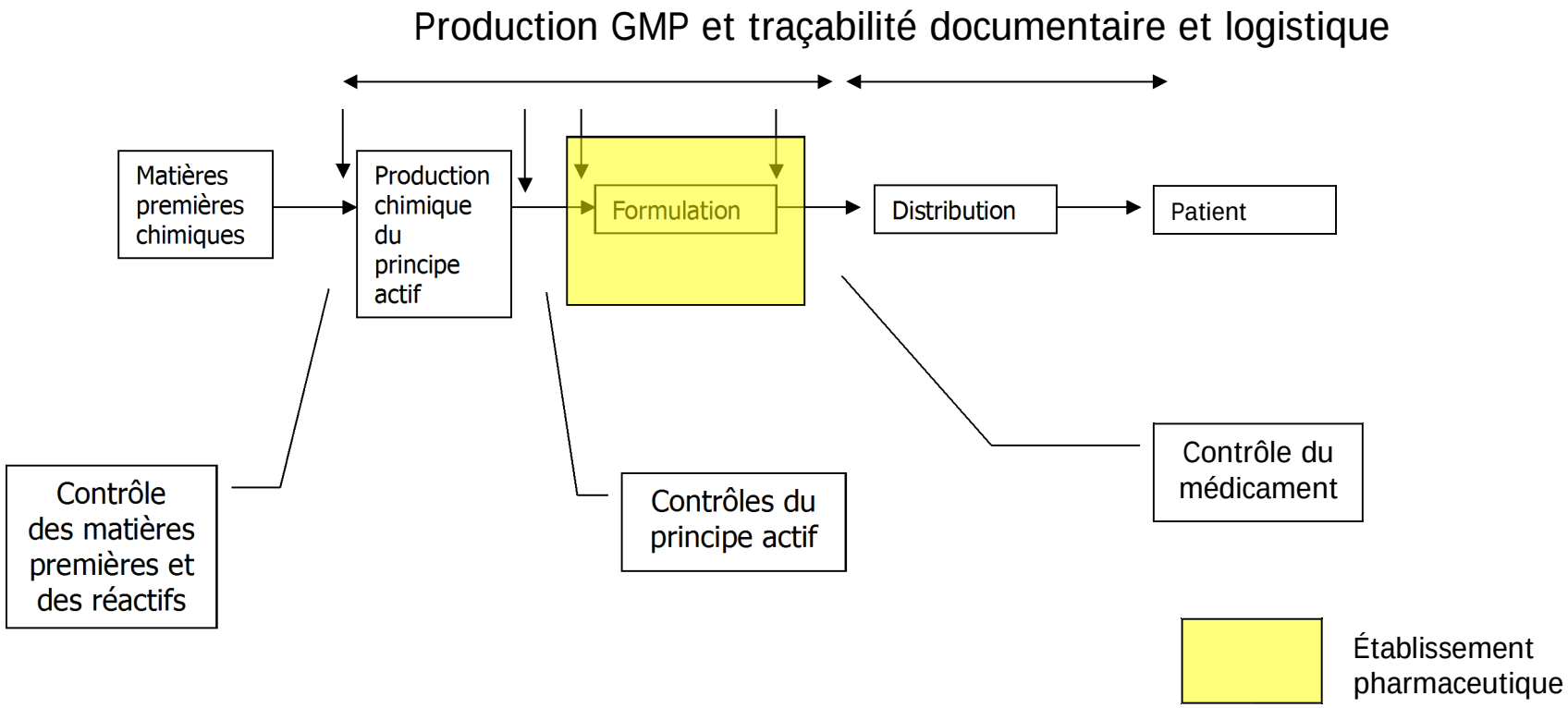
Chimie Pharmaceutique 4

Contrôle de la fabrication d'un médicament



Libération du principe actif pharma avant utilisation dans l'usine pharmaceutique

- **Conformité aux spécifications**
  - Méthodes analytiques valides
  - Fixation des spécifications au vu des textes réglementaires

- **Production du principe actif selon les BPF (GMP)**
  - "Quality is in the process"
  - Référence aux "guidelines" dans le texte ICHQ7a
    - Au moins une étape chimique et une purification en BPF
    - Étapes chimiques déterminantes pour le profil d'impuretés

