Seminar PC2 « Hospital Mergers and the centralisation of production services »

Technical issues of Centralisation of Production

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Disclosure

- Conflict of interest: nothing to disclose

Self assessment questions

1. Is centralisation a tool for improving quality of compounded drugs? YES /NO
2. Is dose standardization of drug compounded a key for centralisation of ready to administer preparation? YES/ NO
3. Is process automation achievable for all ready to administer preparations? YES / NO

Agenda

- Who I am
- French background of compounding in hospital pharmacies and future perspectives
- Technical issues of the standardization and centralisation
- Examples of merging process of production services
- Conclusion
- Aknowledgements
- Take home message

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Who I am

- Professor of Pharmaceutical Technology, Bordeaux University
- Researcher on nanovectors
- Hospital Pharmacist: Head of the preparation departement of University Hospital of Bordeaux

université de BORDEAUX

cnrs Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

CHU Hôpitaux de Bordeaux

Groupe d'Evaluation et de Recherche sur la Protection en Atmosphère Contrôlée
GERPAC 2017 20 years
Group of Evaluation and Research for Protection in Aeras under Control

- President of non-profit European Association of Hospital Pharmacists: GERPAC dedicated to pharmaceutical technology in hospital pharmacy

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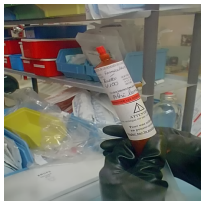
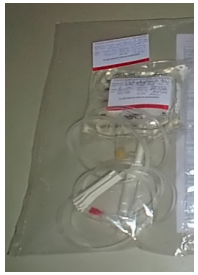
What is the French background of compounding in hospital pharmacies?

Sterile productions

- Ready To Administer (RTA)





- Cytotoxics (risk for operators)
- Monoclonal antibodies (cost)
- Parenteral nutrition admixtures (risk for patient)

- Miscellaneous: depending on the local institutional choices and human ressources (e.g. antibiotics antifungics.. for paediatrics)

- Very few hospital pharmacies in France producing Ready To Use (RTU)

Non-steriles (prepared only by hospital pharmacies when no avaible commercialized drug or not adapted)

- Capsules (+++) or oral solutions (+) for paediatric / geriatric – orphan diseases
- Topic formulations



- Mandatory to be declared to French National Agency for Evaluation of Health Products (ANSM)

French regulation on hospital pharmacy preparations

- « Magistral preparation » one preparation adapted for one unique patient
- Mandatory to be done in all hospital pharmacies

MANDATORY

- « Hospital preparation »

Preparation of the same drug and potency for a group of patients

- Optional activity only for hospital pharmacies agreed by inspectors

OPTIONAL

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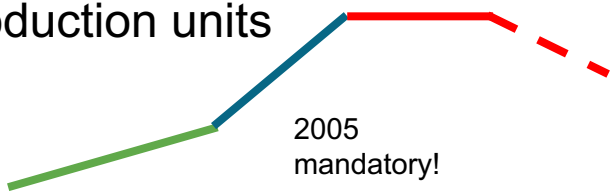
What are the French perspectives for compounding sterile drugs in hospital pharmacies?

Mainly Cytotoxics drugs

- End of the 70's: discovering the toxic risk of handling drugs…
- Development of centralized units for preparation of « RTA cytotoxic drugs »
- Mandatory for cancer treatment of patients to create centralized production units



- 2013: 700 centralized units in France/ 2640 hospital pharmacies (26%)
- Too many… Projects for developing big district platforms (one for each new french district ?)
- 22 ➔ 13

Carte des possibles 13 nouvelles régions de France

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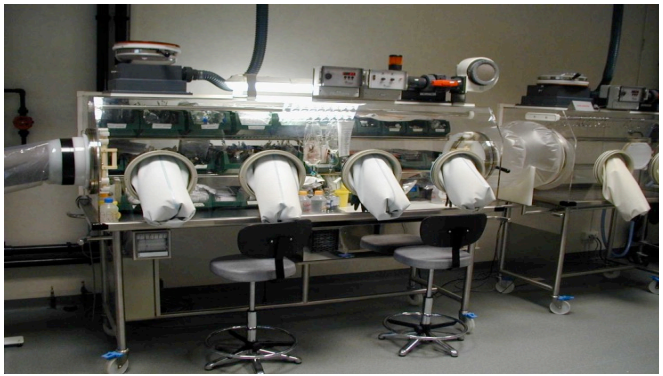
What are the facilities and equipments used in France for sterile preparations?

