Current regulatory framework of in vitro diagnostic medical devices, perspectives and Afssaps's innovation policy

Jean-Claude Ghislain, AFSSAPS, France

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Overview of the presentation

- 1) Current legislation based on the New Approach

  (DIRECTIVE 98/79/EC - 27 October 1998)

  http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0079:20031120:en:PDF

- 2) EU Perspectives : European IVD-WG, Revision of the directive 98/79/CE ?
- 3) Afssaps's innovation policy

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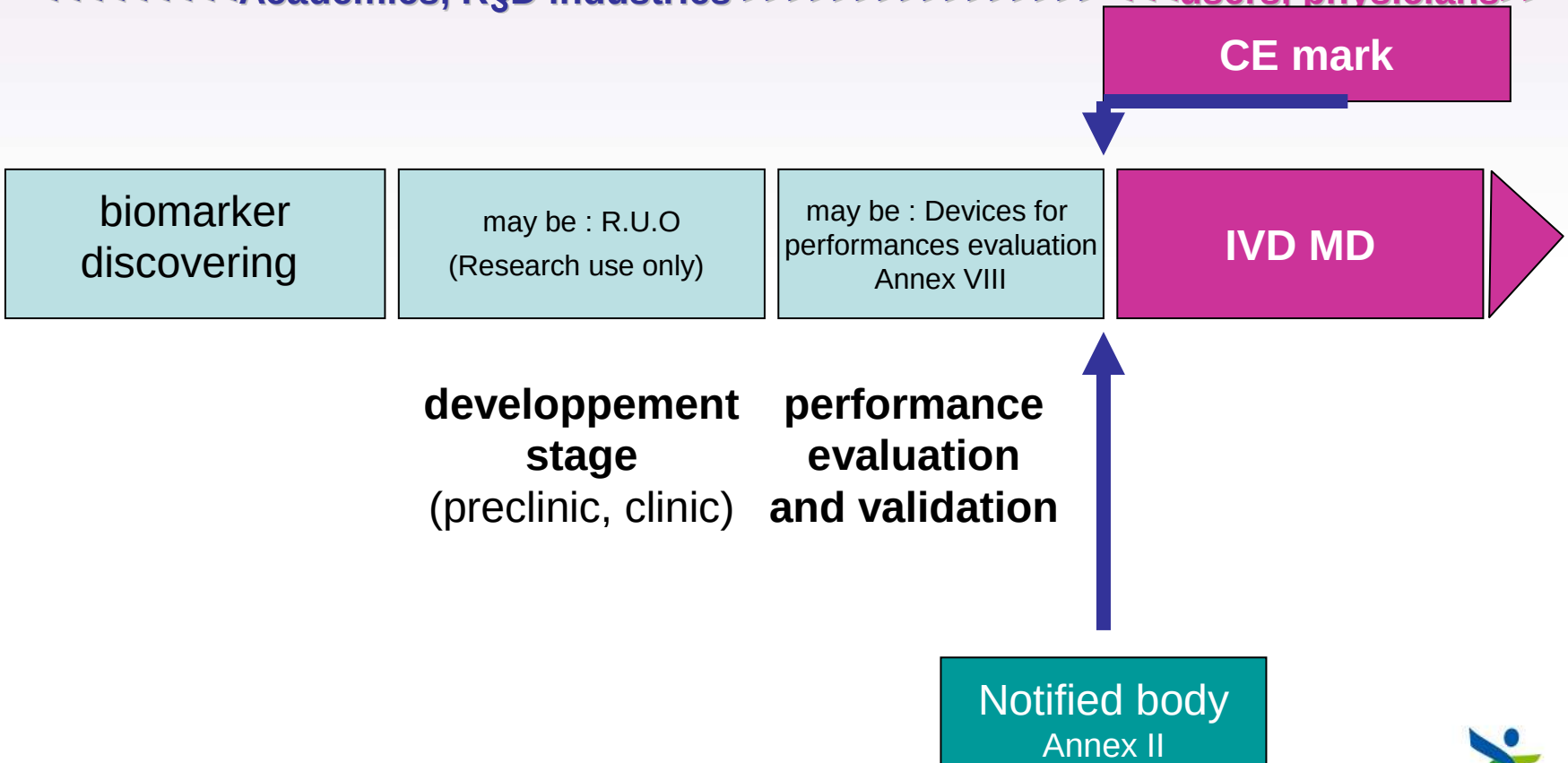
From biomarkers to IVD MD

<<<<<<<<<Academics, R§D industries >>>>>>>>>>>>>>>>> <<<users, physicians>>



Regulatory framework : New Approach

New approach

- Free movment
- Mutual recognition (CE mark).
- Definition of essential requirements that devices have to meet.
- Risk assessment and risk/benefit analysis.
- Reference to harmonized european standards.

