EMA – The Next 5 Years
The Innovators Perspective

Elias Zerhouni M.D.
President, Global R&D, Sanofi
HAPPY 20th BIRTHDAY EMA!

- ENHANCING REGULATORY SCIENCE

- CONVERGENCE vs DIVERGENCE in GLOBAL REGULATION

- INTENDED AND UNINTENDED CONSEQUENCES ON PUBLIC HEALTH
EMA over the next 5 years:  
Progress through Partnership

- Scientific Innovation and Regulatory Innovation must work hand-in-hand
- Together we ensure that biomedical research can be translated into safe and effective treatments.
- EMA has been leading the way for 20 years, based on:
  - scientific excellence
  - integrity
  - reliability
  - transparency
The Changing Face of Pharma?

- Pharma R&D operates very differently today.

- Large, internal research efforts are being replaced by access to external innovation – Biotechs, universities, foundations, and other Pharma companies.

- Actively seeking and participating in public-private partnerships, e.g., IMI (EU), AMP (NIH)

- Building a precompetitive “COMMONS” to enhance knowledge

- Looking for newer R&D models, adaptive virtual innovation networks – the “UBERification” of R&D

- Scientific advances in modalities and technologies still hampered by lack of human disease biology understanding

- The face of the major players today will likely change dramatically over the next 10 years.
Investing in innovation – Investing in the future for patients

- We invest more of our revenue into R&D than any other industry

- Today, more than 5,000 medicines are in development globally

<table>
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<th>Share of revenue spent on research and development</th>
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<tr>
<td>Pharmaceuticals and biotechnology</td>
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<tr>
<td>Internet service provider and web search</td>
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<td>Software and paper publishing</td>
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<td>Physical, engineering, and life sciences</td>
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<td>Computer and electronics manufacturing</td>
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<td>Medical devices</td>
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<td>Aerospace and defense</td>
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<td>Computer software and systems design</td>
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<td>Data processing and hosting</td>
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<td>Machinery</td>
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<td>Automobiles and parts</td>
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<td>Chemicals</td>
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<td>Plastics, minerals, and metal products</td>
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<tr>
<td>Mining, extraction, and support activities</td>
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<td>Architectural engineering</td>
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<td>Food and beverage</td>
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<td>Telecommunications</td>
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<td>Utilities</td>
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<td>Banking, credit, and securities</td>
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<td>Health care services</td>
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How well does our investment turn into new treatments?

- Our investment into new treatments is only as successful as the regulatory system that governs us.

- Innovation is the key. Innovative science, innovative products and innovative regulatory pathways.

Patients and their families are waiting!
Strong Regulatory Science is critical to successful biomedical innovation

- If regulatory science keeps pace with biomedical research, it can fuel the furnace of innovation

- But if regulatory science lags behind, it may stifle innovation

- Without a clear development and regulatory pathway to the patient, investments dry out.

- Major trend towards specialty vs primary care therapies: IS THIS GOOD FOR PUBLIC HEALTH?

“Regulatory science: the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated products.”
Science Drives Innovation: EMA needs to be prepared to receive the pass!

- Science drives Innovation: Regulation impacts investments

- A regulatory system designed in the 1950s for small molecule pill-based medicines will not meet the needs of 21st Century science

- Regulatory reform needs to match the pace and trajectory of scientific innovation

- The EMA is the access enabler as the key link between the science and the patient

Complex Biologics, Gene Therapy, Regenerative Medicine, Precision Medicine, Diagnostic/device/drug combos, Nanomedicine, Synthetic Biology...
Talented Regulatory Scientists are crucial for regulatory agency success

● A regulatory agency needs a continuous inflow of new, young, trained, regulatory scientists, if it wants to keep pace with the science.

