1st Latin America Pharmacogenomics & Personalised Medicines Congress
S. Juan - Puerto Rico
May 12-14 2010

Pharmacogenomics: a case study of international regulatory collaboration

Marisa Papaluca Amati
Section Head Scientific Support and Projects - European Medicines Agency
Outline

- The European Medicines Agency (EMA) and pharmacogenomics
- Global development and international collaboration
- Latin America’s contribution to pivotal clinical trials in EU MAA
- Genomics and personalised medicines: way forwards
The Birth of the European Medicines Agency

25 January 1995
official opening
A scientific body of the European Union (HQ London -UK)

Coordination of 4,500 experts network in the 27 EU Member States

Scientific work with Academia, HCP, patients

Collaboration with WHO, FDA, PMDA, Health Canada....

INPUT: scientific data
OUTPUT: scientific opinions -> EC legally binding decision in EU
European Medicines Agency in EU
Genomics and drug adverse reactions
Variability in drug response
CPMP guideline on pharmacokinetic studies in man

CPMP guideline on Bioavailability and Bioequivalence

CPMP guideline on drug interaction

ICH/CPMP guideline on ethnic factors in the acceptability of foreign clinical data

ICH/CPMP guideline on dose-response information to support drug registration
Current regulatory approach

When clinically significant differences in drug response are anticipated as linked to a specific clinical variable, e.g. renal or hepatic disease, age-related differences, then studies are requested in the specific subgroup identified.

The same general principle may apply to genetic or genomic variables.
Genomics and public perception
Consumer Genomics
Hematologic Cancers


100 Years Ago

80 Years Ago

“Disease of the Blood”

60 Years Ago

Leukemia or Lymphoma

Chronic Leukemia
Acute Leukemia
Preleukemia

Indolent Lymphoma
Aggressive Lymphoma

Today

~38 Leukemia types identified:
Acute myeloid leukemia (~12 types)
Acute lymphoblastic leukemia (2 types)
Acute promyelocytic leukemia (2 types)
Acute monocytic leukemia (2 types)
Acute erythroid leukemia (2 types)
Acute megakaryoblastic leukemia
Acute myelomonocytic leukemia (2 types)
Chronic myeloid leukemia
Chronic myeloproliferative disorders (5 types)
Myelodysplastic syndromes (6 types)
Mixed myeloproliferative/myelodysplastic syndromes (3 types)

~51 Lymphomas identified:
Mature B-cell lymphomas (~14 types)
Mature T-cell lymphomas (15 types)
Plasma cell neoplasm (3 types)
Immature (precursor) lymphomas (2 types)
Hodgkin’s lymphoma (5 types)
Immunodeficiency associated lymphomas (~5 types)
Other hematolymphoid neoplasms (~7 types)

5 Year Survival

~0%

70%
A critically ill Turkish boy has had his life saved after scientists were able to read his genome quickly and work out that he had a wrong diagnosis.

The scientists writing in the journal, Proceedings of the National Academy of Sciences, say they completed the analysis of his blood in just 10 days.

They were able to see that he had a mutation on a gene that codes for a gut disease and tell his doctors.

Clinical tests proved that the boy had the disease and he is now recovering.

**Simultaneous analysis**

Richard Lifton, of Yale University Medical School who co-ordinated the research with teams in Beirut and Turkey, said: "The boys physicians sent a blood sample - they only had a very broad diagnosis of what was happening to this five-month-old child and were suspicious that he had a genetic disorder affecting his kidneys.

"Rather than looking one gene at a time hoping to guess which was the right gene causing the problems, we used a new method were we..."
How genomics change the approach to diseases: e.g. breast cancer  
(Detlef Niese 2010)

<table>
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<td>Clinical stage and response to treatment, Her-2, BRCA-1,2</td>
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<td>Treatment decisions:</td>
<td>Her-2</td>
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Support to genomics and personalised medicines

• Briefing meetings/VGDS with Pharmacogenomics WP
• Scientific Advice and Qualification of novel methods
• Evaluation of genomic submissions in Marketing Authorisation Applications (MAA)
• Evaluation of new genomics information for products on the market
• Guidelines
WORLD PLAN FOR THE PHARMACOGENOMICS WORKING PARTY (PGWP)
2010

CHAIRPERSON: Dr Eric Abadie

1. Meetings scheduled for 2010

Dates of Plenary meetings:
- 13-14 January 2010
- 1-2 March 2010
- 1-2 June 2010
- 6-7 October 2010
- 6-7 December 2010

2. Product-related issues

Contribution to the scientific advice and protocol assistance provided by the Scientific Advice Working Party of the CHMP, and to CHMP marketing authorisation or post-authorisation procedures on relevant pharmacogenetics and pharmacogenomic aspects, upon request.

