Workshop on "Enhancing Translational Research and Clinical Development in Alzheimer's Disease and other Dementia: The Way Forward"

11-12 November 2014, Lausanne, Switzerland

Hosted by the Swiss government, and in cooperation with the Global CEO Initiative on Alzheimer's Disease, and with Alzheimer's Disease International

Draft Agenda

The Workshop will provide an international forum for stakeholders to articulate achievements and opportunities in biomedical research and health innovation for Alzheimer's disease and other dementia. It aims to discuss the challenges and barriers to the development of disease-modifying treatments and diagnostics for Alzheimer's disease and other dementia. This includes the need to invigorate biomarker R&D, adopt more innovative clinical trials, and encourage an adaptive regulatory process. Stakeholders will engage in discussions to consider options towards more innovative research and governance models.

Through an exchange on good practices, representatives from governments, regulatory agencies, academia, industry, and patient organisations will hear about progress in:

- Implementing innovative biomedical research tools in product development and regulatory models, including the scope for adaptive regulatory processes, enhanced clinical trial designs and a strengthened diagnostic environment;
- Addressing the individual needs, challenges and options of all stakeholders in biomedical research and health innovation through open, collaborative research approaches;
- Enabling a global paradigm shift from treating symptoms to changing the underlying progression of the disease – identifying challenges and gaps in the development of disease-modifying treatments in Alzheimer's disease and other dementia.

The Workshop in Lausanne is a follow-up event to the OECD Workshop on "Better Health through Biomedicine: Innovative Governance" that took place in Berlin, Germany, 2010. It is intended to provide input to ongoing international policy discussions on Alzheimer's and dementia, including the work of the World Dementia Council.

Day 1, 11th November 2014

- **Welcome and Opening Remarks**

  09:00 – 09:20

  Isabella Beretta, Chair of OECD Working Party on Biotechnology, Swiss State Secretariat for Education, Research and Innovation, SERI, Switzerland

  Dirk Pilat, Deputy Director, Directorate for Science, Technology and Innovation, Organisation for Economic Cooperation and Development, OECD

  Tania Dussey-Cavassini, Vice-Director General of Swiss Federal Office of Public Health, Ambassador for Global Health, Switzerland

- **Keynote: Accelerating a global paradigm shift in biomedical research and health innovation for Alzheimer's disease and other dementia - the challenge**

  09:20-09:40

  Dr Dennis Gillings CBE, World Dementia Envoy

Accelerating innovation for Alzheimer's disease and other dementia is a key challenge. In response to this challenge, the World Dementia Council (WDC) was established at the invitation of the UK government following the G8 Dementia Summit in December 2013. It aims to stimulate innovation, development and commercialisation of disease-modifying therapies, and care for people with dementia. The WDC follows a collaborative approach with all stakeholders along the value chain of biomedical research, health innovation, and care. Examples of issues it seeks to address are: How to achieve transparent and predictable governance in a fast moving multi-stakeholder environment? What are the key components of "integrated drug development" and what are the measures for simultaneous support? In a resource-limited environment, what are the most critical and achievable global actions needed in research, drug development and regulatory science as the focus shifts to developing disease-modifying treatments? The Council has established a framework to enable and incentivise the eco-system around dementia and a plan to achieve its goals.

- **Session 1 – Driving a Global Paradigm Shift to Stop Alzheimer's by 2025**

  09:40 – 12:30 (170 min)

  20 min each Presentation, 30 min Coffee Break

  60 min Panel Discussion and exchange with Workshop Participants

  Moderator: Raj Long, Bill & Melinda Gates Foundation, Senior Regulatory Officer - Integrated Development, Global Health, United Kingdom

The purpose of this session will be to discuss the translation of progress in the scientific basis of Alzheimer's disease and other dementia into recent and future clinical and regulatory approaches. Current evidence suggests a long preclinical phase of Alzheimer's disease, which provides a critical opportunity for therapeutic intervention, and which needs

to be considered by both the research community and policy makers. These changes require new trial designs, assessment tools and regulatory processes to monitor disease progression and to evaluate therapeutic efficacy in patients with preclinical Alzheimer's disease. A joint engagement amongst all stakeholders is needed in order to strengthen innovative research strategies and to accelerate its translation into clinical practice.