Spécifications des produits en essais cliniques phase I

- **Cas BNC tartrate**
  - identification – 1H NMR, HPLC
  - assay by HPLC 95-100%
  - related substances total <2% individuals NMT 0.5%
  - tartrate assay (by nmr or hplc assay)
  - residual solvents (GC)
  - moisture (KF ?)
  - Pd spec (ICH limit) and/or heavy metals assay (ICH limit)

Spécifications des produits en essais cliniques phase I

Cas des produits SXXX

Tests / Valeurs cibles	SXXX	SYYY
Caractères		
Aspect	Poudre sensiblement blanche à beige	Poudre sensiblement blanche à beige
Identification		
Spectre de masse	En accord avec la structure de la molécule	En accord avec la structure de la molécule
Spectre RMN ^{1}H	En accord avec la structure de la molécule	En accord avec la structure de la molécule

Essais		
- Pouvoir rotatoire spécifique ou angle de rotation optique	-	Pour information
- Point de fusion (DSC)	*°C à *°C	*°C à *°C
- Teneur en eau	≤ 1.0 %	≤ 1.0 %
- Cendres sulfuriques	≤ 0.20 %	≤ 0.20 %
- Métaux lourds	≤ 20 ppm	≤ 20 ppm
- Palladium	≤ 5 ppm	≤ 5 ppm
- Cuivre	≤ 15 ppm	-
- Solvants résiduels (par CPG)		
Tétrahydrofurane (THF)	≤ 720 ppm	≤ 720 ppm
Méthyltétrahydrofurane (MeTHF)	≤ 1000 ppm	-
Acétate d'isopropyle (AcOiPr)	≤ 5000 ppm	≤ 5000 ppm
Triéthylamine (Et_3N)	≤ 1000 ppm	≤ 1000 ppm
Pyridine	≤ 200 ppm	-
Toluène	-	≤ 890 ppm
Méthylcyclohexane	-	≤ 1180 ppm
Ethanol	-	≤ 5000 ppm
Méthanol	-	≤ 3000 ppm
Acétonitrile	-	≤ 410 ppm
N,N Diméthylformamide (DMF)	-	≤ 880 ppm
- Total solvants résiduels	Pour information	Pour information
- Substances apparentées (par CLHP, en % *m /m*)		
Impureté	≤ 2.0 % chacune	≤ 2.0 % chacune
Total impuretés	≤ 5.0 %	≤ 5.0 %

- Pureté énantiomérique (CLHP chirale)	-	≥ 98 %
<u>Pureté calculée</u>		
% *m/m* de SLVxxx/SLVyyy dans le produit tel quel (100 - Σ impuretés - Σ solvants résiduels - teneur en eau)	≥ 90.0 %	≥ 90.0 %
<u>Essais complémentaires</u>		
Etat cristallin (Rayons X)	Pour information	Pour information

Référence aux ICH : www.ich.org

- International Conference on Harmonization
  - The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.
  - The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.
  - The objective of such harmonization is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

ICH Guidelines

- The ICH Topics are divided into four major categories and ICH Topic Codes are assigned according to these categories.
- **Q**
- *"Quality" Topics*, i.e., those relating to chemical and pharmaceutical Quality Assurance. Examples: Q1 Stability Testing, Q3 Impurity Testing
- **S**
- *"Safety" Topics*, i.e., those relating to in vitro and in vivo pre-clinical studies. Examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing
- **E**
- *"Efficacy" Topics*, i.e., those relating to clinical studies in human subject. Examples: E4 Dose Response Studies, Carcinogenicity Testing, E6 Good Clinical Practices. (Note Clinical Safety Data Management is also classified as an "Efficacy" topic - E2)
- **M**
- "Multidisciplinary" Topics, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories.
  - M1: Medical Terminology (MedDRA)
  - M2: Electronic Standards for Transmission of Regulatory Information (ESTRI)
  - M3: Timing of Pre-clinical Studies in Relation to Clinical Trials
  - M4: The Common Technical Document (CTD)
  - M5: Data Elements and Standards for Drug Dictionaries