3. Briefing meetings with Applicants

At request of Applicants briefing meetings will be held in conjunction with WP plenary meetings. An appropriate joint discussions with the FDA will be organized.

4. Reflection Papers and Guidelines

- Guideline on the use of PG in PK studies (in collaboration with the EWP-PK group)

- Reflection paper on co-development of PG biomarkers and test platforms

- Reflection paper on statistical and methodological issues associate with PG biomarkers (in collaboration with the EWP)

- Reflection paper on genomics and personalised medicines
Briefing Meetings – highlights

- The PGWP group is multidisciplinary (includes independent Academia experts)

- The aim of the briefing meetings is to highlight technical, scientific and regulatory issues

- Submissions are voluntary and strictly confidential

- Sponsors provide background information within a defined timeline; they do not commit to a strategic approach

- Regulators do not provide formal advice

- PGWP reports to the CHMP
Briefing Meetings – objectives

Brainstorm together about opportunities, limitations and regulatory value of explored genes and expression profiles at all stages of drug development

• anticipate scenarios and potential implications the use of PG biomarkers may have in regulatory processes

• contribute to dynamic regulatory thinking in support of the field

• provide good operational model for supporting at EU and global level research and applications of emerging technologies
Therapeutic areas

- CNS: 18%
- Diabetes/Metab: 15%
- Oncology: 24%
- Immunology: 21%
- AI: 3%
- Blood: 6%
- Musculo-schel: 15%
Context and intended biomarker use

- 26% Safety BM
- 44% Pts Selection
- 15% Dose optimisation
- 15% References develop

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Prospectively defined PG analysis of collected samples and data is largely used across the studies presented.

50% of submissions consider ethnicity.

Pg test before randomization in 70% of case studies presented.
Scientific Advice

- Total number of SA requests increased from 2007-2009
- % SA letters with questions specific to BM doubled every year from 2007-2008 and 2008-2009

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<table>
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<tr>
<th><strong>COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)</strong></th>
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| **QUALIFICATION OF NOVEL METHODOLOGIES FOR DRUG DEVELOPMENT:**
**GUIDANCE TO APPLICANTS** |

| **DRAFT AGREED BY SAWP** | **27 February 2008** |
| **ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION** | **24 April 2008** |
| **END OF CONSULTATION (DEADLINE FOR COMMENTS)** | **30 June 2008** |
| **FINAL AGREED BY CHMP** | **22 January 2009** |

| **KEYWORDS** | **EMEA. CHMP. Novel methodology. Qualification. Scientific Advice.** |
Qualification of novel methodologies

Goal: support/guide innovative methodology (1st phase: emphasis on Biomarkers)

Input: Protocols and results of studies performed by consortia, networks, public/private partnerships, learned societies or pharmaceutical industry for a specific intended use in pharmaceuticals R&D.

Operations: based on existing Scientific Advice procedure; public consultation prior to a Qualification Advice.

Output:
(i) Scientific Advice on future studies required for qualification purposes.
(ii) Qualification opinion and assessment (public document).

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Figure 1: Procedure for the qualification of novel methodologies and/or scientific advice on future protocols and methods for further method development towards qualification.

Day -30: Letter of Intent

Day 0: Start of procedure

Preparatory meeting

Day 30: SAWP 1

Evaluation of draft dossier

Appointing of Coordinator and QT

Day 60: SAWP 2

Discussion of List of Questions; 1st Q&A with Applicant

Day 90: SAWP 3

Meeting with Applicant

Day 180: CHMP 1

Finalisation of report

Day 210: CHMP 2

Draft Report

Day 250: CHMP 3

Submission of draft Qualification Opinion

Day 300: CHMP 4

Adoption of Qualification Opinion

Public Consultation
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

FINAL CONCLUSIONS ON THE PILOT JOINT EMEA/FDA VXDS EXPERIENCE ON QUALIFICATION OF NEPHROTOXICITY BIOMARKERS.