- Isolator (80%)
- Background environment ISO 8 or 7 (grade D or C) depending on pressure of the isolator

- Unidirectional LAF for non-toxic drugs or BSC II or III (20%) for toxic drugs
- Background environment ISO 5 or 7 (Grade B or C) depending on the process



Based on french regulation: « Good Manufacturing Pratices for preparation in hospital and community pharmacies » 2007-revision 2018 in process

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Challenges of the centralisation of production of RTA preparation

General

- Cultural
- Time
- Human ressources to conduct the merging

Technical

- High volume of activity without extendible human ressources
- Production platform in conformity with good manufacturing standards (close to pharmaceutical industry)
- Needs for innovation: facilities… equipments… and brain!

Technical aspects for merging production services « big » centralisation of RTA

Benefits expected

- Optimization of human resources
- Optimization of skills with dedicated team
- Optimization of controlled areas and facilities
- Financial expected gain

Limits

- Logistic issues
- Loss proximity with the patient

Means: Need for changes!

- Prescription habits towards dose standardization of RTA
- Compounding processes to increase efficiency

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Keys for standards RTA implementation

- Physician's agreement of standard doses
- Number of doses to be produced should be limited: 3 to 5 maximum per drug

Methods available:

Dose banding initally *developed for cytotoxics in UK*[1] extended to monoclonal antibodies

- Acceptable **maximum variation** between prescribed calculated dose & standard dose is predefined with physician (usually +/-5% , +/-10% and could be higher for drugs with high therapeutic indexes)
- One single preparation (infusion/syringe) or a combination to provide the standard dose

Flat Fixed Dosing

- two or three pre-defined standard doses for all patients

NHS England

National Dose Banding Drug Summary
Drug and concentration list as at 17 Oct 2017

Always check the website for the most up-to-date version of the drug tables.
https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/

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Plumridge & Sewell, Am J Health-Sys Pharm, 2001, 15;58(18):1760-4

Keys for standards RTA implementation

Pharmaceutical issues

Drug stability

- Physico-chemical & microbial
  - « Long-term » expected minimum 3-4 weeks
  - Short term 48h-72h minimize the interest but could allow some anticipation…

Drug Cost !

To be balanced: the financial risk to destroy a high-cost drug due to anticipation of the preparation!

Stability studies to be done prior routine implementation for determination of the beyond-to-use date:

- Physico-chemical tests for potency must be stability indicating!
- Interaction risks drug-final container assessed
- Microbiological risk must be controlled:
  - Use of classified environments (grade A/B/C rooms and facilities)
  - Aseptic process validation and operator's qualification

Process control:

- in process/post-process for drug identification and potency
- environmental control
- sterility testing

Optimized compounding process for efficiency

- Productivity
- Quality

Determine a short list of drugs combining low cost drug with high physicochemical stability

Standardized RTA therapy - benefits

For patients

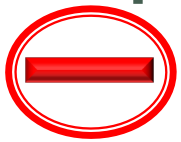
- Risk reduction
  - Avoid errors in ordering and preparation
- Correct time for administration and limit waiting time

For Pharmacy

- Treatment of a majority of patients
- Answer for increasing needs
- Improvement of daily organization and workload capacity
- Improvement / solving logistic issues
- Avoid errors in ordering and preparation
- Improvement of quality (controls & stability)
- Reduced stress pressure
- Reduce drug waste
- Time and cost saving expected

Standardized RTA therapy - Limits

- Treatments for individualized medicine: i.e. clinical trials…
- Low therapeutic index drugs (i.e. anticancer drugs)
  - Risks of inefficacy or toxicity
- Drugs with poor physico-chemical stability



- A part of production will be still individualized
- Needs for investments
  - For production automation equipments (semi-automates or robots)
  - For quality control (analytical automates, robots)

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Standard RTA Compounding process

Batch production:

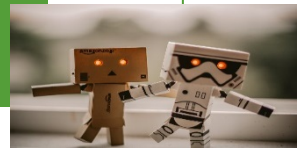
- Bulk solution of drug of big volume 3-5 liters
- Distributed in empty vials, bags or syringes
- One batch = X bags of the same dose

