Strengthening Medicine Quality Assurance in Mali: Installing Minilabs® and Training in Fourier Transform Infrared Spectroscopy

Bamako, Mali
June 14-25, 2010

Trip Report

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About PQM

The Promoting the Quality of Medicines (PQM) program, funded by the U.S. Agency for International Development (USAID), is the successor of the Drug Quality and Information (DQI) program implemented by the United States Pharmacopeia (USP). PQM is USAID's response to the growing challenge posed by the proliferation of counterfeit and substandard medicines. By providing technical leadership to developing countries, PQM helps build local capacity in medicine quality assurance systems, increase the supply of quality medicines to priority USAID health programs, and ensure the quality and safety of medicines globally. This document does not necessarily represent the views or opinions of USAID or the United States Government. It may be reproduced if credit is given to PQM and USP.

Abstract

The Promoting the Quality of Medicines (PQM) Program facilitated the installation of Minilabs® at sentinel sites and trained staff from the Laboratoire de la Santé (LNS) in Fourier Transform Infrared (FTIR) spectroscopy. Teams at the following sentinel sites also received refresher training in basic tests at the time of the installation of Minilabs®: Mopti, Ségou, Sikassou, and Kolikouro. Seven participants from LNS received training in FTIR, including sample preparation and proper use of the FTIR spectrometer, Spectrum RXI. The training was conducted at Medicine Quality Control division of LNS. In addition to the training, PQM held a meeting with the Centre National d'Appui Contre la Maladie (CNAM) and Direction de la Pharmacie et du Médicament (DPM) to discuss pharmacovigilance (PV) activities.

The installation of Minilabs® at the sentinel sites marked the start of the first round of sampling and testing of antimalarial medicines.

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Key Words

Basic tests, training, medicines quality monitoring, antimalarials, Minilab®, pharmacovigilance, FTIR, Mali

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- Pr. Ousman DOUMBIA, Director of DPM, for his availability and support of PQM

- Dr. Samba SOW, Dr. Oumar MAIGA, and Dr. Modebo KEITA, from CNAM, for their support of PV activities

- Dr. Enias BAGANIZI, CDC resident at USAID/Mali, for his support

- Mrs. Fanta Sangho SANGO, Head of Quality Assurance at DPM, for her support

- PQM administrative staff and editors for their assistance with logistical arrangements and for editing the trip report

- Mr. Anthony BONI at USAID Washington for his support

- PMI for funding the program and making this trip possible

ACRONYMS

ACT	Artemisinin-based Combination Therapy
ADE	Adverse Drug Event
CDC	Centers for Disease Control and Prevention, USA
CNAM	Centre National d'Appui pour la lutte contre la Maladie
CNRPV	Centre National de Référence de Pharmacovigilance
DQI	Drug Quality and Information Program
DPM	Direction de la Pharmacie et du Médicament
FDC	Fixed Dose Combinations
FTIR	Fourier Transform Infrared spectroscopy
LNS	Laboratoire National de la Santé
MOH	Ministry of Health
MQM	Medicine Quality Monitoring
PMI	President's Malaria Initiative
PNLP	Programme National de Lutte contre le Paludisme
PQM	Promoting the Quality of Medicines Program
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
TLC	Thin Layer Chromatography
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Background

PQM/DQI has been assisting the Ministry of Health (MOH) of Mali in strengthening their medicine quality assurance systems. The activities focus on strengthening the capacity of DPM and LNS in pharmacovigilance, drug registration, and medicines quality control.

In 2009, following an assessment of Mali's quality assurance and quality control (QA/QC), PQM facilitated a workshop to establish a national pharmacovigilance system, a training workshop on drug registration and drug import verification using SIAMED software, and provided training to the staff of medicines quality control laboratory at LNS. The lab training included Good Laboratory Practices and testing antimalarial samples with High Performance Liquid Chromatography and Dissolution.

A follow-up visit focused on the evaluation of the lab training in Dissolution and the planning of PV activities. PQM provided refresher training in Dissolution and conducted a thorough inventory of the lab equipment and supplies. All the lab staff attended the refresher training and participated in the inventory. PQM also reviewed the lab quality manual and procedures.
In March 2010, in collaboration with LNS and DPM and with the participation of Programme National de Lutte contre le Paludisme (PNLP), PQM established a Medicine Quality Monitoring (MQM) program focused on antimalarial medicines. In addition to staff from LNS and one participant from PNLP, two agents each from the sentinel sites of Gao, Kayes, Koulikoro, Mopti, Segou, Sikasso, and Tombouctou received training in sampling and basic tests using Minilabs®.

Purpose of Trip

Dr. Mustapha HAJJOU traveled to Bamako, Mali to facilitate the set-up of Minilabs®, provide training in FTIR to staff from LNS, and discuss PV activities with local partners.

Source of Funding

This trip was supported with funds from USAID/Mali through PMI.

Overview of Activities

Briefing USAID/Mali

Dr. HAJJOU briefed Dr. Enias BAGANIZI, U.S. Centers for Disease Control (CDC) resident, on the activities that PQM was to conduct during this trip.