Manufacturer is the only responsible for placing on the european market products conform with the essential requirements.

⇨ Directive related to IVD MD 98/79/EC (27 octobre 1998).

Manufacturer issued the EC certificate of conformity for the EC marked products.

⇨ Essential requirements, Annexe I.

For high risks products, manufacturer shall ask for certification from a Notified Body.

⇨ Annexe II liste A et B, autotest.

Legal manufacturer places the products on the market under his own name.

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Essential Requirements

« Devices must meet the essential requirements set out in Annex I which apply to them, taking account of the intended purpose of the devices concerned.»

- Annex I
- ..be used …under the conditions and the purposes intended
- any risks which may be associated with their use must be acceptable when weighed against benefits and to the patient…
- they must achieve the performances …in terme of analytical and diagnostic sensibility and specificity, relevant interferences, repetability…
- requirements for the labelling and the instructions for use.

- Requirements for self testing

- Annex II
- Conformity with common technical specifications drawn up for List A, and where necessary, List B.
- Notified Body

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Member States

- Sauvegarde clauses require the Member States to take all appropriate measures to withdraw unsafe products from the market
- Member States are still responsible for the protection requirements on their territory : Market Surveillance and Vigilance system.

- Member States are responsible for designation and surveillance of Notified Bodies.
- Member States must provide information to other Member States and to Commission.

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News challenges

- Revision of directive 98/79/EC (IVD-WG)
- Take in account new products

- Pharmacogenomics test
- Direct to consumer genetic test
- Predictive test
- Genetic test without medical purpose
- Theranostics
- Personalized medicine

clinical utility and validity

diagnostic services and internet

software (stand-alone)

new classification

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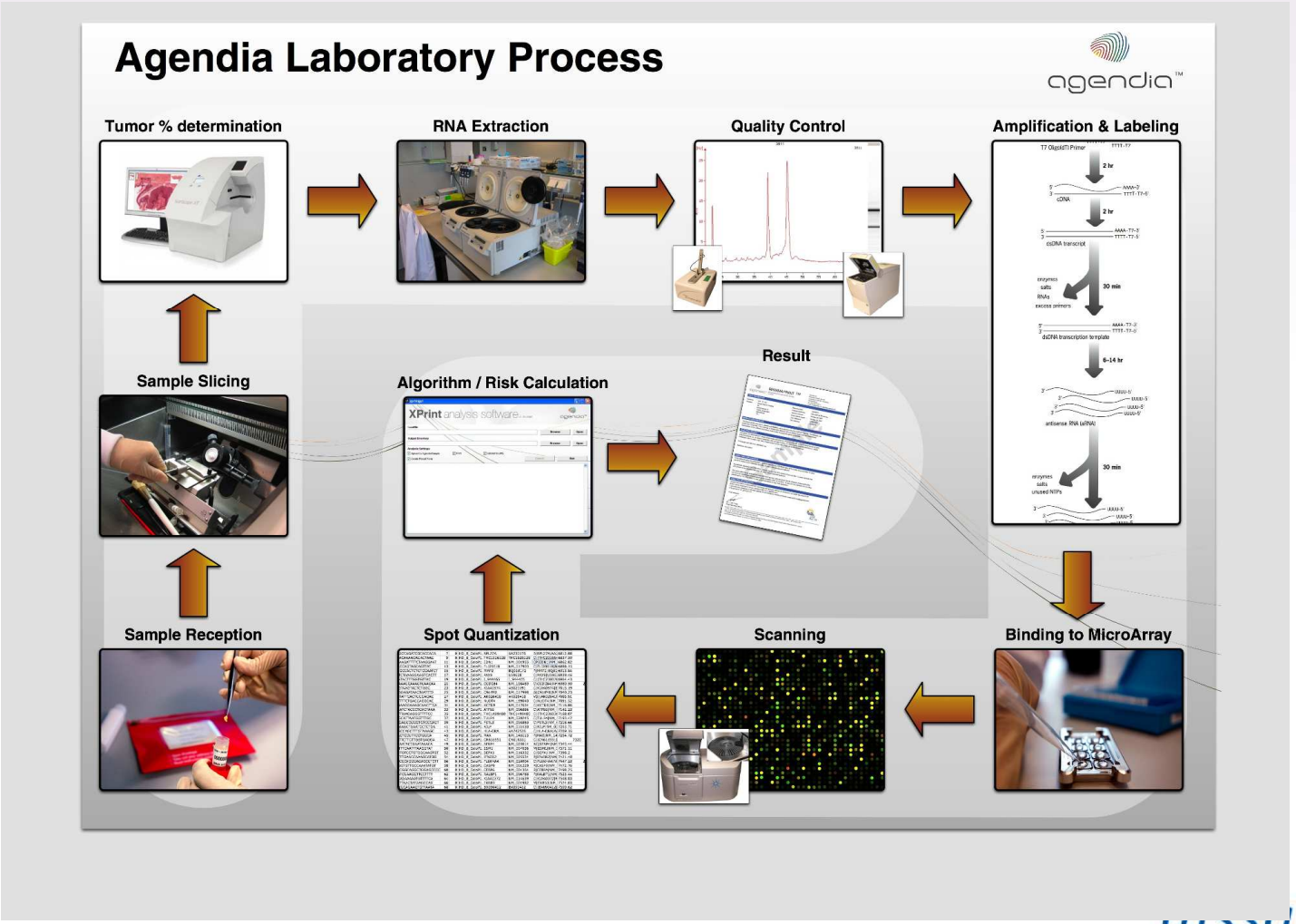
MammaPrint from Agendia