(or syringes or vials)

« Series » production:

- Repeated compounding of the same drug at the same potency
- One batch = one bag (or syringe or vial)

Both methods achievable by manual compounding but should be automated for productivity and quality and to limit musculo-squeletal disorders



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Means for improving compounding process

- Computer system for:
  - prescription
  - preparation of batches
  - storage (management of the beyond-to-use date)
  - distribution (management of traceability, temperature control and distribution)

Specific equipments for:

- Production
  - Robots or semi-automate for series or batch production of syringes or bags
- Quality control
  - « in process » gravimetric, pictures RFID Bar Code../…
  - « post-process » Quantification (end-product) Spectrophotometry (UV/vis/Raman), HPLC, …

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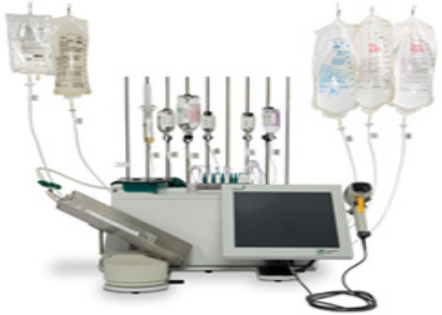
Examples of robots and semi-automates

Semi-automate

- Peristaltic / volumetric



Baxter

Hemedis

ICU

Robots

Apoteca

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Equipments for quality controls

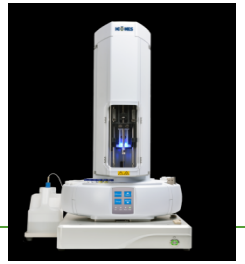
« In-process » control

- Identification of raw material, drug, diluent. Data matrix…pictures
- control of volumes gravimetric, pictures, camera recording…

- Included in robots

« Post-process » control

- Identification of the right drug and final quantity diluted in the right diluent
- Analytical instruments such HPLC-UV or spectrophotometer combining UV/Raman or IR



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Automation / robotisation

Benefits:

- Gain in productivity limits the need for human resources
- Gain in quality with systems implemented on the technology for controlling « in-process » production and « post-process »
- Limitation of human contact with preparation:
  - Protection of the drug against microbial contamination
  - Protection of operator and environment against toxic drugs

Limits / Pitfalls:

- limited productivity for individualized medicine
- Valuable only for the standardized and anticipated part of the production
- Comparison batch/ production / robots to be balanced in terms of cost and productivity for standardized medicines

Semi-automate

Benefits:

- batch production
- gain in productivity
- gain in quality

Limits:

- Needs for anticipation
- Short stability of drugs
- Risky for high-cost drugs

Keys for robots implementation

- Adoption by the team
- High rate of standardization: more than 50% of the workload

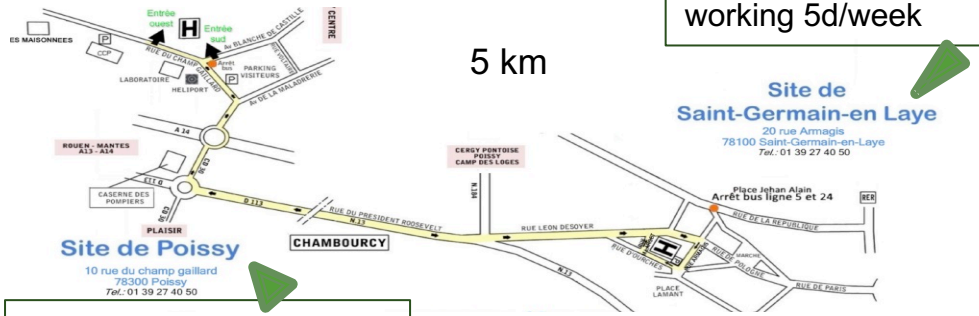
Pitfalls:

- Underestimation of qualifications steps in terms of duration and human resources
- Poor rate of anticipation and standardization
- Expecting high productivity level for taylorized preparation

Example 1: « Proof of concept » neonate parenteral nutrition

Merging production services of two general hospitals in Paris Suburb

Hospital pharmacy with control area, dedicated personnel for parenteral nutrition preparation working 5d/week



Hospital pharmacy with no controlled area but with the clinical needs for neonate parenteral nutrition with special resuscitation unit