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<td>January 2009</td>
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Comments should be provided electronically in word version to SAWPsecretariat@emea.europa.eu

KEYWORDS | Biomarker Nephrotoxicity Qualification Process, Non-clinical
Consultation on the Qualification Opinion ILSI/HESI Submission of Novel Renal Biomarkers for Toxicity

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<td>Agreed by Scientific Advice Working Party</td>
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<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>18 March 2010</td>
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<tr>
<td>End of consultation (deadline for comments)</td>
<td>1 July 2010</td>
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Comments should be provided using this template. The completed comments form should be sent to SAWPsecretariat@ema.europa.eu

Keywords: Non-clinical, renal biomarkers, nephrotoxicity
Genomic and prediction of T response

Figure 4  Comparison of gefitinib and carboplatin/paclitaxel treatment arms for PFS based on their EGFR mutations status – IPASS study

- Gefitinib EGFR M+ (n=132)
- Gefitinib EGFR M- (n=91)
- Carboplatin / paclitaxel EGFR M+ (n=129)
- Carboplatin / paclitaxel EGFR M- (n=85)

- EGFR M+  
  HR=0.48, 95% CI 0.36, 0.64  
  p<0.0001

- EGFR M-  
  HR=2.85, 95% CI 2.05, 3.98  
  p<0.0001
Genomic and prediction of T response

A

Estimated Probability of Survival

Nonmutated
Mutated

$P = 1.4 \times 10^{-7}$

No. at risk
KRAS nonmutated
KRAS mutated

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Genomic and Drug Labels

Drugs with Tests Required (4.1 – 4.2)

• Abacavir: Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing (see section 4.4 and 4.8).

• Carbamazepine: “Before deciding to initiate treatment, patients of Han Chinese and Thai origin should whenever possible be screened for HLA-B*1502 as this allele strongly predicts the risk of severe carbamazepine-associated SJS (see section 4.4)”

• Herceptin (HER2/neu over expression necessary for patients appropriate for therapy)
Drugs with Tests Required (ctd’)

- **Tasigna** (nisotinib) for imatinib-resistant Ph+ CML
- **Sprycel** (dasatinib) for imatinib-resistant Ph+ CML
- **Trisenox** (arsenic trioxide) for PML/RARα gene+ [or t(15;17)t ranslocation] acute promyelocytic leukemia
- **Erbilux** (cetuximab) for EGFR+ metastatic CRC after failure ofirinotecan; KRAS wild-type metastatic CRC
- **Tarceva** (erlotinib) for advanced NSCLC (« no clinically relevant effects demonstrated for patients with EGFR– tumours, i.e. ≤ 10% cells - »)
- **Vectibix** (panitumumab) for EGFR+ non-mutated KRAS, metastatic, previously treated CRC – conditional MA
- **Tyverb** (lapatinib) in combination with capecitabine for Her2+ BC after failure of taxanes and trastuzumab – conditional MA
- **Iressa** (gefitinib), for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with activating mutations of EGFR-TK.
Hypersensitivity reaction strongly associated with presence of HLA-B*5701

Originally documented by two independent studies in 2002

Warning in the labeling

Barriers to widespread adoption of genetic test

- Retrospective or small prospective clinical trials
- Small number of patients and limited predictive power
- Homogeneous population geographically
- Lack of racial diversity
- Case study definition of hypersensitivity

Source: Lancet 2002;359:727-732,
Lancet 2002;359:1121-1122

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Does prescreening HIV-1 patients for HLA-B*5701 before abacavir reduce incidence of hypersensitivity reaction?

1956 enrolled and randomly assigned to two arms with ~ 800-850 evaluable, matched patients per arm

- Significant differences in clinically diagnosed hypersensitivity reaction (3.4% vs. 7.8%)
  - Immunologically confirmed (0% vs. 2.7%)
  - PPV ~ 48% and NPV ~ 100%

- HLA-B*5701 screening required prior to prescription

PG and Safety: HLA-B*5701

HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin

OR = 80.6
P < 10^{-30}
Allele freq (ctlS) = 0.05

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FDA Approved Drug Labels With Pharmacogenomic information 1945-2005

Number of Drug Labels


- 37%
- 27%
- 25%

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Take away message

- Genomics plays an increasing role in pharmaceuticals development/approval/information
Genomics global regulatory dimension

- **June 2000:** 1\textsuperscript{st} European Agency workshop on Pharmacogenetics

- **2001:** Innovation Task Force (ITF) - Launch of briefing meetings concept and set up of the Pharmacogenetics Working Party

- **2002:** FDA public meeting in Bethesda: (inter alia) Abacavir genomics, the “safe harbour” and the need for an international global thinking

- **2004:** EMEA workshop on pharmacogenomics (with FDA, PMDA)

- **2005:** Start of pilot Joint EMEA/FDA VGDS briefing meetings

- **2006:** Official agreement on the joint VGDS

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PUBLIC STATEMENT
EU (European Commission and EMEA) and FDA agree on
guiding principles for joint FDA EMEA voluntary genomic data
submission briefing meetings

The European Commission (EC), the European Medicines
Agency (EMEA) and the U.S. Food and Drug Administration
(FDA) have agreed to a procedure for joint FDA EMEA briefing
meetings with sponsors following voluntary submission of
genomic data.