(suceptibility of breast cancer reccurrence)



Clinical utility – Clinical validity

Definitions :

- Clinical utility :
  - demonstration of the potential usefulness
  - added value to patient management decision-making
- Clinical validity : - diagnosis sensibility and specificity, predictive value

Issues :

- **what is covered by these concepts to take into account IVDs specificities / MD specificities ?**
- **how to demonstrate the conformity of IVDs for these concepts ?**

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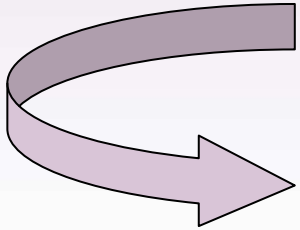
Diagnostic services and internet

D. 98/79/EC : «placing on the market and putting into service»



Manufacturer
- products manufactured and used in a commercial context without being marketed
- results

Internet
easy to by - no control

specimens

results

Issues :
- **MD IVD?**
- **Prohibit specific analysis ?**
- **Control access to internet ?**
- **Confidentiality ?**
- **Advice to patient ?**
- **Responsability of the result ?**

Clinical laboratories

Insurance

Lay person

Doctors

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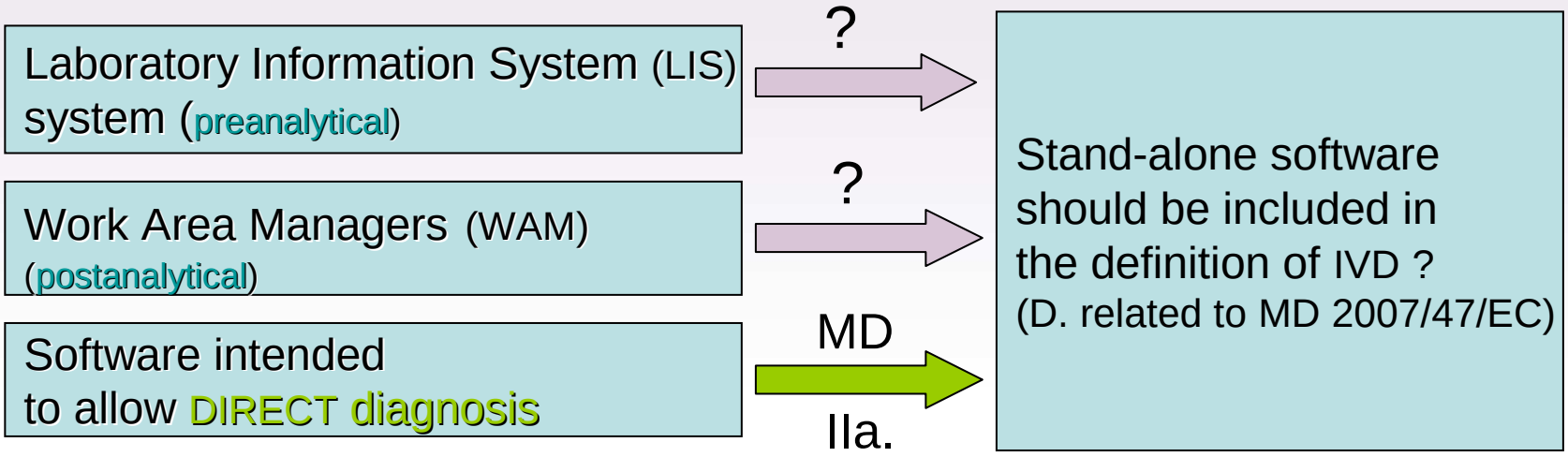
Software, stand-alone