Set-up of Minilabs®

Pr. Benoît KOUMARE, Director General of LNS; Mr. Ousmane SIDIBE, a student pharmacist preparing his thesis on the QC of medicines at LNS; and Dr. HAJJOU travelled to the sentinel sites of Mopti, Sikasso, Ségou, and Koulikoro to install Minilabs®.

At each sentinel site, the team met with the director/deputy director of the Regional Directorate of Health, the accounting agent, and the sentinel site team (see *Annex 1*for more information). The team delivered the Minilab® and provided resources needed to carry out one round of sampling and testing of 100 samples of antimalarials. Assisted by Mr. SIDIBE, Dr. HAJJOU provided refresher training in basic tests with a focus on visual and physical inspection and Thin Layer Chromatography (TLC) tests. During the refresher training, different samples of antimalarial medicines were used (see *Annex 1*for more information). The sentinel site teams the

considered the refresher training useful because of the time elapsed since PQM provided the formal training in basic tests.

LNS planned visits to set-up Minilabs® at the remaining three sentinel sites of Gao, Kayes, and Tombouktou.

Installation of Minilabs®: Refresher training in basic tests – Mopti Sentinel Site

Pharmacovigilance Activities

A meeting was held at CNAM to discuss the progress of PV activities. The participants in the meeting were:

Fanta SANGHO SANGO, Head of Quality Assurance, DPM
Samba O. SOW, Director, CNAM
Oumar MAIGA, Deputy Director, CNAM
Modibo KEITA, Focal point - PV Technical Activities, CNAM/CNRPV
Mustapha HAJJOU, PQM

Mrs. SANGO gave an overview of the status of PV program, covering the role and responsibilities of CNAM in supporting the Centre National de Référence de Pharmacovigilance (CNRPV) to carry out its activities. Dr. SOW recognized the importance of PV and requested clarification about the role of CNAM and the level of its responsibilities. Dr. HAJJOU explained that CNRPV's role was to handle all technical aspects of the national PV program and pointed out that this was a very important role that required dedication from the technical staff. The fact that CNRPV has only one technical staff makes this requirement even more pressing; the center should hire additional staff. Dr. KEITA has been involved in a phase 4 clinical trial monitoring the effects of a vaccine at CNAM, but he will be available to focus on CNRPV activities by the end of August 2010. The group agreed that Dr. KEITA will receive intensive training to enable him to carry out technical PV activities.

Dr. SOW indicated that one more medical doctor working at CNAM could join CNRPV. He pointed out that CNAM has a budget and an action plan that includes PV, but PV activities were

not detailed in the plan. He also inquired about the support that could be provided to CNRPV. To better plan next year's activities, CNAM will provide PQM with details of the PV activities budgeted in the action plan. PQM will budget for different and/or complementary activities.

It is noteworthy to mention that CNRPV and DPM have started receiving adverse drug event reports.

Training Workshop

Item	Description
Training Objectives	✓ Training on sample preparation for FTIR ✓ Training on FTIR analysis
Venue	LNS, Bamako, Mali
Trainer	Dr. Mustapha HAJJOU
Local Organizers	LNS
Course Proceedings	Day 1: • Setup the lab for training • Prepare artesunate sample • Prepare amodiaquine sample and reference standard Day 2: • Familiarization with Spectrum RXI spectrometer • FTIR analysis of amodiaquine sample and reference standard Day 3: • FTIR analysis of artesunate reference standard • Repeat FTIR analyses • Presentation on Infrared Spectroscopy (*Annex 4*) • General discussion • Closing
Participants	Seven staff from the LNS attended the training (*Annex 2*).
Lab supplies Provided	All materials provided by PQM are indicated in the List of Supplies (*Annex 3*).
Course Outcomes	At the end of the course, participants were able to: • Prepare samples appropriately for FTIR analysis • Use Spectrum RXI FTIR spectrometer to test samples for Identification Test

Training in FTIR

LNS Quality Assurance

Dr. HAJJOU met with Mrs. Simpara Aminata FOFANA, Deputy Director of Quality Assurance at LNS, to discuss the quality systems of the lab. Mrs. FOFANA provided the list of all the documents relating to the quality system and identified the areas that needed improvement, including management of projects and lack of compliance with procedures. She related these gaps to the lack of QA culture in general and suggested that the staff be trained periodically in this area. Other gaps were identified including the following:

- The lab does not have an internal audit program
- The lab staff are not involved in drafting standard operating procedures (SOPs) relating to their daily activities
- Supervision of analysts is not adequate

Next Steps

- PQM to facilitate the training of the CNRPV staff in PV (causality assessment and Vigiflow software) – September 2010
- LNS to complete the set-up of Minilabs® at the sentinel sites of Gao, Kayes, and Tombouktou –July 2010
- PQM to provide LNS with Karl Fischer titrator – September 2010
- LNS to submit a report on the first round of sampling and testing of antimalarial medicines – September 2010
- CNAM to provide PQM with FY11 action plan for pharmacovigilance – August 2010

Conclusions

- The set-up of Minilabs® at the sentinel sites marked the start of the first round of sampling and testing of antimalarial medicines.
- The training of LNS staff in FTIR will help expand the testing capacity of the national laboratory.