The procedure has been agreed to within the scope of the
confidentiality arrangements between the EC/EMEA and the
FDA and is based on prior experience with joint briefings.
FDA and the EMEA have agreed to expand the VGDS process to include the option for sponsors to have joint FDA-EMEA VGDS Briefing meetings. How requests are received processed reviewed
Genomics global Regulatory dimension

- **2007-2008: Pilot joint Biomarkers qualification process (PMDA Observers)**

- **2009: ICH E15 guideline: Terminology for genomics biomarkers**

- **2010: ICH E16 guideline: Context, structure and format of BM submissions**
Global Regulatory Thinking

Europe

- Innovative Medicines Initiative (IMI)
- EMEA roadmap
- CHMP PG Working Party
- Innovation Task Force
- International conferences

North America

- FDA Critical Path
- IPRG
- Collaboration within US
- International conferences

Guideline on PG Briefing Meetings

VGDS Pathway

Notice of Submission of PG Data

- Guidelines on PK and PD and DDI
- PG Discussion Group
- Issues for conducting PGx studies
- International conferences

Japan
ICH Topic E15
Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories

Step 5

NOTE FOR GUIDANCE ON DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES
(EMEA/CHMP/ICH/437986/2006)
ICH Topic E16
Genomic Biomarkers Related to Drug Response:
Context, Structure and Format of Qualification Submissions

Step 3

NOTE FOR GUIDANCE ON GENOMIC BIOMARKERS RELATED TO DRUG RESPONSE: CONTEXT, STRUCTURE AND FORMAT OF QUALIFICATION SUBMISSIONS
(EMEA/CHMP/ICH/380636/2009)

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<th>June 2009</th>
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Take away message

Global drug development: early and continued interaction between FDA and European Medicines Agency on genomics has paved the way to new international collaboration tools.
Geographic origins of patients recruited in the pivotal trials included in MAAs (CP)
Geographic origins of patients recruited in the pivotal trials included in MAAs (CP)

Number of patients in pivotal trials submitted in MAAs to the EMEA per region and year.

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<td>%</td>
<td>Σ</td>
<td>%</td>
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Latin America patients recruited in the **pivotal trials** included in MAAs (CP)

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<th>2008</th>
<th>2009</th>
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<td>104</td>
<td>468</td>
<td>8,081</td>
<td>131</td>
<td>644</td>
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**Note:** The data includes Latin America patients recruited in the pivotal trials included in MAAs (CP) from 2005 to 2009. The **TOTAL** column represents the cumulative number of patients recruited across the years.
Geographic origins of patients recruited in the pivotal trials included in MAAs (CP)
### GCP inspections conducted Central South America countries at the request of CHMP

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<td><strong>Total (world-wide non-EU)</strong></td>
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Genetic Mutations Offer Insights Into Human Diversity:
key for global development

Thousands of minor variations in the DNA of individuals divide the world’s people into distinct groups.

The Bedouin show unusual genetic diversity, with ancestry traceable to the Middle East, Europe, Central Asia and even Africa.

The Yakut, native to eastern Siberia, are most similar to other East Asians, but also have European and Native American relatives.
Take away message

- European Medicines Agency’s survey identified Latin America's important role in contributing to pivotal clinical trials for centrally approved products
Regulatory issues with genomic-driven trials

Definitions of the clinical phenotype
Genomic sampling
Testing and assays development or (co)development

Harmonisation of multicentre-multinational trials

Development of best genomic practices across biobanks, clinical labs and institutions

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Retrospective

All subjects → Drug → Responder

Responder → Test is +

Responder → Test is -

Non responder → Test is +

Non responder → Test is -
Prospective, stratified, where there is possible effect in the (-) group and/or where toxicity in the (-) group needs to be evaluated (Ph III)
Prospective, screened - no possible effect in (-) group (Ph III)

- All subjects
- All PG tested
  - Test is +
    - Drug
  - Test is -
    - Placebo
- Enriched population may not represent a real population in the clinical practice
- Enriched approach may limit the indication for approval and increase risks in off label use
- Safety package limitation – no surrogate for population safety
Regulatory issues and Genomic-driven trials

- How much enrichment effect is useful and reasonable?