● Attracting and retaining talent will ensure the EMA can continue to improve on regulatory science, including:
  ● Stimulating innovation in clinical evaluation
  ● Supporting new approaches to improve product manufacturing and quality
  ● Ensuring Agency readiness to evaluate innovative emerging technologies
  ● Harnessing real world evidence and big data analytics to improve health outcomes
  ● HOW CAN WE HELP?
A well-equipped drug development toolbox: e.g. Biomarkers

- Drug development needs to be more efficient, as the number of targets and our understanding of the etiology of disease is growing.

- Biomarkers are key, but clinical utility of biomarkers is limited by lack of international consensus regarding qualification.

- EMA has a process that shows promise:
  - Request submitted by C-Path March 2013
  - Consultation period ended Aug 2013
  - Adopted by CHMP Sept 2013

- International agreement on biomarker qualification (e.g., evidentiary standards) would increase their utility.
Companion Diagnostics: the right drug for the right patient

- With better understanding of disease and patient stratification, companion diagnostics allow us to better target treatments to patients that will benefit from them
- This will also enable us to move towards new models for paying for performance
- Approval of both drug and diagnostic is often crucial to getting treatments to patients
- EMA flexibility on companion diagnostics encourages innovation
Adaptive Trial Design: Collaborating on New Models of Evidence Generation

- Shifting away from RCT as the ‘Gold Standard’
- Flexibility in clinical trial design will reduce the cost, complexity and time of drug development for both patients and industry
- Continuous Trials: use databases for major diseases
- Expanded use of single-arm open label clinical trials
- Movement toward adaptive clinical trial designs
Adaptive Pathways: The value of experimentation

- EMA’s willingness to actively explore new approaches to drug approval
  - NEWDIGS: multi-stakeholder think-tank leading to development of Adaptive Licensing concept.
  - Adaptive Pathways pilots underway
  - THIS COULD REVERSE THE TREND AWAY FROM PRIMARY CARE THERAPIES FOR CHRONIC DISEASES

- Sharing experience with other regulatory agencies
  - Breakthrough Therapy Designation discussions underway
  - Parallel submission of Joint Letter of Intent for biomarker qualification – a good start…
Brave New World – Working together to make Use of Real World Data in Regulatory Decision-Making

- Assessing Effectiveness?
- Informing patient stratification?
- Tracking Safety?
- Enriching post-approval commitments?
- Informing the label?
Regulatory use of Big Data – are we ready to change our mindset?

- Can we learn to start with the data, not the hypothesis?

- Can we get comfortable with knowing there is a correlation without necessarily understanding the causality -- knowing ‘what’, not ‘why’?

- Can we learn to change the tires on a moving car - making good use of real-time big data demands analysis in motion?

- Are we ready to explore approaches that examine the whole population and not a controlled samples?

- Many policy and technical challenges ahead – boundaries, privacy, data localization…
Working Together to Build the Science of Benefit-Risk Assessment: Engaging the Patient

- Building on the work of the EMA on benefit-risk communication
- EMA’s notable ability to focus on benefit and risk associated with safety and efficacy amidst the panoply of other decision factors e.g., promotion, payment, access.
- Patients may have different perceptions of risk than regulators
- What can we learn from the EEA, EPA and other agencies about conversations around risk?
- Recognizing that the science of patient engagement in risk-benefit is complicated by:
  - Translation of technical information
  - Sense of loss of power or control
  - Rumor and speculation
  - Uncertainty
Clinical Trial Transparency: a twisting path to a good outcome

- We agree that the sharing of data is good for science!
- The sharing of data also brings some risks
- The PhRMA-EFPIA Principles were ground-breaking
- EMA has its own Data Sharing Policy and our positions are now aligned
- Could we have done it better?
  - Earlier understanding of each others goals and concerns?
  - Let’s remember to talk early and often
The current state of affairs: different pathways in each country

Adaptive Pathways
Breakthrough Therapy
Fast Track
Priority Review
Accelerated Approval
Conditional Approval
Drug development: the challenge for global companies

- Sanofi conducts clinical trials in 112 countries and market our drugs in more than 130 countries

- Despite all the good work done by ICH, different rules and regulations apply in different countries
REGULATORY CONVERGENCE OR DIVERGENCE AROUND THE GLOBE?