Annex 1

Set-up of Minilabs®

Sentinel Site	Attendants	Refresher training
Mopti	• Dr. COUMARE, Head of Regional Health Directorate • Dr. DOUNGNON, Regional Pharmacist, MQM Focal point • Dr. KAMISSOKO, Malaria focal point	• Lumefantrine-Artemether tablets: Visual-Physical inspection and TLC testing of artemether
Sikasso	• Dr. MAIGA, Planning Services of the Regional Health Directorate • Dr. DEMBELE, Regional Pharmacist, MQM Focal Point • Dr. KASSOGUE, Head of the Regional Hospital Laboratory	• Visual-Physical inspection and TLC testing of artesunate tablets
Ségou	• Mr. TRAORE, Head of the Division of Hygiene of the Regional Health Directorate • Dr. COULIBALY, Regional Pharmacist	• Visual-Physical inspection and TLC testing of quinine sulfate tablets
Koulikoro	• Dr. GINDO, Director of the Regional Health Directorate • Dr. KONATE, Head of the Planning at the Regional Health Directorate • Dr. DICKO, Regional Pharmacist, Focal Point	• Visual-Physical inspection and TLC testing of Sulfadoxine-Pyrimethamine tablets

Annex 2

List of Laboratory Supplies

Unit	DESCRIPTION OF GOODS	VALUE (US$)
2	MORTAR AND PESTLE	311.66
1	SYRINGE FILTERS (0.2 µ), PACK OF 50	216.44
1	USP AMODIAQUINE HYDROCHLORIDE REFERENCE STANDARD	167.00
TOTAL		**695.10**

Annex 3

List of Participants in FTIR Training

Name	Contact Information
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Atelier de Formation PQM en IRTF

Bamako, Mali ◆ Juin 22-25, 2010

Spectroscopie Infrarouge

Mustapha Hajjou, PhD

Promoting the Quality of Medicines Program

Exécuté par la Pharmacopée Américaine (USP)