1.A: The scientific basis for a paradigm shift

Philip Scheltens, Director of the Alzheimer Center at VU University Medical Center, Professor of Cognitive Neurology at VU, Netherlands

There has not been a new Alzheimer's treatment on the market in over a decade. A recent publication cited a near 100% failure rate in Alzheimer's drug development from 2002 – 2012. Overall, drug development in CNS has had a single digit success rate. At the same time, given the high attrition rate of drug development for Alzheimer's disease, stakeholders have been analysing the reasons behind failure, for example: wrong pathophysiological and translational models, lack of appropriate animal models, inappropriate trial design, and intervention too late in disease progression. Researchers now focus on the development and early administration of disease-modifying treatments, the elucidation of pre-symptomatic disease processes, and the translation of innovative research approaches into new clinical trial designs. In order to manage financial risks and efficiently use limited resources, clinical programmes are designed to allow an early verification of the therapeutic hypothesis through iterative processes in translational studies. These measures create additional challenges for the delivery of a robust evidence base on the early pathological mechanisms of Alzheimer's and on potential pharmacological targets and biomarkers that are predictive of symptomatic presentation. The question remains to be answered whether the multifactorial nature of Alzheimer's disease can be addressed through the traditional model of a single-target therapy or whether it requires combination approaches with associated regulatory adjustments.

1.B: The regulatory context – US and European perspectives (20 min each)

United States: Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, United States

Europe: Karl Broich, President, BfArM and Chair of CNS Working Party, EMA; Manuel Haas, Head of Central Nervous System and Ophthalmology Scientific and Regulatory Management Department - Evaluation Division, EMA

Medicines regulation defines the frameworks and approval processes for the delivery of safe and effective diagnostics, preventive medicines and treatments. Regulatory agencies are a key, independent partner for innovators in drug development for Alzheimer's disease. The unique needs of the disease, persistent knowledge gaps and failure in the delivery of disease-modifying drugs have shaped regulatory processes and governance models for product development. In close collaboration with stakeholders, regulatory agencies identify and address the barriers in the translation of research discoveries into innovative therapies. Understanding the molecular and biochemical underpinnings of Alzheimer's disease is of significant importance to fill drug development pipelines and to enable evidence based decision making in medicines regulation. This session will explore what has been achieved in

recent years, what are the challenges in adapting existing regulatory frameworks to the needs of innovative research strategies aimed at early stage and pre-symptomatic populations, and what can be expected from regulatory agencies in supporting the development of disease-modifying therapies as a new standard of care in Alzheimer's disease.

1.C: Benefits and opportunities to accelerate Alzheimer's disease research and development

Troy Scott, Senior Economist, RTI International, United States

The development of disease-modifying treatments for Alzheimer's disease faces a number of barriers. Among these are the lack of surrogate biomarkers, the exceptional size and duration of clinical trials, difficulties in identifying appropriate populations for clinical trials, and the limitations of monotherapies in addressing such a complex multifactorial disease. This presentation provides a first estimate of the quantified cost-benefits resulting from coordinated, joint efforts addressing the barriers to developing disease-modifying treatments for Alzheimer's disease, and from the use of innovative research tools and infrastructure.

Lunch Break, 12:30-13:30

- **Session 2: Biomedical Research, Diagnostics and Regulatory Science**

  13:30 – 15:30 (120 min)

  20 min each Presentation

  60 min Panel Discussion and exchange with Workshop Participants

  Moderator: Zoltan Bozoky, Chief Strategy Officer, Dementia Innovation Unit, Cabinet Office/ Department of Health, United Kingdom

This session will explore recent progress and challenges in biomedical research, therapeutics and diagnostics development, and regulatory science related to Alzheimer's disease. The presentations and dialogue with a range of stakeholders will elaborate on how new insights into the biochemical and molecular underpinnings of Alzheimer's disease has led to a paradigm shift in research from symptomatic to disease-modifying therapeutics.

2.A: New insights into Alzheimer's disease and future therapeutic options

Andrea Pfeifer, Professor, CEO AC Immune SA, EPFL Innovation Park, Switzerland

Although the underlying cause of Alzheimer's disease remains unknown, amyloid-beta aggregates and tau tangles are the targets of many drugs in development. Other approaches address the oxidative damage and inflammation that are also seen. Failures in translational and clinical research for Alzheimer's disease have triggered a rethinking of current disease models. The formulation of new conceptual models of the disease will increase the prospects of developing effective treatments and possible combination therapy approaches.

2.B: The potential of emerging technologies in translational research, diagnosis and therapy

Diane Stephenson, Executive Director, Coalition Against Major Diseases (CAMD), Critical Path Institute, United States

Emerging biomedical technologies can provide the resources to fill the persistent knowledge gaps in Alzheimer's disease. Innovative research approaches, such as genomics, synthetic biology, artificial neuronal networks, and cell therapy can help to test hypotheses in pre-clinical research and to develop biomarkers for diagnosis and drug development. However, the impact of an increased knowledge base and of the emergence of sophisticated molecular research tools on the health of patients remains limited. The pharmaceutical industry is still falling short in terms of implementing emerging biomedical technologies into its processes because of the limited experience with such approaches to date. There is a need for standardisation and validation to support the comparability of data and to enable evidence based decision making in clinical research and medicines regulation.