Quality guidelines

- **New Codification as per November 2005**

- **Stability**
- **Q1A(R2)** **Stability Testing of New Drug Substances and Products**
- **Q1B** **Stability Testing : Photostability Testing of New Drug Substances and Products**
- **Q1C** **Stability Testing for New Dosage Forms**
- **Q1D** **Bracketing and Matrixing**
  Designs for Stability Testing of New Drug Substances and Products
- **Q1E** **Evaluation of Stability Data**
- **Q1F** **Stability Data Package for Registration Applications in Climatic Zones III and IV**

- **Analytical Validation**
- **Q2(R1)** New title: Validation of Analytical Procedures: Text and MethodologyPreviously: Text on Validation of Analytical Procedures*Q2A* Validation of Analytical Procedures: Methodology

- **Impurities**
- **Q3A(R2)** **Impurities in New Drug Substances**
- **Q3B(R2)** **Impurities in New Drug Products**
- **Q3C(R3)** **Impurities: Guideline for Residual Solvents**

Quality guidelines

- **Pharmacopoeias**
- **Q4** Pharmacopoeias
- **Q4A** Pharmacopoeial Harmonisation
- **Q4B** Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC)

Quality of Biotechnological Products

- **Q5A(R1)**
  Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- **Q5B**
  Quality of Biotechnological Products : Analysis of the Expression Construct in Cells Used for Production of r-
- **Q5C** Quality of Biotechnological Products : Stability Testing of Biotechnological/Biological Products
- **Q5D** Derivation and Characterisation
  of Cell Substrates Used for Production of Biotechnological/Biological Products
- **Q5E**
  Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

Specifications

- **Q6A**
  Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: (
- **Q6B**
  Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

- **Good Manufacturing Practice**
- **Q7** Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

Pharmaceutical Development

- **Q8** Pharmaceutical Development

Quality Risk Management

- **Q9** Quality Risk Management

Validation des méthodes analytique

- Démonstration statistique
  - Spécificité
  - Limite de quantification
  - Limite de détection
  - Linéarité (5 points)
  - Fidélité : répétabilité et fidélité intermédiaire : étudiée sur l'intervalle de mesure sur des solutions essais dopées : 3 fois 9 points minimum c'est-à-dire 3 x 3 points x 3 techniciens/appareils
  - Exactitude : étudiée sur les données de fidélité par calcul des recouvrements puis expression du recouvrement moyen et de l'intervalle de confiance associé (risque 5 %)
  - Stabilité de la solution

Principes actifs commerciaux

- Forme définitive des spécifications selon ICH dans le dossier d'AMM (ou NDA)
- Monographie selon une pharmacopée (minimum requis) pour les médicaments générique. En Europe, la PE (Pharmacopée Européenne) éditée par l'EDQM à Strasbourg.
  - Mais toujours respecter les ICH !!!

Tests requis pour un principe actif

- Aspect (forme, couleur)
- Identification (IR +)
- Titre (HPLC)
- Impuretés (HPLC) et sommes des impuretés
- Solvant résiduels (GC headspace)
- Teneur en eau (KF, LOD)
- Métaux lourds
- Répartition granulométrique (laser)
- Autres tests appropriés : quantification d'une impureté métallique (ICP), forme cristalline (RX), quantification d'un sel, cendres sulfuriques

大邦（湖南）生物制药有限公司
ARGUS PHARMACEUTICALS, LTD.

Certificate of Analysis

Orlistat
(Bulk Material)

Batch No:	20100110	**Quantity:**	25kg
M.F. Date:	Feb 1, 2010	**Test Date:**	Feb 3, 2010
Retest Date:	Jan 31, 2012		
Standard	Enterprise standard		