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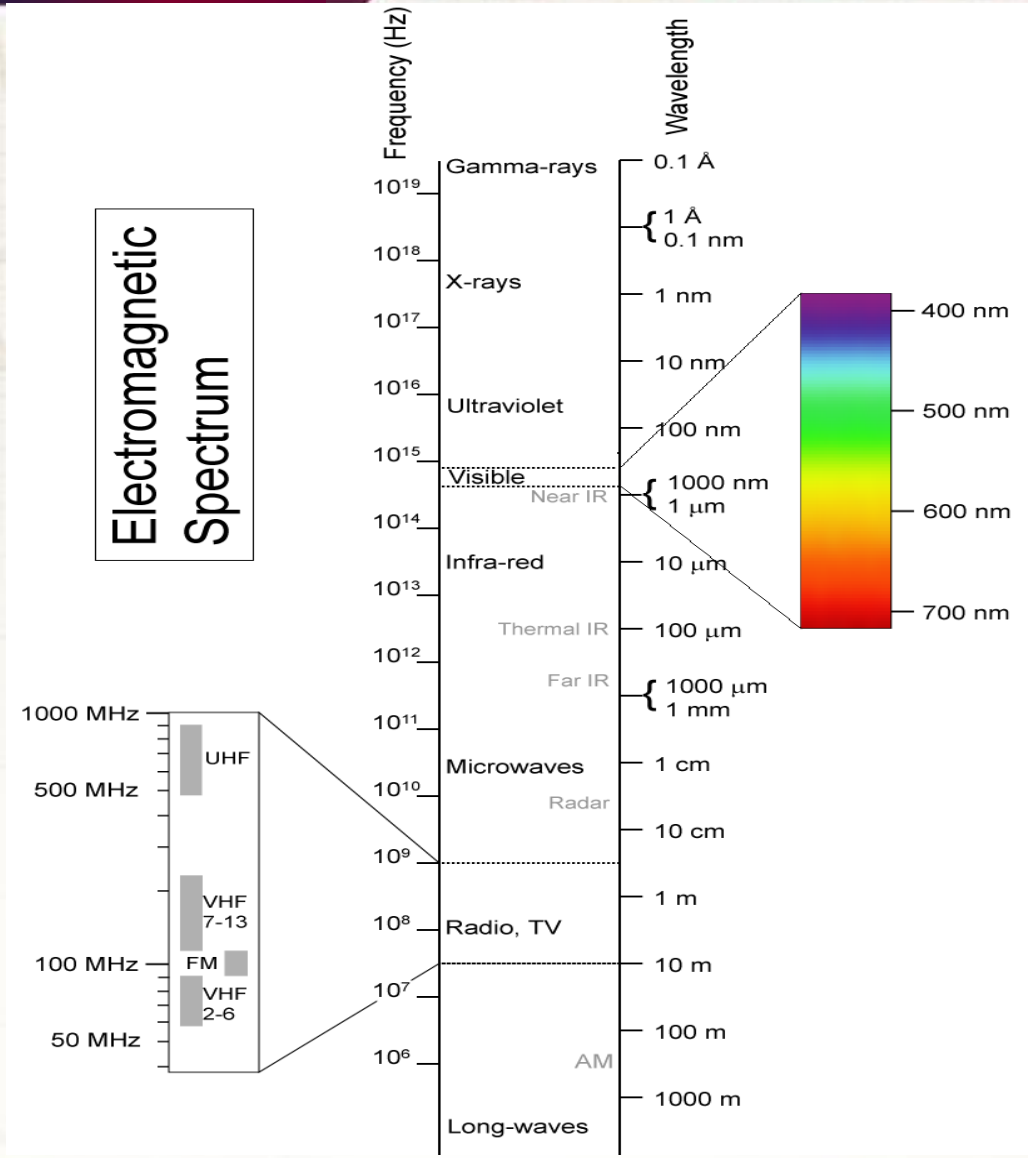
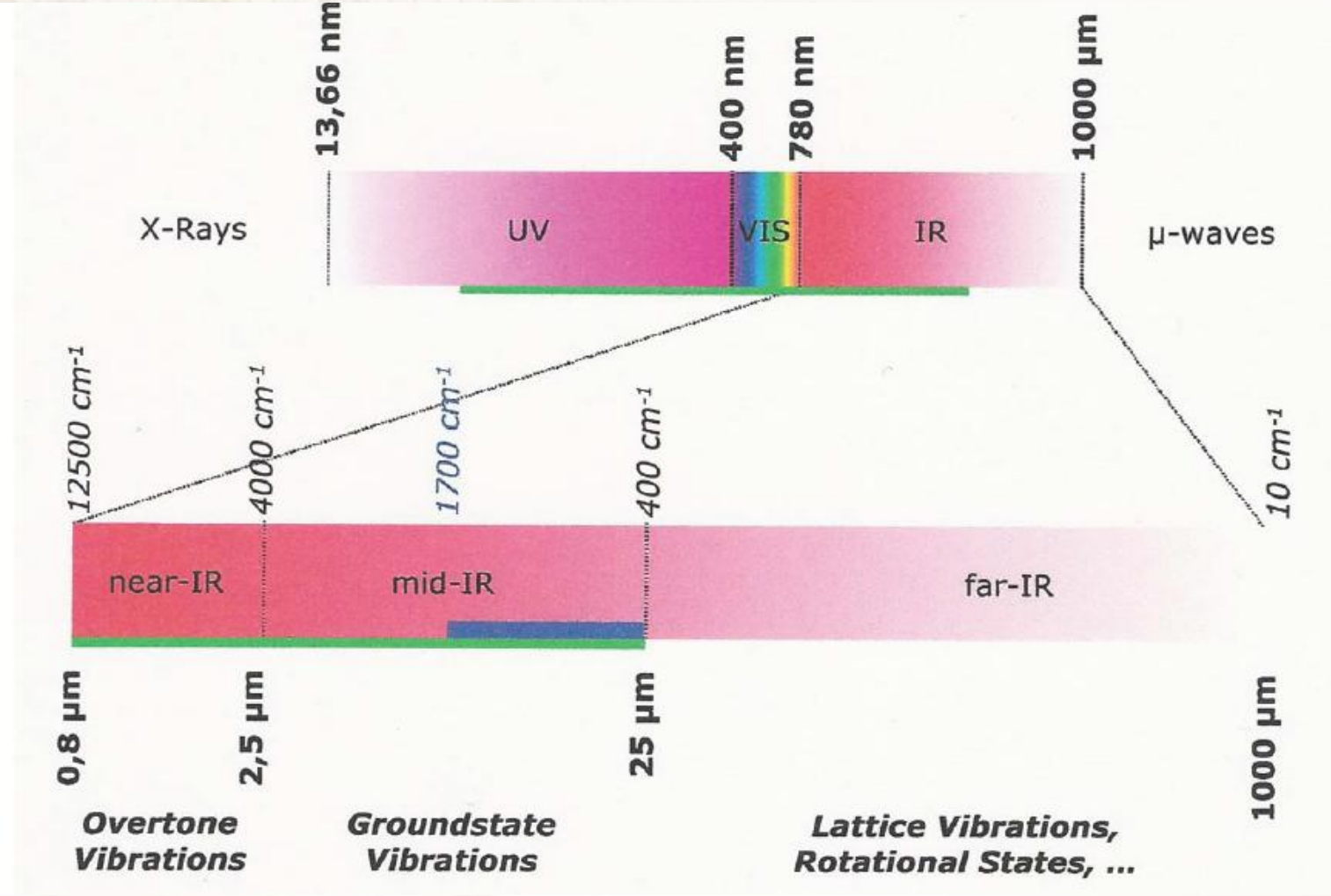
Régions Electromagnétiques