2.C: Progress in Alzheimer's disease diagnostics – validation and use of cognitive endpoints and surrogate markers

Randall Bateman, Director, Dominantly Inherited Alzheimer's Network Trials Unit, Washington University School of Medicine

Diagnostic tools and biomarkers in particular, are at the centre of current research strategies to permit early disease detection and to facilitate prevention strategies. Until recently, research on biomarkers mainly focused on abnormal protein and peptide accumulations in the brain (i.e., amyloid-beta and tau). The development of disease specific, sensitive and accessible fast-readout biomarkers would be a significant step forward. Researchers and regulators are seeking quantitative and qualitative diagnostic information, to 1) deliver guidance for biomedical research in very early disease stages, 2) develop explicit biomarker-based regulatory frameworks, and 3) support evidence-based decision-making in safety and efficacy assessments.

Coffee Break, 15:30-16:00

- **Session 3: Speeding Innovative Medicines to Patients and Those at Risk**

  16:00 – 18:00 (120 min)

  20 min each Presentation

  60 min Panel Discussion and exchange with Workshop Participants

  Moderator: Claus Bolte, Division Head - Clinical Review, Swissmedic, Switzerland

This session will explore measures to expedite and de-risk the drug development process for Alzheimer's disease. A cross-sectoral, collaborative effort among governments, regulators, public research, the pharmaceutical industry, and patient organisations is needed to address medical, scientific and organisational barriers to the successful development of disease-modifying treatments for Alzheimer's disease. Questions remain how to generate a robust

evidence base at the entry of point of clinical research and allow for early failure without further extending the lag-time between discovery research and clinical use.

3.A: Opportunities in developing more efficient, flexible, and global clinical trial systems for Alzheimer's disease

Luc Truyen, VP Neuroscience External Affairs, Janssen R&D LLC, United States (20 min)

Ana Graf, Global Program Head Neuroscience, Novartis Pharma AG, Switzerland (20 min)

Alzheimer's is a global disease affecting people with different co-morbidities, genomic characteristics, and of different social-economic status. Because of the unique disease characteristics, and the heterogeneity of at-risk populations, clinical trials have become increasingly complex and long with high failure rate. In order to speed up the development process we need to learn faster and confirm more effectively. The set-up of a standing Global CT Platform comprised of trial ready cohorts of well characterized subjects and highly qualified sites and use of adaptive- and randomised-start trial designs will significantly shorten timelines and increase efficiency, flexibility and quality. However, the lack of sensitive and specific biomarkers in Alzheimer's disease remains a critical need for more efficient translational and clinical research.
As an alternative model for a public-private partnership, Novartis has entered a collaboration with Banner Alzheimer's Institute (BAI), also supported by National Institutes of Health, on a study in Alzheimer's disease prevention. The multi-national study will determine whether two investigational anti-amyloid treatments can prevent or delay the emergence of symptoms of Alzheimer's disease. Using an innovative trial design, the two treatments will be given in cognitively healthy people at genetic risk of developing the build-up of amyloid protein in the brain that may eventually lead to Alzheimer's disease.

3.B: Using open science to shorten the time lag between discovery research & clinical use

Martin Rossor, NIHR National Director for Dementia Research, University College London, United Kingdom

The need to harness big data, and to promote global collaboration and data sharing, in order to accelerate research and development of new therapies and care models for Alzheimer's disease and other dementias is undisputed. A substantial number of multi-site federated data networks and regional collaborative consortia have emerged. However, these efforts will only lead to earlier and effective treatments if they are implemented at scale in the context of a robust global policy environment. Policy challenges cross national borders and need to be tackled at the international level. Questions remain to be answered about the benefits of and obstacles to the linking and sharing of patient data for research and care.

Reception - End of Day 1

Day 2, 12th November 2014

- **Session 4: Perspectives from Stakeholders: Challenges & Options in Making a Paradigm Shift**

  09:00 – 11:00 (120 min)

  15 min each Presentation

  60 min Panel Discussion and exchange with Workshop Participants

  Moderator: George Vradenburg, Convenor, The Global CEO Initiative on Alzheimer's, United States

This session will provide an opportunity for different stakeholders to offer suggestions as regards the way forward, including the role they can play in making progress towards effective therapies.

