Role of Institutional Committees for admission of new medicines and innovative medical devices in French Hospitals

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DIA DEVELOP INNOVATE ADVANCE

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Public hospitals in France are under « close monitoring» by National and Regional Health Authorities

- « Contrat de bon usage » (= Good therapeutic management contract) between hospitals and regional health agencies (ARS)
- Many quality and safety items are measured about therapeutic management issues such as implementation of computerised prescription, morbi-mortality reviews, prevention of « never events », nominative dispensation of drugs, centralised chemotheray preparations by pharmacists etc…
- Hospital payment by public health care system under conditions of performance and results on the different points of such contract
- Inspections by regional health agencies and health insurance authorities

Role of institutional medicine and device committees in French Hospitals (1) : Three targets

- **Efficacy** : Implementation of good clinical use of medicines (according to SPC labeling and « official » recommendations for prescription by physicians, validation by pharmacists, administration by nurses) and of devices

- **Safety** : Prevention of drug induced adverse reactions and drug / device supply organisation related errors (objective = attribution of the good medicine at the right dose to the good patient at the right time)

- **Cost « containment » :** Admission of medicine and devices at the best cost/effective ratio for the institution (optimal benefit/risk ratio for the patients at the lowest costs for the institution)

Role of institutional medicine and device committees in French Hospitals (2) : Main tasks

- **Decisions on admission of innovative drugs and devices** for the institution = based on criteria of medical benefit for hospitalised patients (« hospital interest ») with the objective to **provide patients access to therapeutic innovations (medicines and devices) according to « medical need »** ***or « yet unmet medical need »***

- **Monitoring of prescriptions** (detection of off label prescriptions) and Publications of recommendations of good clinical practices, in order to restrict prescriptions to the appropriate patients and reduce drug induced adverse reactions and medical errors (example with the overprescription of Antibiotics with the risk of highly resistant bacteria developpment)

- **Cost analyses of therapeutic innovations**

Different steps before hospital admission of a new medicine in France (1)

1

Marketing autorisation by **EMA or ANSM** for medicines

2

Health Technology Assessment (HTA)
Haute Autorité de Santé (HAS)

- **Therapeutic value (amplitude of treatment effect versus placebo or versus absence of treatment)**
- **Relative benefit/risk evaluation compared to reference therapies in the applied indication**

Different steps before hospital admission of a new medicine in France (2)

3 **Health ministry and Health care system authorities**

- **Agreement to hospitals**
- **Level of reimbursement for drug delivered outside the hospitals**
- **Level of drug prices**
- **Inscription on the hospital « retrocession list » (direct drug sale by hospitals to non hospitalised patients)**
- **Inscription on the Hospital list of high cost drugs (« hors T2A ») which will be directly reimbursed by the health care system to hospitals**
- **Decisions on possible restrictions of such reimbursements among accepted indications by Marketing Authorisation for some very expensive drugs (ex: new antiviral drugs for hepatitis C)**

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- **Public commercialisation** (outside hospitals by pharmacists)
- **Decision of Hospital admission** by drug and devices committees (« comedims »)

Steps before hospital admission of a new implantable medical device (Type III)

Much more simple with the EC certificate ?...

Financement des dispositifs médicaux

Marquage CE + commercialisation

↓

Prise en charge financière

Autres modalités possibles : MIGAC, PRME, PHRC.

4 caractéristiques obligatoires pour être éligible à une inscription sur la LPPR (DMI) :
- Implanté **en totalité** dans le corps humain
- Implantable uniquement par un **médecin**
- Dans l'organisme pour une **durée > 30 jours**
- Objet **principal** de l'intervention

Tout DM non éligible à une inscription sur la LPPR

Si DMI et à l'initiative de l'industriel auprès de la CNEDIMTS (HAS)

DM pris en charge intra GHS

Généralisation de l'usage : radiation de la LPPR

DM pris en charge hors GHS : Inscription sur la LPPR
(durée d'inscription : 5 ans)

Pas d'évaluation de la CNEDIMTS sauf pour certaines catégories de DM fixées par arrêté ministériel

2 modalités possibles, selon le choix de l'industriel

Dépôt dossier CNEDIMTS

Inscription sur une ligne générique :
Tout DM qui répond à la définition et aux spécifications d'une des lignes génériques de la LPPR
(1 ligne / service rendu)

Perte du caractère innovant ou concurrent identifié

Inscription sous nom de marque :
Si revendication d'un caractère innovant et/ou d'un suivi particulier
+/- création acte CCAM
(1 ligne / DM)

Auto-inscription:
Pas d'évaluation de la CNEDIMTS à l'inscription mais programme annuel de révision des lignes génériques
+ déclaration ANSM

Evaluation CNEDIMTS = délai de 90 jours

Attribution d'un Service Attendu (SA) par indication:
bénéfice/risque, place dans la stratégie thérapeutique, intérêt de santé publique