Régions Electromagnétiques



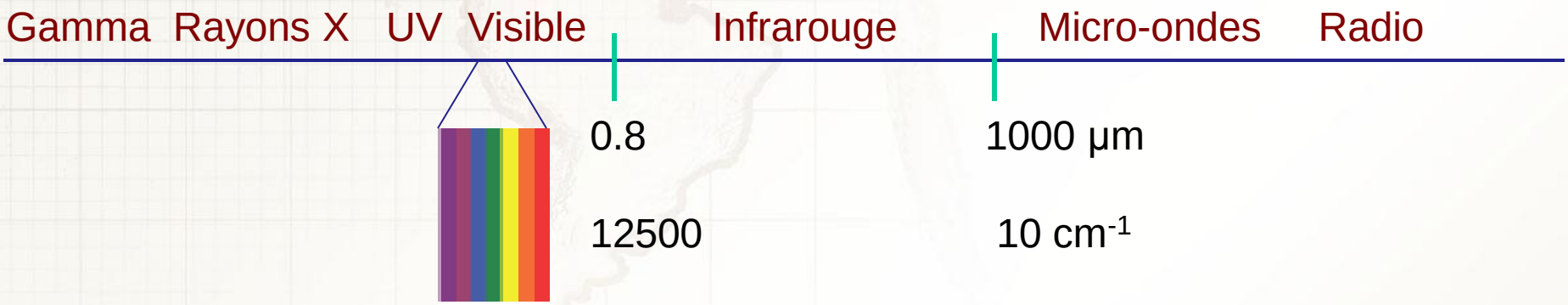
Nombre d’onde

- Nombre d’onde = nombre de longueur d’onde (λ en µm) compris dans une distance de 1 cm

$$v = (1/\lambda) \times 10^4$$

Régions Electromagnétiques

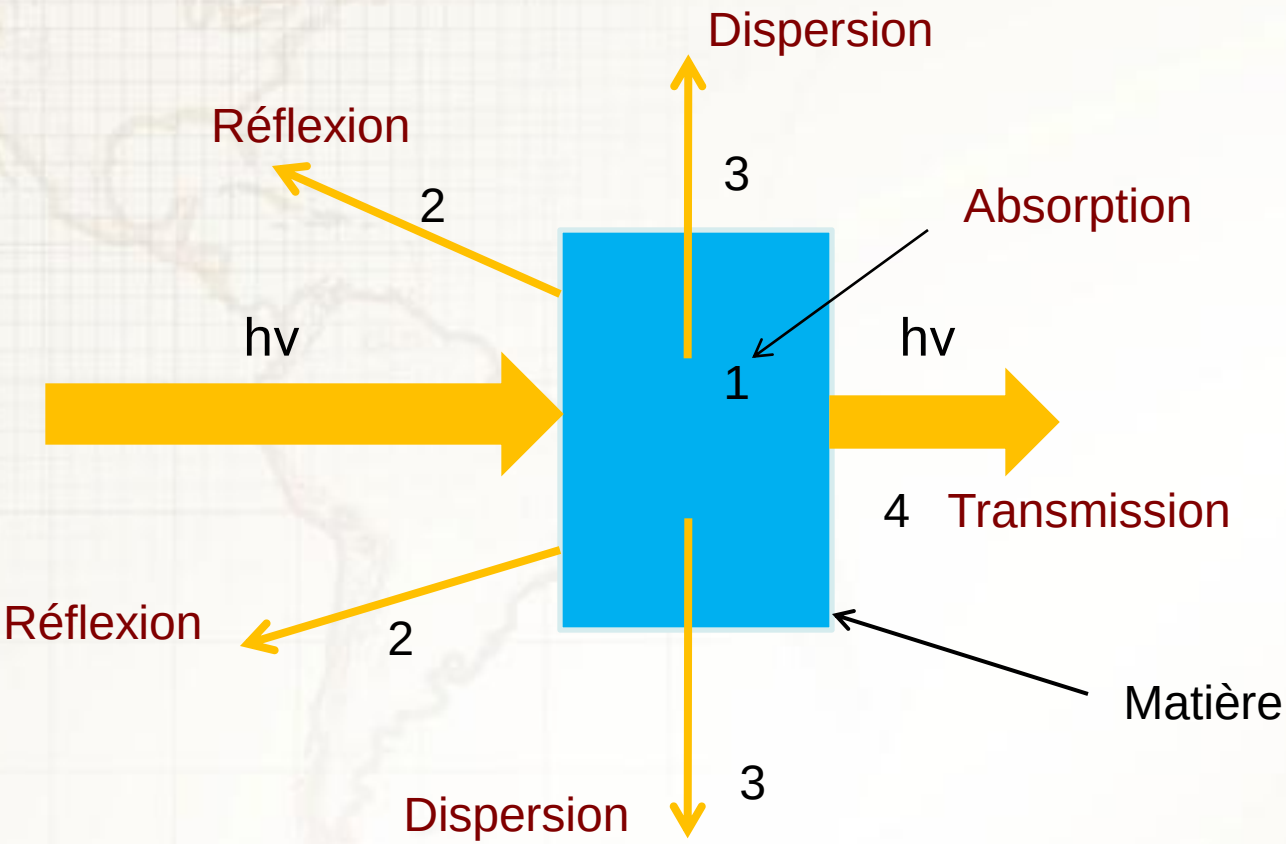
- Plus la longueur d'onde est courte plus l'énergie est grande



Régions Electromagnétiques

- Rayons Gamma et X: Ionisation d'atomes et rupture des liaisons
- Ultraviolet: Rupture des liaisons et ionisation de molécules
- Infrarouge: Excitation des vibrations moléculaires
- Micro-onde et radio: augmentation du mouvement moléculaire (élévation de la température)