Storage: in well closed container at temperature below 30°C

Item	**Results**	**Specifications**
Description	White crystalline powder	White to off-white crystalline powder
Identification	HPLC retention time	HPLC retention time
HPLC	Conforms with the reference	Conforms with the reference
IR	Conforms	Conforms
Melting Point	43~44°C	42-45°C
Specific Optical Rotation	-36.4°	-31.0°- -41.0°
Purity	98.4%	NLT 98.0%
Max. individual impurity	0.4%	NMT 0.5%
Total impurity	1.6%	NMT 2.0%
Water content%(K&F)	Less than 0.1%	NMT 0.5%
Residual solvents	EtOH: Not detected EtOAc: Not detected n-Heptane: Less than 0.1%	EtOH: NMT 0.5% EtOAc: NMT 0.5% n-Heptane: NMT 0.5%
Residue on ignition	Less than 0.1%	NMT 0.2%
Heavy Metals as Pb	Less than 20ppm	NMT 20ppm
Assay by HPLC (Orlistat)	98.4%	NLT 98.0% on anhydrous basis

Conclusion: The results conform with the specification

QC Chemist

QA Chemist

Approved by Manager of QA/QC

ARGUS PHARMACEUTICALS, LTD. QC RELEASE

ARGUS PHARMACEUTICALS, LTD. QA APPROVAL

This document is approved and is electronically released without personal signature.

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HUASHU PHARMACEUTICAL CORPORATION

NO.29, GAOYING STREET, SHIJIAZHUANG, P.R.CHINA
TEL:++86 311 85612265 FAX: ++86 311 85618454

CERTIFICATE OF ANALYSIS

PRODUCT:OXYTETRACYCLINE HCL		RECORD NO.: 090403	
BATCH NO.: 09080300	NET WEIGHT: 25KG/DRUM	MANUFACTURING DATE:	AUG.18,2009
QUANTITY:1000KGS	NO.OF PACKAGE:40DRUM	ANALYSING DATE:	AUG.19,2009
ACCORDING TO: BP2007/EP6TH		EXPIRY DATE:	AUG.18,2013

TEST	SPECIFICATION	RESULTS
1. Characters	Yellow crystalline powder, hygroscopic, freely soluble in water. Solution in water become to Turbid on standing, owing to the precipitation of oxytetracycline.	Complies
2. Identification	a) TLC results b) Color reaction with sulfuric acid c) Color reaction with silver nitrate	Positive Positive Positive
3. PH	2.3 to 2.9	2.50
4. Specific optical rotation	-188° to -200°	-188.0°
5. Specific absorbance at 353nm	270 to 290	271.0
6. Light-absorbing impurities	a) At 430nm ≤ 0.50; b) At 490nm ≤ 0.20.	0.40 0.14
7. Related substances	a)4-Epioxytetracycline: ≤ 0.5% b)Tetracycline hydrochloride: ≤2.0% c)Total mixture of α,β-Apo-oxytetracycline:≤2.0% d)Peak on the tail of the main peak: ≤2.0%	0.3% 1.5% 1.5% 1.7%
8. Sulphated ash	≤0.5%	0.07%
9. Water	≤2.0%	1.70%
10. Heavy metals	≤50ppm	Complies
11. Assay	Between 95.0% and 102.0% based on anhydrous substance	96.2%
12. Methanol	≤0.3%	0.3%

Storage: Store in airtight container, protected from light.

CONCLUSION: THIS PRODUCT FULFILS BP2007/ EP6TH.

APPROVED BY:

Mrs. Yan Guixia
Chief Manager of
Quality Control Department

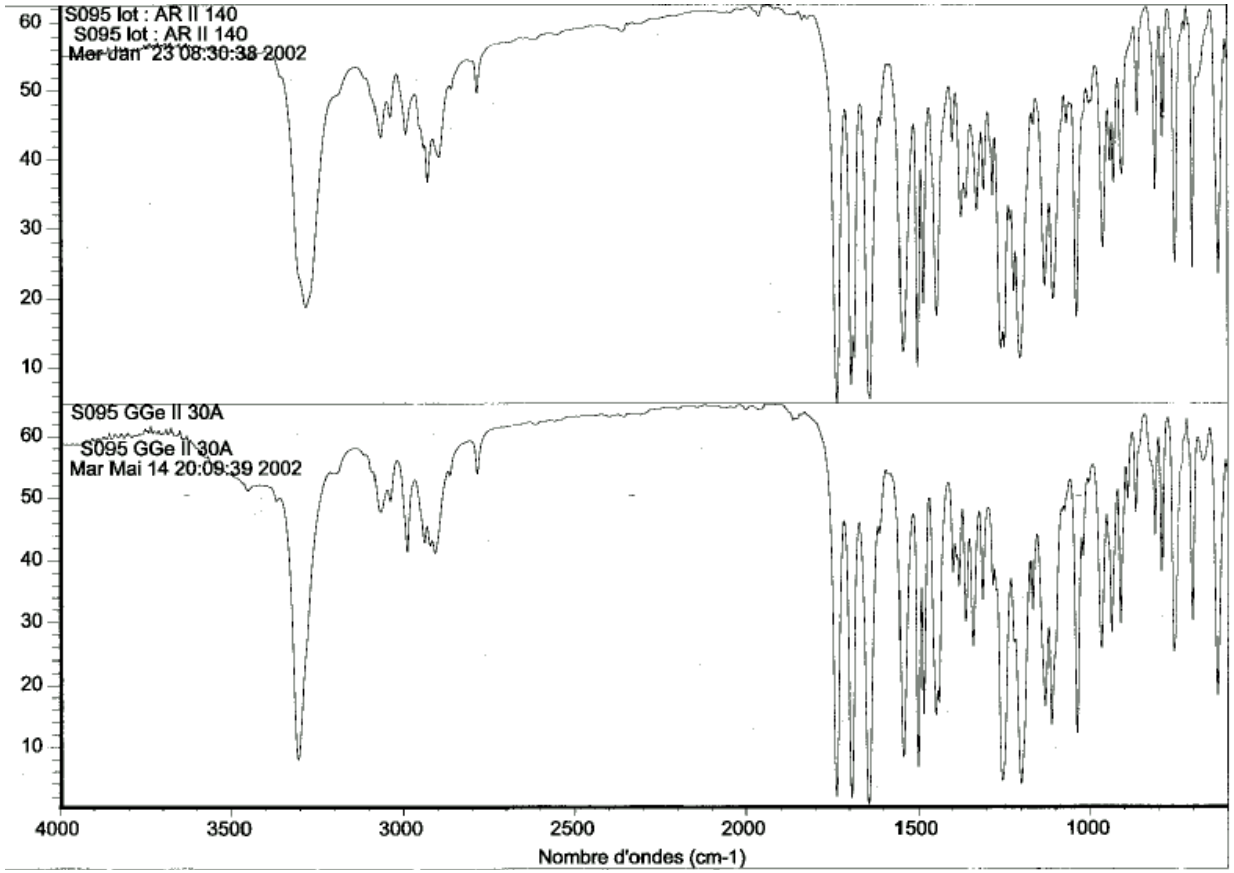
Product Name: Omeprazole (lab reference form C)			
Cas No.:	73590-58-6	Analysis No.:	P20090316
Batch(LOT) No.:	200811011	Quantity:	400g
Mfg Date :	Nov. 24th, 2008	Date of Release:	Mar. 26th,2009
Retest Date:	Oct, 2010	OCS#:	S107
Storage:	Store in cool place. (Temperature of 2~8°C) Keep container tightly closed in a dry and well-ventilated place.		

Test Items	Specification	Results
Characters:	A white or almost white powder	Complies
Assay(on dry basis):	99.0~101.0%	99.91%
Solubility:	Very slightly soluble in water soluble in methylene chloride, sparingly soluble in ethanol (96 per cent) and in methanol. It dissolves in dilute solutions of alkali hydroxides.	Complies
Identification:a.IR b. UV absorbance c. TLC	IR Conforms to the CRS A305/A276=1.6 to 1.8 As per EP6	Complies
Appearance of solution:	Solution S is clear	Complies
Impurities F and G:	≤0.035%	Complies
Impurity C (by TLC):	Not more intense than 0.1%	Complies
Related substances(HPLC): Impurity A: Impurity B: Impurity D: Impurity E: Any other individual impurity:	≤0.1% ≤0.1% ≤0.1% ≤0.1% ≤0.10%	Complies
Residual solvents: a. Acetone b. Methylene chloride c.Toluene d. Methanol	≤1500ppm ≤100ppm ≤300ppm ≤1000ppm	1300ppm 25ppm 10ppm 70ppm
Loss on drying:	≤0.2%(w/w)	0.10%
Sulphated ash:	≤0.1%(w/w)	0.06%
Heavy metal:	≤0.002%	Complies
Reference items:		
Polymorphism:	No form A	Complies
Granularity:D10 D50 D90	D10<3.0um D50 between 3.0 um and 10.0 um D90<25 um	2.8 um 9.8 um 23um