Code LPPR, remboursement hors GHS = **tarif de la ligne générique**

insuffisant

suffisant

Pas d'inscription sur LPPR, **pas de remboursement hors GHS**

Amélioration du SA (ASA) par rapport au comparateur de référence:
Efficacité, tolérance, qualité de vie

ASA I à IV (majeure à mineure)

ASA V (absence d'amélioration)

Si intérêt potentiel souligné : avis favorable pour bénéficier d'un **financement temporaire et dérogatoire**
(article L165-1-1 CSP)

Inscription sous **nom de marque**

délai de 90 jours

Avis CEPS
Détermination du tarif de remboursement : SA, ASA, du DM mais aussi des comparateurs, tarifs des actes

Ministère de la santé :
Arrêté d'inscription sur la LPPR :
prix remboursement + code LPPR

Inscription **sur la ligne générique** (sauf exceptions)

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Procedural steps leading to the decision by the ad-hoc committee of hospital admission of therapeutic innovation

- External demands : Pharmaceutical companies willing hospital admission of a new medicine or a new device (procedure instruction on APHP-COMEDIMS website)

- Internal requests : Possible demands by physicians or by hospital pharmacists (38 hospitals for APHP) in front of a medical need

Different steps of evaluation by the « medicine and medical device » committee

- Internal Expertise (scientific team of the committee)
- External experts (physicians in the different fields)
- Discussion and decision taken during meetings of the committees (medicines, devices, anti-infectious drugs)
- Answers sent to applicant
- Publication of committee decisions

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Hospital admission criteria and questions for new medicines : What is the therapeutic hospital need ? Do we really need it ? Can we afford it ?

- **Marketing autorisation labeling of indications**

- **HTA evaluation (Commission de transparence de l'HAS)**
  - –Therapeutic value, relative benefit/risk assessment
  - –Position of the new medicine in the therapeutic strategy according to **reference treatments and available alternative therapies :**

    How much innovative is the new proposed tretament ?

  - –Population target : in general population ? Among hospitalised patients ?

    How many patients are expected to be treated in APHP hospitals ?

- **Cost / Status**
  - –retrocession list, payment by the Health care system or not (« hors T2A list »)
  - –Marketted outside hospital or not

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Hospital admission of new medicines :Criteria and questions
Which Impact of the new medicine on organisation of hospital activities (« rupture treatment effect »)?

- Major points of impact :
  - Duration / type of of hospitalisation
  - Impact on hospitalisation requirements
  - Ambulatory surgery versus surgery requiring more than one day hospitalisation
  - Impact of expected or avoided Adverse reactions or complications
- Minor points of impact :
  - Adequation of formulation and presentation to hospital use : multiple use vials versus unitary dose presentations (allowing nominative dispensation)
  - Informations on administration through enteral nutrition devices or on the possibilities of crushing pills or opening capsules (pediatric and geriatric uses)
  - Security of package labeling and manipulations for nurses
  - Ready to use formulations versus reconstitutions (powder to be diluted in saline versus pre-filled syringes or auto-injector pens)
  - Duration of stability for chemotherapy preparations and reconstitutions

Many of theses points are not considered by HTA as important therapeutic improvements (translated by ASMR gain) but have a potential impact on daycare management and costs of hospitalised patients

Hospital admission of new medicines
Criteria and questions : Evaluation of costs

- Hospital Cost for treatment of patients with the reference treatment
- Expected impact of the new medicine on direct costs
  - price of the drug itself compared to available drugs
  - the expected number of patients to be treated by the new medicine
  - Status of the medicines (reference and new treatments) regarding reimbursement by health care system
- Assessment of potential reduction (or increase) of hospitalisation related costs by the new medicine ?

- It is not a classic cost/effectiveness study but a specific hospital cost/benefit study

Hospital admission of new medicines
Other parameters and criteria to be taken into consideration

- Interaction between GP Medical practice and Hospital care
  - Impact of hospital prescriptions on out of hospital prescriptions (possible differential costs)
  - Management of Patients hospitalised with their personal treatments that can be not available in hospital pharmacy ?...
- Potential of off label prescription
- Strong pressure form physicians to obtain any new medicine or device…
- Early access programms (ATU/RTU/Early Access Programms by companies with Clinical trials) for medicine still under developpment (before MA) induce a situation of therapeutic demand from physicians and patients with a feeling of established benefit

Hospital admission of new medicines : Criteria and questions Application of the of therapeutic « equivalence » principle

- Basic principle : Hospitals have to provide personnal treatments to all admitted patients (at least those reimbursed by the Health care system)

- However, Hospitals cannot manage to buy and stock all marketed medicines in their Pharmacy…(too many, too expensive, not enough room, many losses if unused after conservation limit)

- What happens if a treatment is prescribed by a physician to a patient which is later hospitalised in one hospital where such new treatment is not available ?