Régions Electromagnétiques



Spectroscopie Vibrationnelle

- Il existe différents types de spectroscopie
- Spectroscopie vibrationnelle:
  - Illumination pour susciter des vibrations moléculaires
  - Absorption, réflexion et dispersion d'une quantité discrète d'énergie

Vibrations Moléculaires

- La position des atomes dans les molécules est sujette à des vibrations
- Il y'a deux types de vibrations moléculaires:
  - Etirement: changement de la distance le long de l'axe de la liaison entre deux atomes
  - Flexion: changement d'angle entre deux liaisons

Vibrations Moléculaires

- Il y a 4 types de flexions:
  - Frétillement (agitation hors du plan)
  - Bascule
  - Cisaillement
  - Torsion

Vibrations Moléculaires

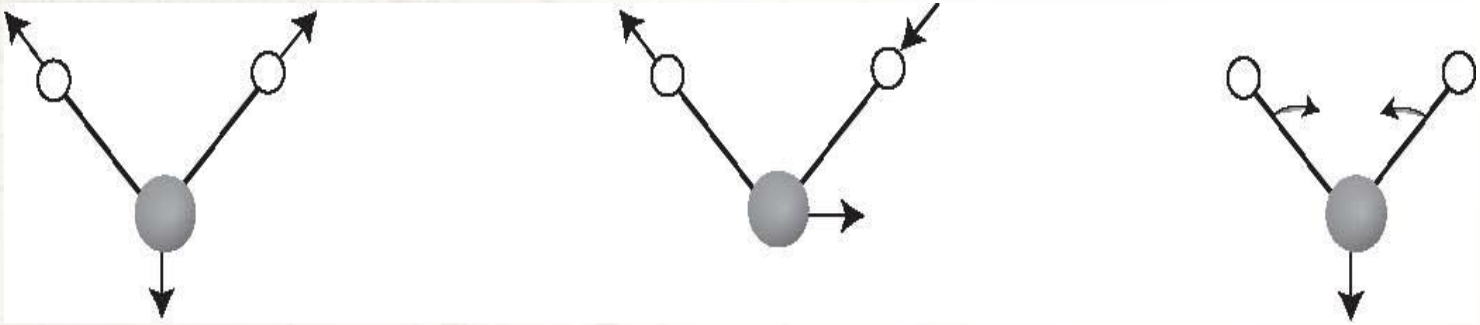
Le nombre de vibrations fondamentales

Molécule linéaire	Molécule non linéaire
3n - 5	3n - 6

n = nombre d'atomes de la molécule

- Les modes vibrationnels de torsion et d'extension de H2O

Nombre de vibrations = (3x3) – 6 = 3



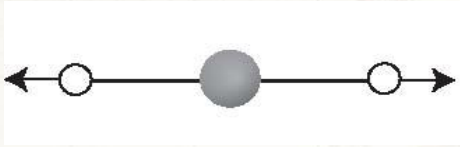
Etirement symétrique Etirement asymétrique Cisaillement

Les modes vibrationnels de CO2

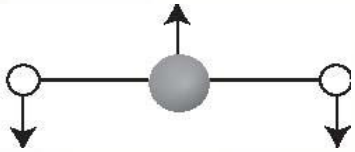
Nombre de vibrations = (3x3) – 5 = 4

Etirement asymétrique

Cisaillement (dans le plan)



Etirement symétrique

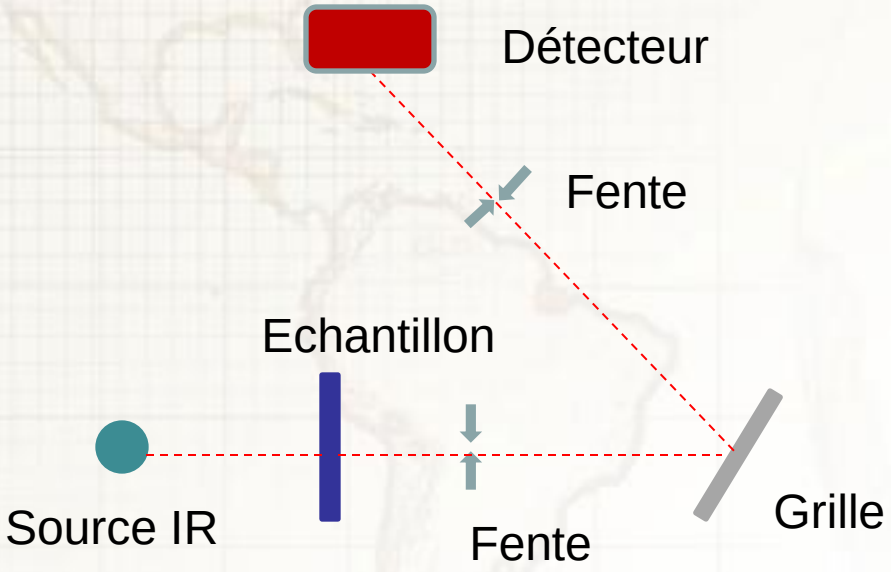


Cisaillement (hors du plan)