Challenges:

- Supplementary activity without any additional human resources allocated
- 5 km between both sites and daily needs for TPN

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Example 1: « Proof of concept » neonate parenteral nutrition

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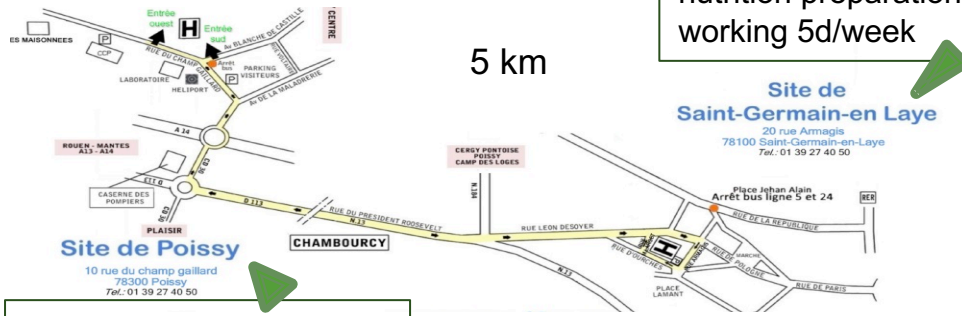
Hospital pharmacy with control area, dedicated personnel for parenteral nutrition preparation working 5d/week



Hospital pharmacy with no controlled area but with the clinical needs for neonate parenteral nutrition with special resuscitation unit

Pharmaceutical solution offered:

- Standardisation of neonate TPN formulations and no individualized preparations
- Anticipated and batch production of the standards

Limits of the model:

- Will not fit with high-specialized academic centers with very low body weight of birth and pathologic cases

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Results - Patient Benefit

- Retrospective study on pre-term infant < 32-week gestation
- Comparison standard (STD) (D0-D1 /D2-D4/ >D4) vs Individualized (IND) admixtures

First week of life:

- Higher amino acid intakes & calcium phosphate better balanced in STD group
- Biochemical parameters similar in both groups – good biological tolerance

Eur J Pediatr (2006) 165: 512–518
DOI 10.1007/s00431-006-0124-1

ORIGINAL PAPER

Richard Lenclen · Sylvie Crauste-Manciet · Philippe Narcy · Saida Boukhouna · Amélie Geffray · Marie-Noëlle Guerrault · François Bordet · Denis Brossard

Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants

Main reasons:

- Limitation of risk of prescription deviation from protocol
- Early intake due to the immediate availability of the admixture

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Results - Pharmaceutical benefits

	IND admixture	SD admixture
Total activity indicators points*	1 659 300	616 600
Whole Time Equivalent (WTE)	6,07	2,26
Total cost : (0.15€ per point)	248 895 €	92 049 €

Comparison of annual activity when preparing with semi-automate Individualized (IND) or Standard (STD) admixtures using batch productions

* Calculated with the help of activity indicators in hospital pharmacies (SFPC)

%	WTE	Cost (€)
-63	- 3,81	-156 846

- Cost saving & productivity by batch production of STD admixtures
- No additional cost for logistic (using planned transportation between two pharmacies sites)

Crauste-Manciet S. Journées Francophone de Nutrition (JFN)– Nice- Novembre 2006

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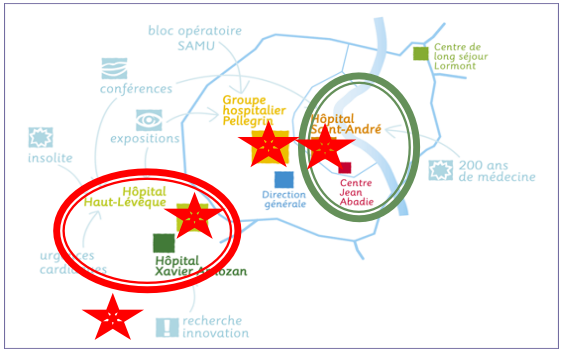
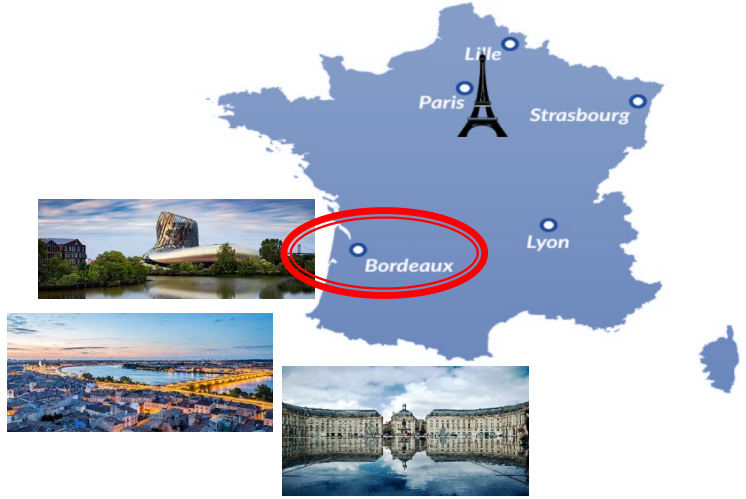
Example 2: Bordeaux University Hospital