Hospital admission of new medicines : Issue of therapeutic equivalence

Question : Can a therapeutic equivalence be established between available medicines (hospital pharmacy) and those being previously prescribed to one patient ?

- Which pharmacological class ? (same ATC level 4 ?)
- Are generic medicines available in Hospital Pharmacy ?
- Not necessarily the same indications between drugs within a same pharmaco-therapeutic class
- In principle, physicians have to stick to SPC labeling differences, BUT :
  - a same active substance (INN) may have different labeling indications with different marketed medicines (ex : Angioedema treatment/prevention)
  - Physician should prescribe using the INN … but MA labeling refers to the commercial name
- Possible tolerance differences within a same pharmaco-therapeutic class
- Patients are used to their treatments and it is not appropriate to change them when hospitalised (diabetic, hypertensive, epileptic, schizophrenic patients etc…)
- Institutional committees may indicate the list of drugs that can be considered as therapeutically equivalent (and then inter-changed if necessary)

Different decisions by the committee on APHP admission of a new drug or device

Approval

- « Marché négocié » = negociation of price with the pharmaceutical company or manufacturer

  APHP Arguments to obtain reduction of prices :
  - High numbers of patients in APHP hospitals
  - Potential significant impact of hospital prescription on out of hospital prescriptions (sourcing effect)
- Tenders (mise en concurrence) for medicines considered as « therapeutically equivalent »

Rejection

- Rejected but possible supply through the wholesaler distributing company (= grossiste repartiteur)

  = availability within 48 h for non urgent treatments for cases related with a very small number of hospitalised patients each year (less than 100 pts / year)

« On hold » decision (Sursis à statuer) :

- Need for complementary informations, data or additional expert opinions

Off label use of authorised medicines
Evidence based medicine versus Marketing autorisation (MA) process

- Scientific publications are well in advance compared to MA labeling for drugs justifying the early access procedures such as ATU, PTT/RTU
- Physicians are enclined to prescribe according to the last published studies results and communications during medical congresses in some exotic paradises…
- For expensive medicines, hospital budget and the national health care system cannot affort such behavior
- Physicians in France have the right to prescribe any medicine in case of strong scientific justifications for a given patient
- Medicine hospital committees are requested to track and ban off label unjustified prescriptions
  - **Especially Xth line of chemotherapy in cancer treatments (which quality of life gain ?)**
  - **Preventive versus curative established therapies : ex defibrotide in veno-occlusive hepatic disease post Stem Cell transplantation : which value in prevention ? (= Off label) = 100KEuros per patient for 21 days of treatment…**
  - **Immunoglobulines in prevention of chronic kidney graft rejection**

Implantable innovative Medical devices

- Similar process of evaluation and decisions by hospital commitees
- EC certificate, small companies in most cases
- Absence of marketing autorisation process and labeling
- Strong interaction with surgeon implanting the device with a necessary « learning period »
- Small number of clinical studies, under-powered in most cases (small numbers of included patients)
- Very often absence of comparison with reference therapies
- Registries are often useless (not exhaustive, uncompleted follow up, poor quality monitoring, unsufficiently financed)

Implantable innovative Medical devices

How to promote innovation for these devices in such a situation ?

= Case by case discussion according to the innovative aspects of the device, the available therapies, the amplitude and nature of clinical expected benefit, the differential costs etc…)

Only in the cases when the new device is listed by HAS on the LPPR list, hospital admission is always accepted since its cost is directly taken in charge by the health care system (and not by the hospital budget)

But hospital admission demand always occurs long time before HAS decision …this is the problem !!

Early access programm for innovative implantable medical devices

- « Forfait innovation » established by HAS in 2015

Allows payment by health care system of innovative devices when demonstration of their clinical efficacy has been obtained but requiring additional clinical studies to be performed to better define their benefit/risk profile (similar to the EMA conditionnal MA for medicines)

- But How to proceed to reach this level of evidence based medicine for innovative devices ? What steps beyond when health care system does not yet pay for them ? Small companies cannot afford to set up expensive large scale clinical trials
- Public academic hospitals have a role to play to support such innovation and may invest part of their budget to such co-developpment with companies :
  - **Provide scientific and methodological environnment and support in order to set up clinical studies**
  - **Provide recruitement of patients**
  - **Valorisation of such investigation is defined by each contract between hospitals and companies developping innovative devices (hospitals have to get their money back… in case of success !!)**

Conclusions

- Hospitals have the obligation to provide patients access to therapeutic innovation
- Financial constraints oblige Hospital to a more strict regulation of care organisation
- Regulatory obligations may induce contradictory debates and results : Off label use, therapeutic equivalence

Look at the debate on MAB biosimilars…

Ask