Instrument

- Spectromètre IR conventionnel
  - Monochromatomètre à double faisceaux
- Spectromètre IRTF
  - Interféromètre simple faisceau

Spectromètre IR Conventionnel



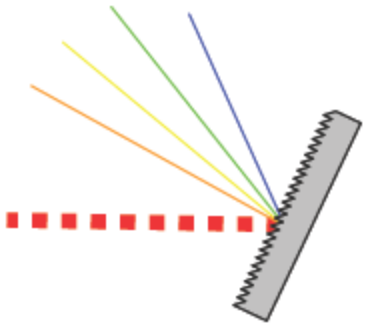
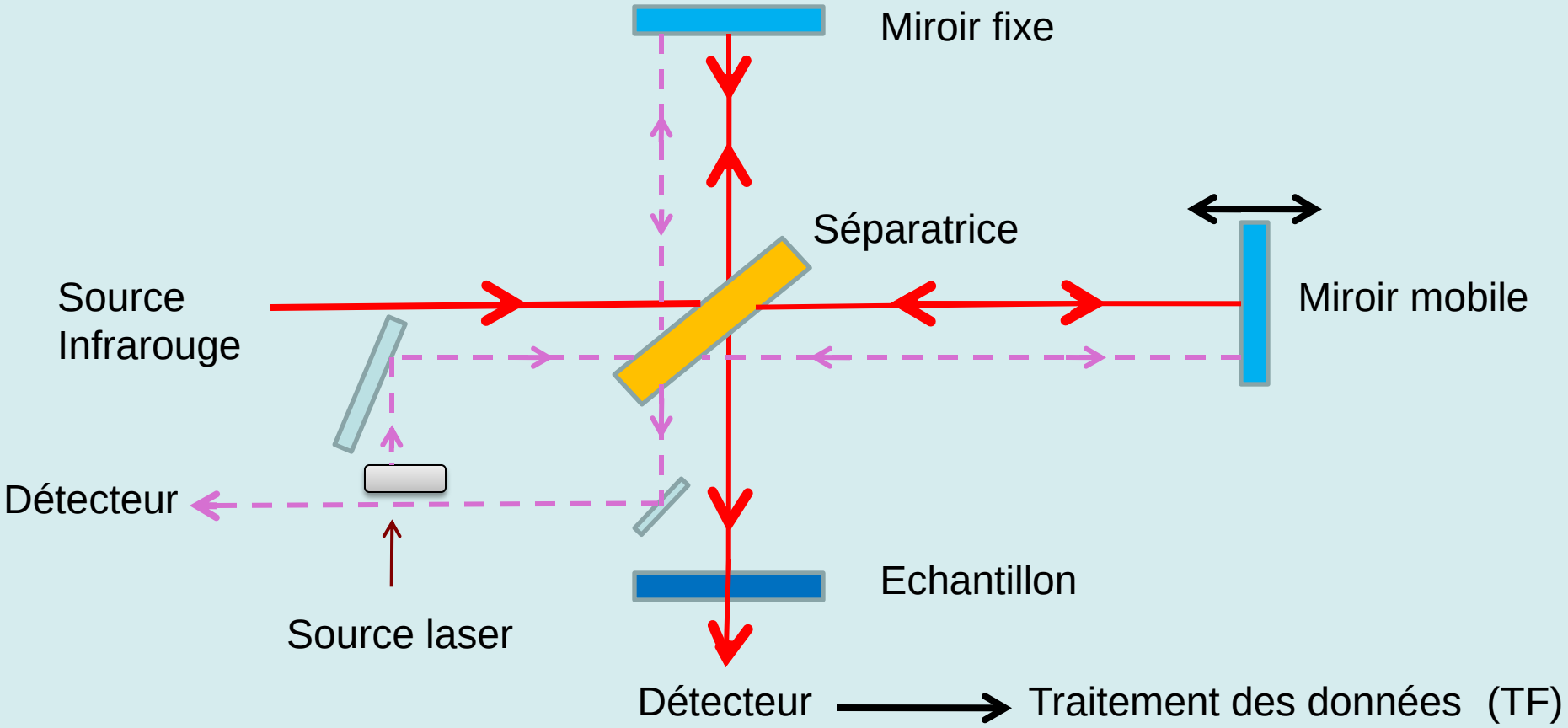


