

AFSSAPS : Inclusion of external experts into the review process

Pr Philippe Lechat

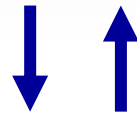
Director of Evaluation of Drugs and of Biological Products, AFSSAPS
CHMP alternate member for France



Agence française de sécurité sanitaire
des produits de santé

AFSSAPS : Assessment of Health products

Internal assessment



External Expertise

AFSSAPS directorates

- Decisions Head Agency's are taken in the name of the state
- General directorate (finances, Informatic, administration, juridic affairs, communication, human ressources) (n=80)
- Directorate of Evaluation (assessment) of drugs and biological compounds (n=350)
- Directorate of inspections (n=150)
- Directorate of control Laboratories (3 locations : Saint Denis, Lyon, Montpellier) (n=200)
- Directorate of Medical Devices (n= 60)
- Direction of cosmetics, biocide and Advertising (n= 40)

Assesment of health products : a major challenge : Role of external expertise

- Help to perform the benefit / risk assessment of health products
 - During their development (Scientific advices)
 - During MAA procedures
 - For products already on the market when safety signals raise
- Provide advices in order for the AFSSAPS to take appropriate decisions
- Participate to the elaboration and transmission of recommendations and all informations to Health Care Professionals and patients

Benefit / risk assessment of health products

- More and more complex given the accumulation of knowledge and available therapies
- Agency assessors cannot in most cases accumulate additional experience especially in the clinical fields
- Internal assessment cannot be in disagreement with the state of art of scientific and medical knowledge and practice
- Internal assessment has then to be connected with the real world of external expertise
- The accurate assessment of a regulatory agency will be obtained based on the collegial scientific debate and the confrontation of experiences

Conditions of reliability of expertise

- Pluralism and collegiality of external expertise which has to be taken among academic structures of research, hospitals and GPs
- Structured interactions between internal assessment and external expertise
- Transparency and effective processes of guarantee of impartiality through the gestion of conflicts of interest

Advantages and limits of interactions between AFSSAPS and external expertise

- Advantages : provides a consolidated scientific assessment of all dossiers
- Enhances the reliability of assessment
- Allows a better transmission of informations and messages
- Limits : AFSSAPS decisions may not always be in agreement with opinion of some experts

AFSSAPS : Agence Française de Sécurité Sanitaire des Produits de Santé

- Internal assessment : Direction of Evaluation of drugs and biological compounds
 - for marketing authorization applications
 - for Clinical trial authorizations
- External expertise : Committees, Working groups, scientific experts lists
- Conflict of interest policy and rules

Internal evaluation of MAA dossiers (European and national procedures) in the Evaluation directorate of AFSSAPS (≠170 assessors + 30 managers)

- Therapeutic evaluation department : 5 units according to the different therapeutic
- Pharmacokinetic,
- Methodology and biostatistics
- Pediatric Investigation Plans
- Pharmaceutical quality department
- Biological products quality assessment
- Viral security assessment
- Pre-clinical assessment and Toxicology
- Safety assessment and pharmacovigilance
- Risk Management Plans and post marketing surveillance
- Regulatory affairs
- Project team leaders

AFSSAPS : External expertise

- More than 2000 external experts
 - One scientific council
 - 25 committees
 - Marketing authorization committee
 - Pharmacovigilance committee, etc...
 - 66 Scientific Working groups
 - Pre-clinical
 - Pharmaco-epidemiology
 - Neurology
 - Infectious diseases, etc...

Working groups for a Marketing Authorisation Procedure

- Corresponding therapeutic fields
- Quality WG (chemicals)
- Quality WG (Biological products)
- Pre-clinical WG
- Safety, Pharmacovigilance
- Risk management plans
- WG on transversal issues : Pre-clinical, pediatrics, interactions, OTC, pregnancy

Complementarity between internal assessment and external expertise

- Internal Assessment

- Dossier recipient
- Document and data extraction
- Redaction of assessment report
- (=comments + synthesis + benefit/risk assessment)
- Redaction of questions to be asked to MAA
- Participation to Teleconf with rapporteurs and MAA
- Preparation of presentations at CHMP sessions

- External expertise in WG

- Analysis of selected parts of MAA dossiers
- Provides a scientific evaluation and a global assessment of benefit, risk, benefit/risk balance
- Provides information of clinical practices and therapeutic alternatives
- Participate to scientific advice sessions

AFSSAPS initiatives to reinforce impartiality of external expertise and of internal assessment

- Renewed process since 2005
- New tools for declaration of conflicts of interest
- Detailed declaration form
- Teledeclaration system on the web
- Algorithm of classification of conflicts of interests
- Set up of a referent group to decide on particular cases
- Justified waivers : rare qualification, without alternative
- Declaration of interest for all AFSSAPS assessors
- More specific and restricted levels of conflicts of interest for chairpersons of committees or WG (independance commitment)

AFSSAPS initiatives to reinforce impartiality of external expertise and of internal assessment

- Recrutement of external experts and members of committees from calls for expression of interest and selection jury
- Publications of committee meeting reports with references to the actual management of conflicts of interests (drafting of a public assessment report for each licensed drug).