<u>Issues</u> :

- **Rules ?**
- **Definition ?**
- **MD or IVD MD ?**
- **Requirements ?**
- **Classification ?**

Classification

D. 98/79/EC :
Safety of blood supply and of organ donation

Annexe II. liste A and B

Review :
- Adoption of a risk-based classification : A→C
- Increased flexibility,
- Protection of public health
- Alignement with GHTF (Global Harmonization Task Force)

Issues :
- **Rules?**
- **Data?**
- **Transitional period?**

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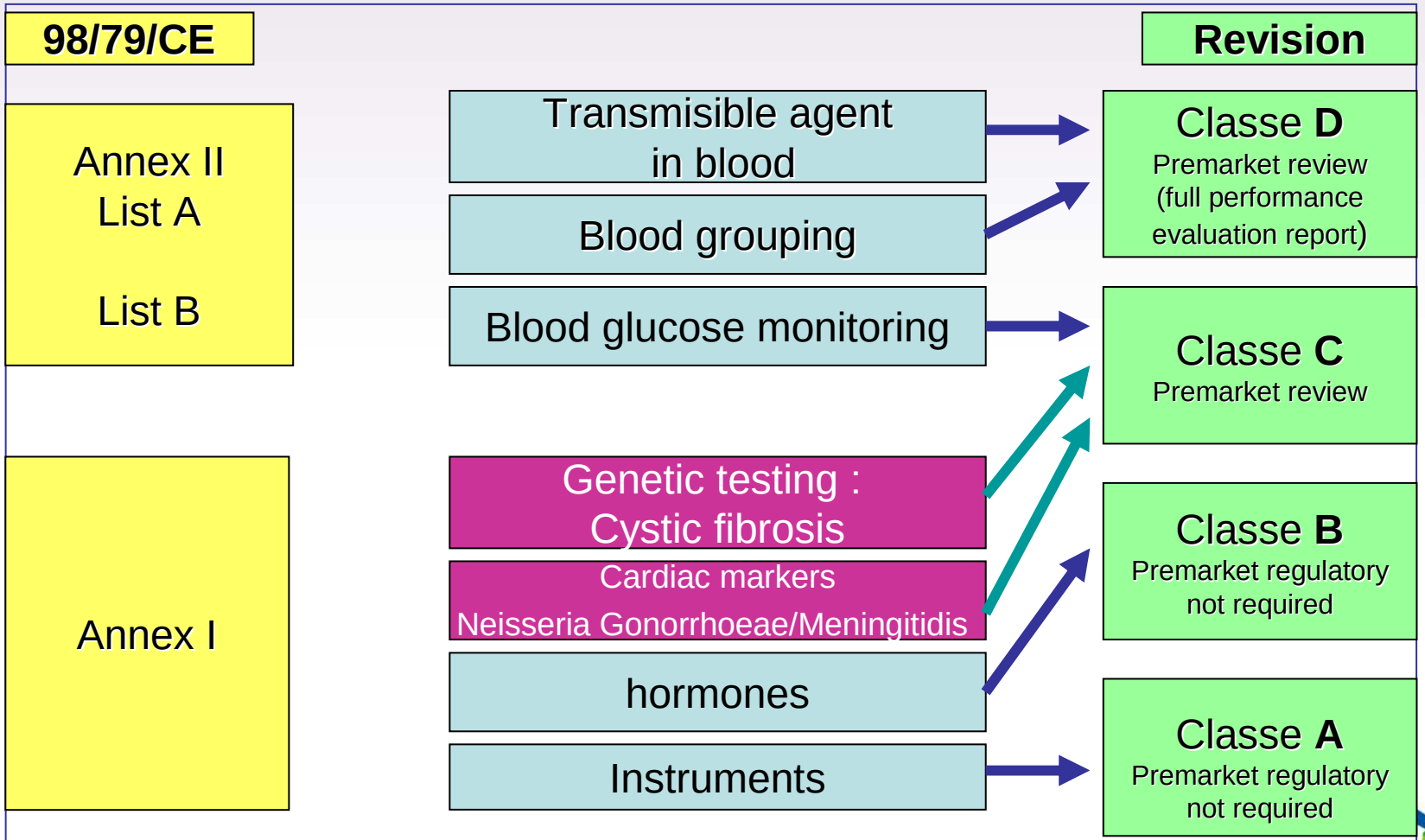
Classification