- 3300 beds
- One hospital pharmacy (merged in 2016) but still operating on the 3 hospital locations



- South West of France



Example 2: Bordeaux University Hospital

Initial Project:

- 3 production areas in 3 hospitals
- Centralization of all non-sterile and sterile preparations on one single location
- Direction aims:
  - No or limited investments on building, facilities, equipments …

  and
  - Reduction of human ressources expected …

Purposes:

- Standardisation
- Robotization with high productivity level

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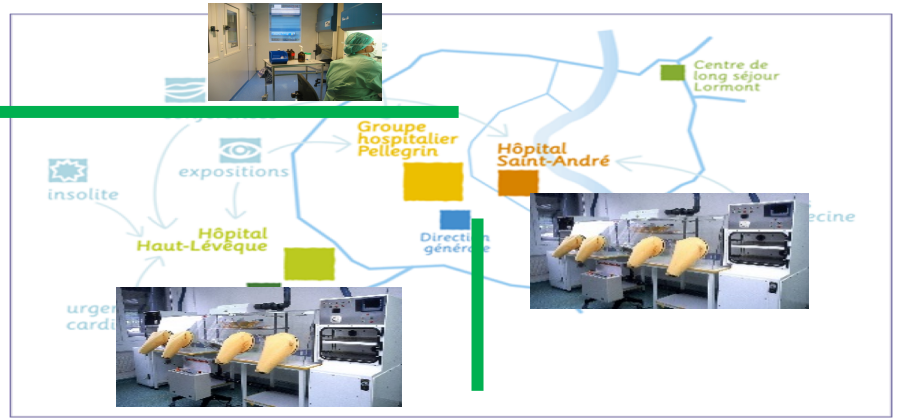
Initial configuration of compounding facilities and human ressources



3 sterile compounding units

Total 90 000 preparations/y

3 non-sterile compounding areas

Total 500 000 units/y

- Technicians: 12
- Pharmacists: 6

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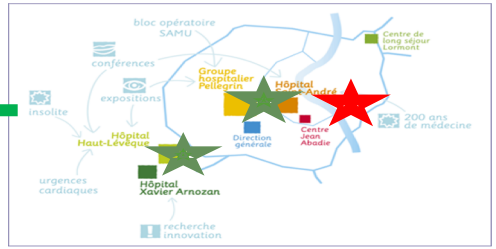
Centralized compounding for non-sterile preparations

- **2 rooms grade D environement**

- Technicians **1 WTE**
- Pharmacists 0.8 WTE



- **1 room grade D environement**

- Technicians **0.5 WTE**
- Pharmacist 0.2 WTE

- **1 room uncontrolled area**

- Technicians **0.5 WTE**
- Pharmacists 0.1 WTE

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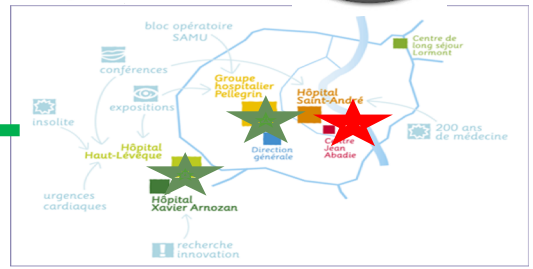
Centralized compounding for non-sterile preparations