Schéma Simplifié d'un Spectromètre IRTF



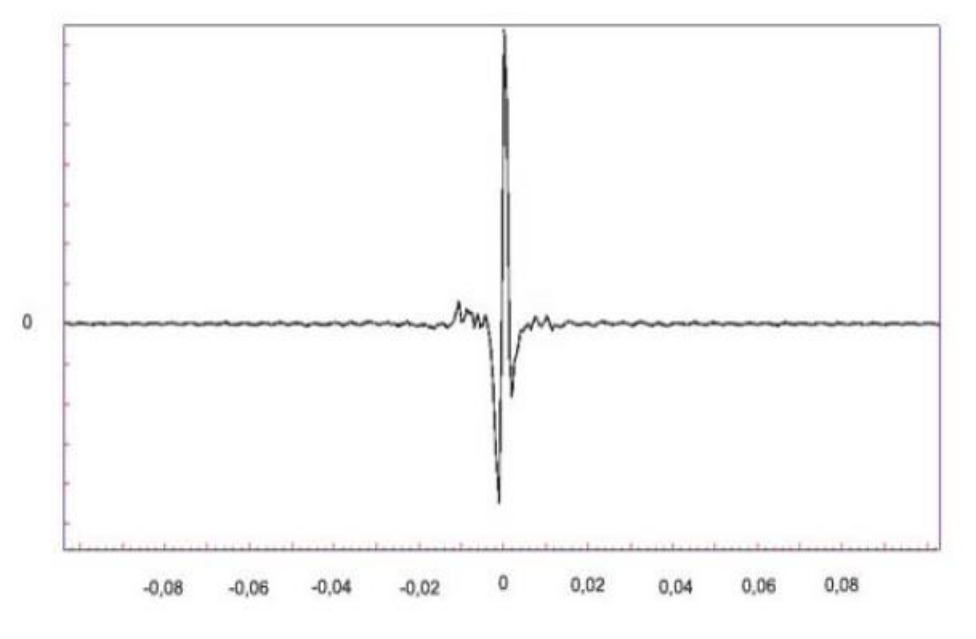
Transformée de Fourier

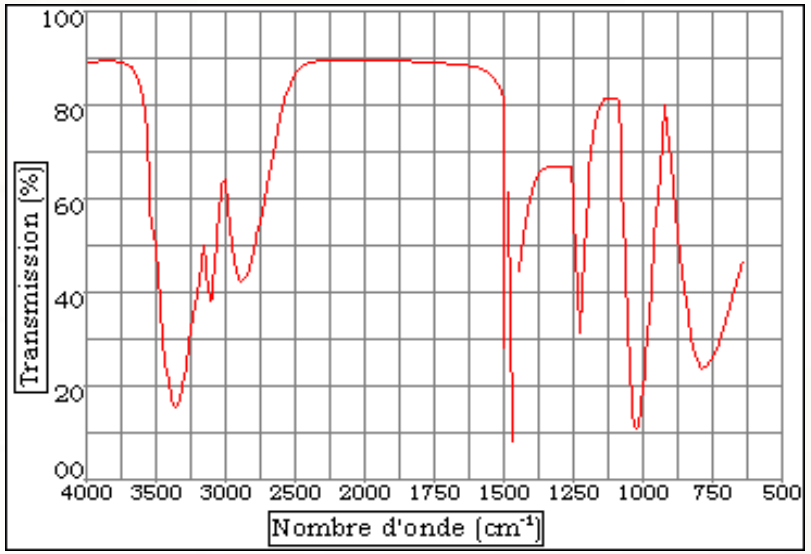
- En mathématiques, la transformée de Fourier (TF) est une opération qui transforme une fonction à variable réelle en une autre fonction.
- En IRTF, TF décrit les fréquences présentes dans la fonction originale. Par analogie, c'est comme décrire des accords musicaux en termes des notes jouées.

Spectroscopie IRTF

Promoting the Quality of Medicines Program

Interférogramme **TF** Spectre IR





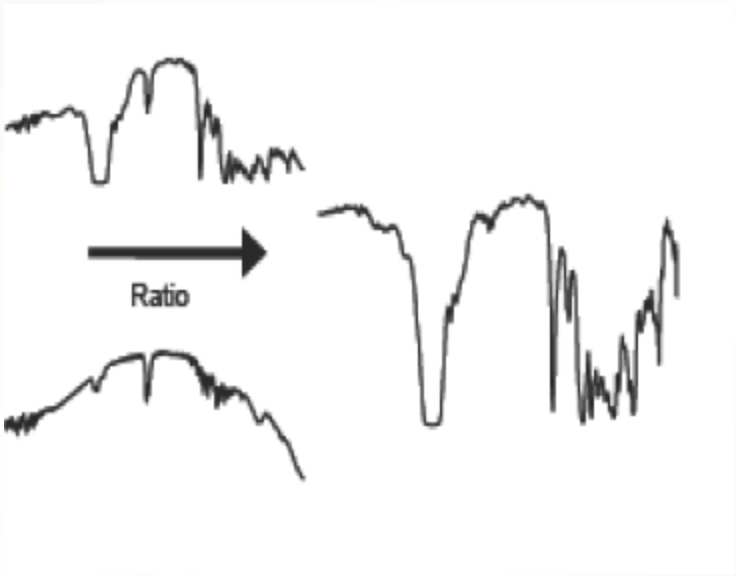
Spectroscopie IRTF

Interferogramme d'échantillon

Apodisation

Interferogramme de fond

Apodisation



Avantages de FTIR

1- Toutes les longueurs d'ondes sont scannées simultanément

- Réduction du temps de collection des données
- Augmentation du rapport signal/bruit de fond

Avantages de FTIR

2- Débit optique plus élevé

- Faisceau lumineux plus large, contenant toutes les fréquences, donc plus d’ énergie à l’arrivée au niveau du détecteur.

Avantages de FTIR

3- Référence interne fixe

- He-Ne laser
- Control du miroir et le timing de la saisie des données

Questions?

Merci

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