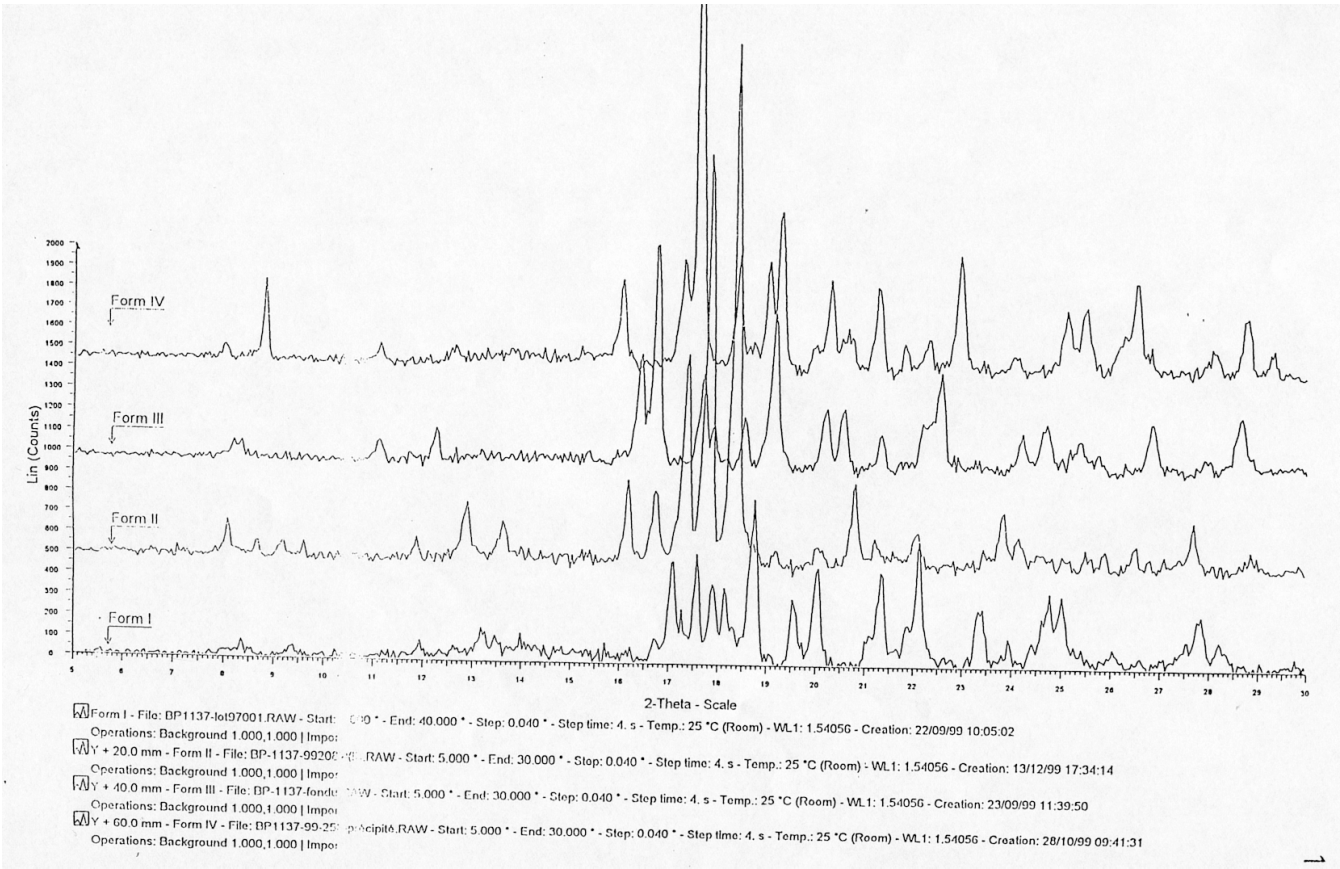
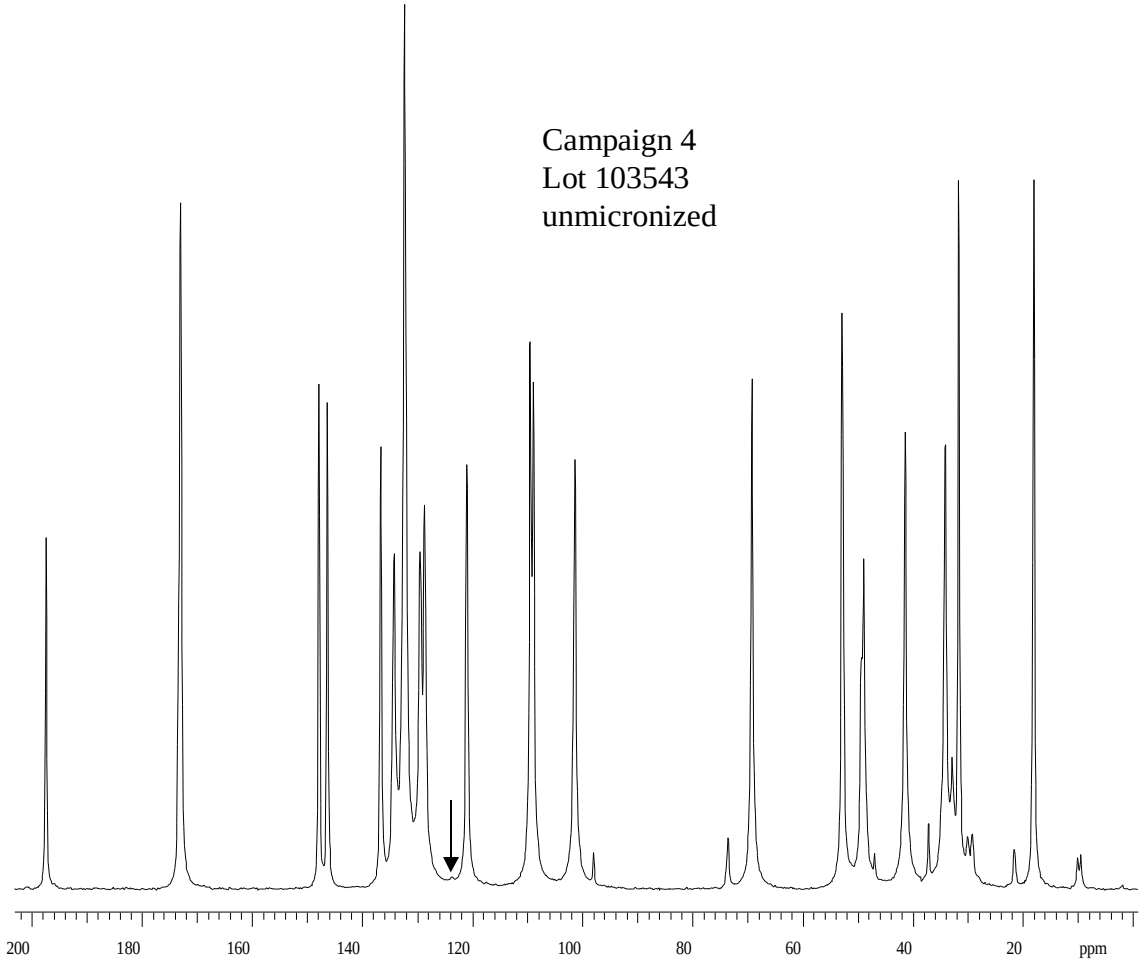
Conclusion: The product complies as per above specification

Analyst: 刘莉 Supervisor: 张旭东 QA Manager: 陈[illegible]

Identification des formes cristallines par IR



Identification des formes cristallines par RX



Identification des formes cristallines par RMN du solide (CPMASS-13C NMR)