- **2 rooms grade D environement**

- Technicians **1 + 1 WTE**
- Pharmacists 0.8 WTE



- **1 room uncontrolled area**

- Technicians **0.5 WTE**
- Pharmacists 0.1 WTE

- **1 room grade D**

→ Requalified for sterile compounding

- Technicians **0.5 WTE**
- Pharmacist 0.2 WTE

High gain – no risk:
No investment for facilities
No new human resources
New opportunities for outsourcing

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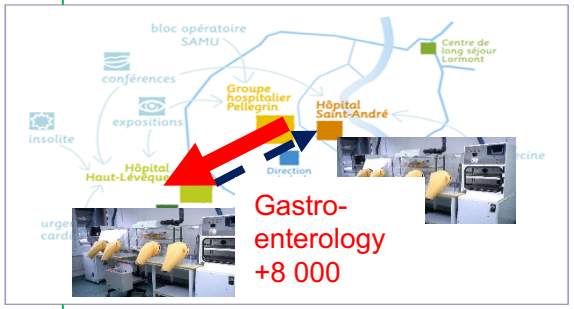
Centralized compounding for sterile preparations

- 1st step: partial transfers of beds between sites

- Activity gain 48 000 →54 000
- Development of standards (batch & series preparations)
- Transfer of WTE
- Technicians **(6+1) 7 WTE**
- Pharmacists **(2+ 1)3 WTE**

- Activity loss 24 000→ 17 000
- Technicians **(3 – 1) 2 WTE**
- Pharmacists **(2 -1) 1 WTE**



Acceptable gain
-Low investment for equiments: peristaltic pumps
-No additionnal human resources

But ….residual activity needing maintaining pharmaceutical staff and facilities on both sites…..

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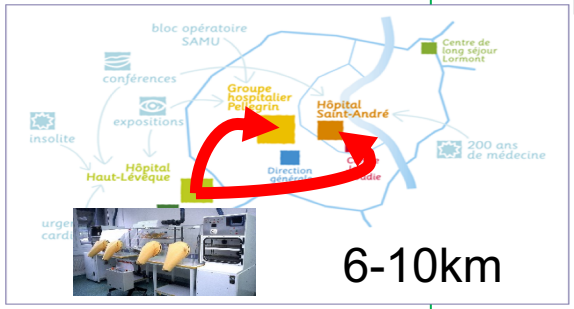
Centralized compounding for sterile preparations

- 2nd step: still « on going »



- 54 000 max capacity of the equipments and facilities
- Technicians: 7 **WTE**
- Pharmacists: 3 **WTE**
-

- Transfer of ~35 000 remaining preparations

Barriers to be removed:

- Investments for new facilities and equipments
- Dedicated logistic for individualized medicine and clinical trials (delay <50 minutes)
- Additional human resources or very high productivity robots….

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Conclusion

STERILE RTA « big centralisation » difficult to achieve:

- Taylor-made/individualized preparation residual
- High cost of drug with physicochemical stability issues difficult to produce by anticipation
- Prep for clinical trials with stability issues and /or investigator's limitations
- Drug candidate should be:
  - Standardized
  - Cheap
  - Stable
- Alternative would be development of RTU…

NON-STERILE preparations « Big centralization » achievable

- Standardization of doses more likely admited by physician even in paediatrics
- Less physico-chemical stability issues: essentially capsules forms

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Self assessment questions

1. Is centralisation a tool for improving quality of compounded drugs? YES
2. Is dose standardization of drug compounded a key for centralisation of ready to administer preparation? YES
3. Is process automation achievable for all ready to administer preparations? NO

Aknowledgements

- Production teams from CHI Poissy-Saint Germain-en-Laye and CHU Bordeaux !

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Take home message!

- Long process
- For human adoption of concept and new technologies implementation
- More the standards can be used more the centralisation will be successful!
- Necessity for investments on facilities and equipments

- Real Potential Gain can be expected
  - Cost
  - Quality
  - Human ressources….
- But mind the gap!
- underestimation of the human ressources and investments i.e. during process implementation
- How to manage intermediate scenarii where centralisation process is not completed
- Don’t let the administrators dream: substantial investments are needed!

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thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
dziękuję
bedankt
sukriya
kop khun krap
go raibh maith agat
dakujem
terima kasih
grazie
arigatō
mochchakkeram
dank je
спасибо
рахмат
Баярлалаа
mauruuru
hvala
sagolun
tapadh leat
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