- Do we know the frequency and prevalence of the genomic marker in given group and in the “population”?

- There is an issues for PGx defined “orphan” conditions?

- Are prescribers provided sufficient information and guidelines so to minimise off-label use?

- Is it ethnicity an issue?
Regulatory issues: Clinical Utility

Risk/Benefit of therapy
- With a positive test(with a negative test/without a test
- Magnitude of clinical effect
- Impact of false positives/false negatives
- Ethnicity and genotype variants

HTA
- How the test impacts on current practice
- Which would be the gain
- Is the test available and affordable
- IVD versus homebrew

Dialogue to timely address these issues
CHMP Risk Management Plans

« Safety specification »: should discuss which populations have only been studied to a limited degree in the presubmission phase [...] and their implications with respect to predicting the safety of the product in the marketplace [...]

Populations to be considered for discussion should include (but might not be limited to):

- Children
- The elderly
- Pregnant or lactating women
- Patients with relevant co-morbidity such as hepatic or renal disorders
- Patients with disease severity different from that studied in clinical trials
- Sub-populations carrying known and relevant genetic polymorphism
- Patients of different racial and/or ethnic origins
Regulatory issues in labelling for mandatory genomic testing

- Co-development or coordination of drugs and testing methods development: promote the dialogue with Industry (pharmaceuticals and diagnostics) and clinical lab genomic testing networks

- Encourage development of best practices for in-house testing

- Reinforce the dialogue on regulation of genomic BM testing platforms with IVD Regulators and IVD Industry to address the limits of current regulatory frameworks
Take away message

Successful genomic applications reality today

The European Medicines Agency and the FDA in the forefront contributing to a favourable environment for PG in drug development, approval and labelling

Genomics is challenging traditional methodologies in clinical trials and epidemiology

Personalised medicine will require further regulatory changes to optimise regulatory oversight of drug/test clinical development and use

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Personalised medicines: scientific Bottlenecks

- Limited knowledge of different genes associated pathways interaction (lessons learned from monogenic diseases and gene therapy failures?)

- Mechanistic studies to support the biological plausibility of genomic BM and their relationship with phenotype

- Inconsistency of phenotypes definitions and of testing methods (limited assays’ cross validation) preventing pooling of genomic data across studies

- Limited availability of and access to adequate quality and quantity of samples associated to well defined phenotypes to establish clinical relevance of associations (bio-banking from randomised studies - longitudinal cohorts) in retrospective analyses

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Personalised medicines: scientific bottlenecks (ctd)

- Limited evidence-based data (prospective randomised trials) to establish clinical usefulness (BM guided treatment/prevention leading to better clinical outcomes)

- Limited data on prevalence and role of BM different variants in different ethnic groups

- Limited availability of consistent “clinically viable” test methods
omics in personalised medicine: research needs

1. Expand knowledge on gene regulation, – epigenetics, silencing RNAs etc, interaction with environmental factors and mechanistic understanding of diseases pathways, of treatment responses and resistance to enhance translational research to clinical applications

2. Develop and standardise genomics data management, bioinformatics and medical informatics systems

3. Large prospective randomised studies/cohorts with
   - consistent case phenotype definition
   - adequate biological sampling and ascertainment to assess both clinical relevance and usefulness of genomic BMs
   - hypothesis' driven flexible design or nested studies
omics in personalised medicine: research needs

1. Further develop knowledge on genetics variants prevalence and clinical effects in different ethnic groups

2. Support networks focussing on reference methods, technologies, materials and probes for development of appropriate assays (fit for clinical purpose)
Take away messages

1. Genomics plays an increasing role in pharmaceuticals development/approval/information

2. Global drug development: early and continued interaction between US FDA and European Medicines Agency on genomics has paved new ways to international collaboration

3. European Medicines Agency’s survey identified Latin America’s important role in contributing to clinical trials for innovative products

4. Genomics is changing the global paradigm of drug development pre and post approval: genomics and ethnicity is an important area of research as we need to know whether differences matter

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Thanks for your attention

Science: our basis
Medicines: our scope
Health: our purpose

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