Impartiality principle

- Impartiality is a general principle for all public administrative actions
- Members of an advisory committee of a public administration cannot take part to debates when they have a direct or indirect interest into the company involved in the corresponding dossier
- Violation of this rule invalid any decisions taken by the administrative authority based on such opinion

Impartiality

- Relies on individual qualities
 - analysis, argumentation, discussion,
- Relies on a the individual situation of experts
 - Absence of any direct or indirect interests into the dossier
 - Profesional, financial or familial

Direct or indirect Conflicts of interests : May impair the impartiality and independence of expertise and introduce biases of assessment by the regulatory agency

- Financial interests
- Durable links (established activities)
- Scientific works (pre-clinical, clinical investigator)
- Expertise reports
- Advice activities for drug development
- Invitations to congresses and meetings
- Others : familial links, punctual interventions

Public declaration of interests

- Declaration (without proof documents) of all direct and indirect links with stakeholders
 - Legal obligation
 - Conditional to any involvement in analysis of any dossier submitted to AFSSAPS
 - Every year update
 - Update when new links are undertaken by experts
- Public declaration
 - Accessible on demand

Classification of conflicts of interests based on two levels : low (1) and high (2)

- According to :
 - Present or past contracted links
 - Level of involvement of the expert in the considered company (continuous versus ponctual links)
 - Level of involvement of the expert in the considered dossier : scientific advice, strategic advice in development, pre-clinical advice, principal investigator of a pivotal trial, statistical analysis etc...)

AFSSAPS policy of management of Conflicts of interest (updated rules since 2005) : Two levels

- High (2) and low (1)
 - Case by case analysis
 - Classification by a specific deontology internal unit connected with responsible staff
 - Follow up and monitoring of CI for each WG or committee meeting by internal specific checking procedures providing the information to the chairpersons before the start of each meeting

Classification of conflict of interests

- Low level 1 (participation without restriction) :
 - Low level of financial interests (<5000 Euros)
 - Non durable links (<3 years)
 - Co-investigator of a clinical trial
 - Intervention in meetings without link with the studied products
 - Close familial relative belonging to the company without any link with the studied product
 - Advisory activity (case by case analysis)

Classification of conflicts of interests

- High level 2 :
 - Personal significant financial interests (>5000 Euros)
 - Durable links (> 3 years)
 - Principal investigator
 - Redaction of Expert report
 - Intervention in symposia on a specific product sponsored by the company
 - Belonging to one institution receiving substantial grants from the company
 - Close Family member being employee of the company with direct involvement into the studied product
 - Advisory activity (cases by case analysis)

Level 1 (low) of CI : Implication on participation to WG, committees and dossiers assessment for experts

- Cannot be chairman of any WG or committee
- Cannot participate to any vote on the corresponding dossier
- Cannot be involved as reference expert in the corresponding dossiers
- Can participate to the debates and stay in the room during the discussions

Levels of conflicts of interest : Implication on participation to WG, committees and dossiers assessment

- High level 2 :
 - No involvement in any dossier related to the direct conflict of interest and with direct competitors (<3 products on the market)
 - No possibility to be chairman of any WG or committee
 - Has to leave the meeting room during the discussion on the dossiers in relation with the conflict of interest
 - Cannot participate to any deliberation (decision) or vote on the corresponding dossiers or direct competitors

Importance of the external expertise

- Provides scientific competence in all fields
- Provides informations based on experience in any fields (pre-clinical, quality, therapeutic areas)
- Allows to the internal assessment teams to be in close connexion with the real world of research, drug development, therapeutic progress and all important issues of public health
- The plurality of expertise garanties the collegial assessment of any dossier (neutralisation of divergent opinions and views)
- Reinforces the accuracy and quality of assessment of MA dossiers by internal assessors

Interest, limits and difficulties

- Provides access to scientific experts to informations on scientific progress and innovation
- Direct and Indirect benefit for the scientific academic community
- High scientific interest to participate and attend the scientific debates on dossiers
- The issue of the conflict of interest has to be balanced between the guarantee of impartiality of expertise and the requirement of the best expertise ! Best experts have often high levels of conflicts of interests
- Strategy of companies to involve « opinion leaders » among their advisers and investigators
- More and more difficulties for AFSSAPS to recruit experts
- Some sub-represented domains (toxicology, pharmacology...)
- Limitation of the level of public indemnisation of the work of experts and low consideration for experts professional careers, even penalty
- Increasing complexity of dossier versus limited availability of the academic experts

Interest, limits and difficulties

- University and public research institutions more and more reluctant to leave their scientific experts spend their time to work for AFSSAPS without appropriate financial compensations !
- Financial sponsoring of medical research by private / public inter-connexions : complexity of conflict of interest determination for experts belonging to academic institution sponsored by pharmaceutical industry
- Organisation of medical congresses impossible without support of pharmaceutical industry
- Most scientific associations are partly sponsored by private fundings

AFSSAPS :External expertise and internal assessment

Conclusions

- Such combination provides the highest updated level of scientific assessment of submitted dossiers and it works !!
- Links AFSSAPS decisions and communication to the national network of health professionals and patients
- Impartiality of decisions is based on independence from MA applicants through public declaration of interest
- The equation is more and more difficult to solve between objective of scientific excellence and independence given the necessary financial interactions between private and public funding of medical research
- Most experts are competent and willing to serve public health...but may become discouraged to spend their time with AFSSAPS (and EMA) if they can no longer go to medical congresses and perform experimental as well as clinical research...
- Private – public interactions are presently the only way of successful fundings of scientific and medical research