- R&D is no longer national but is now global in nature
- Increasing regulatory differences across regions imposes a large opportunity cost on innovation
- Differences in legislation, implementation of regulations, socio-political systems and attitudes and inherent opinion biases within agencies lead to divergence in response to the same evidence
- 50% of labels show significant differences between EMA and FDA
- Discordant decisions of approval or denial in 22 percent of cases
- Significant and increasing differences in timing of regulatory steps across countries, with significant delays impacting conduct of trials

IN MY SHORT EXPERIENCE OF 5 YEARS, I HAVE NOT SEEN A SINGLE REGULATORY DECISION THAT WAS FULLY CONSISTENT ACROSS REGULATORY AGENCIES.
FDA Office of New Drugs, 2009 New Drug Review, A comparison of new molecular entity (NME) outcomes by the FDA and EMA. Review of 81 novel drugs submitted almost simultaneously to both agencies from January of 2006 to October of 2009

Regulatory Outcome

- Approved by both Agencies (49)
- Not approved by either Agency (14)
- Approved by FDA Only (5)
- Approved by EMA Only (13)
Figure 1: NAS approval time for six regulatory authorities in 2004-2013

- Median
- 25th and 75th percentiles

<table>
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<tr>
<th>Approval year</th>
<th>EMA</th>
<th>FDA</th>
<th>PMDA</th>
<th>Health Canada</th>
<th>Swissmedic</th>
<th>TGA</th>
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<tr>
<td>Approval time (days)</td>
<td>1200</td>
<td>1000</td>
<td>800</td>
<td>600</td>
<td>400</td>
<td>200</td>
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On average the EMA takes around six months more than the FDA to approve a new drug or new indication for a drug. This is mainly due to time lost to clock stop and the delay between getting a positive CHMP opinion and approval from the European Commission. Furthermore, in the US almost all cancer drugs are approved under priority review, whereas accelerated assessment is rarely used by the EMA.

*Day 150 for accelerated assessment; Rap – Rapporteur
Figure 4: Number of NAS approvals by review type in six regulatory authorities in 2004-2013

- EMA
- FDA
- PMDA
- Health Canada
- Swissmedic
- TGA

Number of NAS approvals vs. Percentage of expedited reviews

- Standard
- Expedited
- Expedited %
Regulatory Harmonization at the national level – A Good Start

- Joint Submission for Biomarker Qualification

- EMA-FDA cluster meetings
  - Focus on specific topics requiring an intensified exchange of information and collaboration, such as biosimilars, medicines to treat cancer, orphan medicines, medicines for children, blood-based products, among other topics.
  - Health Canada and the Japanese Pharmaceuticals and Medical Devices Agency are also involved in some of these clusters
World harmonization of regulations: The need is urgent!

- Imagine international air travel without regulatory harmonization!

- The Chicago Convention of 1944 emphasized the basic elements of international air traffic control. It recognized the need for universal interoperability of ground and airborne system elements – different rules could not govern airspace by country.

- The International Civil Aviation Organization was created to take into account safety, efficiency and national sovereignty
Global Harmonization: a more aggressive approach may be needed!

- A new Regulatory Authority?

- A Trade Agreement?
Trends in R&D Portfolios and Worldwide Trends in Public Health

- WHO projections show that chronic diseases affecting millions will dominate disease burden
- Investment in cancer R&D dwarfs all other areas
- Investments in Neuropsychiatric diseases has decreased across the industry
- Developing a rare, orphan or specialty therapy is increasingly preferred given the easier hurdles in term of development and regulations.
- Yet 80% of Healthcare spending is due to long term chronic diseases affecting millions
- Developing drugs for primary care diseases is the riskiest part of R&D
- The majority of approved drugs are now orphan or specialty drugs affecting smaller populations

WHAT DO WE NEED TO DO TO REVERSE THIS WORRISOME TREND?
KEEP CALM AND CARRY ON
Thank You