P. Landais and all., Evaluation et validation des tests diagnostiques dans le cadre du ciblage Thérapeutique, Thérapie 2009 Mai-juin ; 64 (3) : 187-194

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Example : drug development and personalised medicine, theranostic

Improve outcomes by using diagnostic tests

- to predict patient response
- side effects before treatement is initiated,
- monitor therapeutic measures

Issues : diagnostic test and drug

- 2 different regulations (authorization or new approach)
- simultaneous and dedicated development : one drug - one test
- putting on the market
- one drug and some other tests ?

HLA-B*5701 and abacavir hypersensitivity reaction <<<<<<HIV

KRAS and Erbitux* (anticorp cetuximab) <<<<<<<<<<<<<colorectal cancer

Her2 and Herceptin* (trastuzumab) <<<<<<<<<<<<<<<<<<breast cancer

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Afssaps's (new) innovation policy

the complexity of the regulatory landscape

specific assignment for interfacing innovators (meetings with « biotech companies")

facilitate their operations while not giving up our assignment as a health safety agency.

Request forms and support documents available on line: http://www.afssaps.fr/Activites/Accompagnement-de-l-innovation/Afssaps-et-innovation/(offset)/0

analysis of the request,

initial meeting in order to support innovation in several potential ways :

- Scientifics and/or regulatory advice
- Step-by-step monitoring of product development,
- Letters of interest to the applicant
- Forwarding information to other institutions

Jean Marimbert
Director General of AFSSAPS
2009 - http://www.focusreports.net

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Afssap's innovation policy in "practical"

•**regulatory issues**
- **about limitations of directive 98/79/EC**
- **qualification (MD or IVD MD or ?)**
- **about self-certification for most of new IVD**
- **complexity of new IVD / central lab services**
- **French clinical trails regulation**
- **responsibilities (results)**

•**scientific issues**
- **patient selection, treatment strategy,**
- **safety or efficacy surrogate endpoint for drug development**
- **impact of false positive / false negative ?**
- **validation of the clinical value of the biomarkers?**

•**ethics issues**
- **predictive risks IVD without available treatment for the disease?**
- **prognostic risks IVD without available treatment for the disease?**

mutual benefits

For Afssaps: anticipation of future market, identification of possible new risks, identification of regulatory gaps…

For Applicant: regulatory lighting and identification of regulatory authorities expectation, helping to build the scientific and strategic plan of development

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Specifics concerns identified for new IVD based on new Biomarkers

others tools available for development plan

FDA : guidance and FAQ

- http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm
- Guidance for industry , clinical laboratories, and FDA Staff :

  - In Vitro Diagnostic Multivariate Index Assays.

  - Pharmacogenetic tests and genetic tests for heritable Markers.

GHTF : IVD group http://www.ghtf.org/

Innovative medicine initiative
http://www.imi.europa.eu/index_en.html

EMEA : -Committee for medical products for humane use**. Biomarkers qualification : guidance to applicants**

-Novel Methodologies Qualification

http://www.emea.europa.eu/htms/human/raguidelines/sa_pa.htm

Eurpean Commission

http://ec.europa.eu/enterprise/sectors/medical-devices/index_fr.htm

GHTF : IVD group http://www.ghtf.org/

MEDDEV : 2.14 IVD

http://ec.europa.eu/enterprise/sectors/medicaldevices/documents/guidelines/index_en.htm

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Thank you for your attention

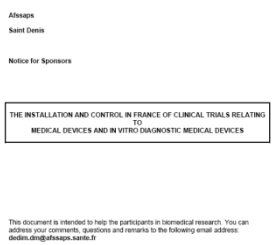
For more :

Web site : WWW.Afssaps.fr

And

Afssaps 2008 annual report in English (but also available in French)

http://www.afssaps.fr/var/afssaps_site/storage/original/application/f041acfdf73129ac6b0487e7bb21a020.pdf



And

Notice for Sponsors of CLINICAL TRIALS RELATING TO MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

http://www.afssaps.fr/var/afssaps_site/storage/original/application/4952b4981d4e71bd8cedfcfeb3ce7b32.pdf

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