4.A: Bridging the "Valley of Death": the potential of public-private partnerships

Elisabetta Vaudano, Coordinator Scientific Pillar, Principal Scientific Manager, Innovative Medicines Initiative (IMI), Belgium

Government, academia and start-up biotech companies focus resources on research and discovery projects upstream in the value chain. In the traditional research and health innovation model academia conducts much of the basic research that leads to the biochemical and molecular understanding of disease. There is a need for closer collaboration between academia, small and medium-sized biotech companies and the pharmaceutical industry in order to expand the precompetitive space further down the value chain of product development and to accelerate the transfer of research findings to clinical applications. Empowering academic research as a source of patient-oriented innovation can help to overcome the translational research gap.

4.B: Strengthening biomedical research and health innovation for Alzheimer's disease: Lessons Learned from Korea

Inhee Mook-Jung, Professor and Chairman, Seoul National University College of Medicine, Department of Biomedical Sciences, Korea

The role of governments as a facilitator of research and innovation spans through the whole life cycle of medicinal products. As science moves forward, regulatory officials worldwide are increasingly having a dialogue about the possible approaches that might be taken to drive research and development in Alzheimer's disease and other dementias. At the interface with public and private stakeholders, governments and agencies seek to foster the translation of biomedical innovation to the point of care. The increasing complexity of the research and drug development environment is triggering a rethinking of government's function in the definition of norms, processes, policies and regulations through which information is shared and decision-making is exercised. Emerging technologies in biomedical research, health innovation and diagnostics development deliver valuable information that needs to be shared and analysed to enable evidence-based decision making. The unique

characteristics of Alzheimer's disease and other dementias, and use of innovative research tools create additional challenges in balancing early access to effective medicines with evidence based decision making.

4.C: Industry: commitment to stopping Alzheimer's disease by 2025

Mark Hope, Global Head of Neuroscience, Ad Interim Head EU/ International Regulatory Affairs, F. Hoffmann-La Roche, Switzerland

The pharmaceutical industry recognises the significant and urgent health burden that Alzheimer's disease represents and remains committed to developing new therapeutics for people living with this devastating disease. This commitment exists despite significant challenges associated with the design and implementation of clinical trials. These challenges include length and cost of trials in the context of limited data exclusivity, lack of validated biomarkers and diagnostics, patient selection and enrolment, and definition of clinically meaningful endpoints. As the scientific understanding of Alzheimer's disease grows, research is moving to examine different pathways and earlier stages of disease where the opportunity for long-term benefit may be greatest. However, in these settings, the traditionally accepted outcomes to measure benefit may not be appropriate. Integrated cross-disciplinary strategies are needed to identify potentially novel measures which may more appropriately capture the clinical benefit associated with different pathways and stages of disease, such as surrogates that measure impact on disease pathophysiology and progression. To continue to foster research in this area and accelerate the discovery of medicines that can slow or stop disease, collaboration and openness to novel approaches must be embraced by industry, academia, regulatory agencies, payers and patient organisations.

4.D: Global Patient Advocacy: the impact on patients, families and communities

Marc Wortmann, Executive Director Alzheimer's Disease International, United Kingdom;
Helga Rohra, Chair, European Working Group of People Living with Dementia, Germany

Patients' rights and therapeutic needs are central in the setting-up of clinical research programmes, especially for the inclusion of patients at the very early stages of the disease or healthy volunteers at risk for Alzheimer's disease. Creating the conditions for translating promising therapeutic options into "first-in-human" studies is one of the biggest challenges in health innovation for Alzheimer's disease. Issues include: patient selection and stratification, the voluntary involvement of well-informed patients, and protection of privacy/confidentiality to prevent unauthorized or inappropriate use of personal information. Patient organisations play a significant role in global Alzheimer's trials to address ethical, legal and regulatory issues, to support patient recruitment and retention in long-term clinical trials and to provide input to regulators assessing the risks and benefits of approving proposed new medicines.

Coffee Break, 11:00-11:30

❖ **Closing session: Conclusions from the Workshop**

The view from here: how to move forward on Alzheimer's disease?

11:30 – 13:30 (120 min)

Moderator: Dirk Pilat, OECD

The purpose of the final session will be for all stakeholders to discuss and conclude regarding potential future steps that could be taken to jointly drive a paradigm shift in biomedical research and health innovation for Alzheimer's disease and other dementia.

Rapporteur, followed by roundtable discussion:

- Key messages from the various sessions and from stakeholder groups;
- Options for global thinking and national action;
- Suggestions and recommendations for policy action;
- Discussion on next steps.

Immediately following the Workshop, OECD will prepare **a summary report** and **a short note with suggestions and recommendations for policy action** that will be provided to policy makers and that will feed into ongoing processes at the international level, including the work of the World Dementia Council.

❖ **Concluding remarks**

Isabella Beretta, Chair of OECD Working Party on Biotechnology, Swiss State Secretariat for Education, Research and Innovation, SERI, Switzerland

End of the Workshop