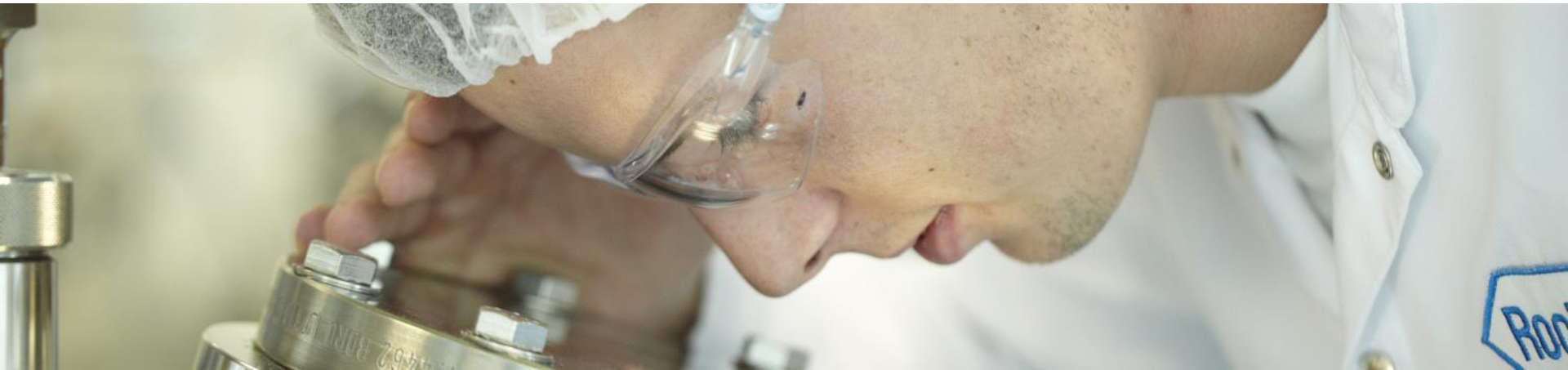
Health technology assessment (HTA) criteria in the light of current R&D trends

Mauro Patroncini

Pipeline Product Strategy Leader

Roche Italy

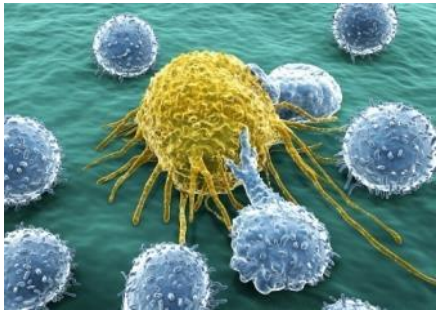


HTA and R&D

- **Meeting HTA requirements from the very beginning of the development process of a new product**
- ***Challenges of early products from an HTA perspective***
- ***Product value and Market access: experiences in outcome based managed entry agreements***

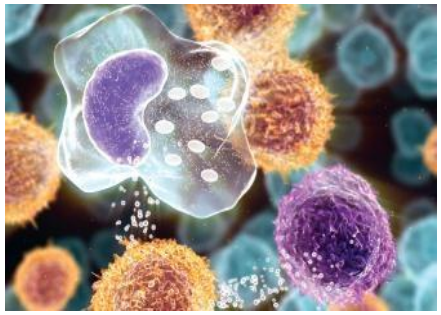
Innovation at Roche is the creation and commercialisation of medically differentiated products and services that lead to tangible improvements in the health, quality of life and survival of patients.

R&D at Roche



Oncology

Developing effective cancer therapies



Infectious Diseases

Developing effective treatments for life-threatening infectious diseases

Ophthalmology

Restoring sight

Neuroscience

Developing medicines for serious brain diseases

Rare Diseases

Tackling rare genetic disorders

Traditional paradigm with regulatory focus necessary but not sufficient

Trend	*What this means for us*
Increasing payer reliance on HTA to understand clinical and economical value	**Access Evidence must be addressed early and often to be able to effectively meet HTA requirements.**
Changing payer evidence requirements	Payers need to understand **comparative effectiveness of medicines, not only benefit/risk.**
Focus on the importance of outcomes for patients and other evidence sources	Evidence must be gathered from a whole variety of different sources including **Real World Data.**
Increasing competition	Meaningful **comparative effectiveness data** must be generated and communicated.
Opportunities to accelerate approval in areas of particular unmet patient need	**Accelerated approval** leaves less time to generate evidence for all our stakeholders.

HTA: Health Technology Assessment

FDA/EMA and HTA requirements are diverging not converging

FDA/EMA

Becoming more flexible and adaptive

HTA

Becoming more stringent on evidence of incremental benefit

Regulators ‘evolving approval’ of safety and efficacy data

- **FDA breakthrough** – single arm lighter weight trials possibly sufficient
- **Adaptive licensing** (AL) – EMA are working on how AL could be achieved.

Payers often will not extrapolate clinical endpoints to patient benefit or to populations outside clinical trial

Some payers will consider:

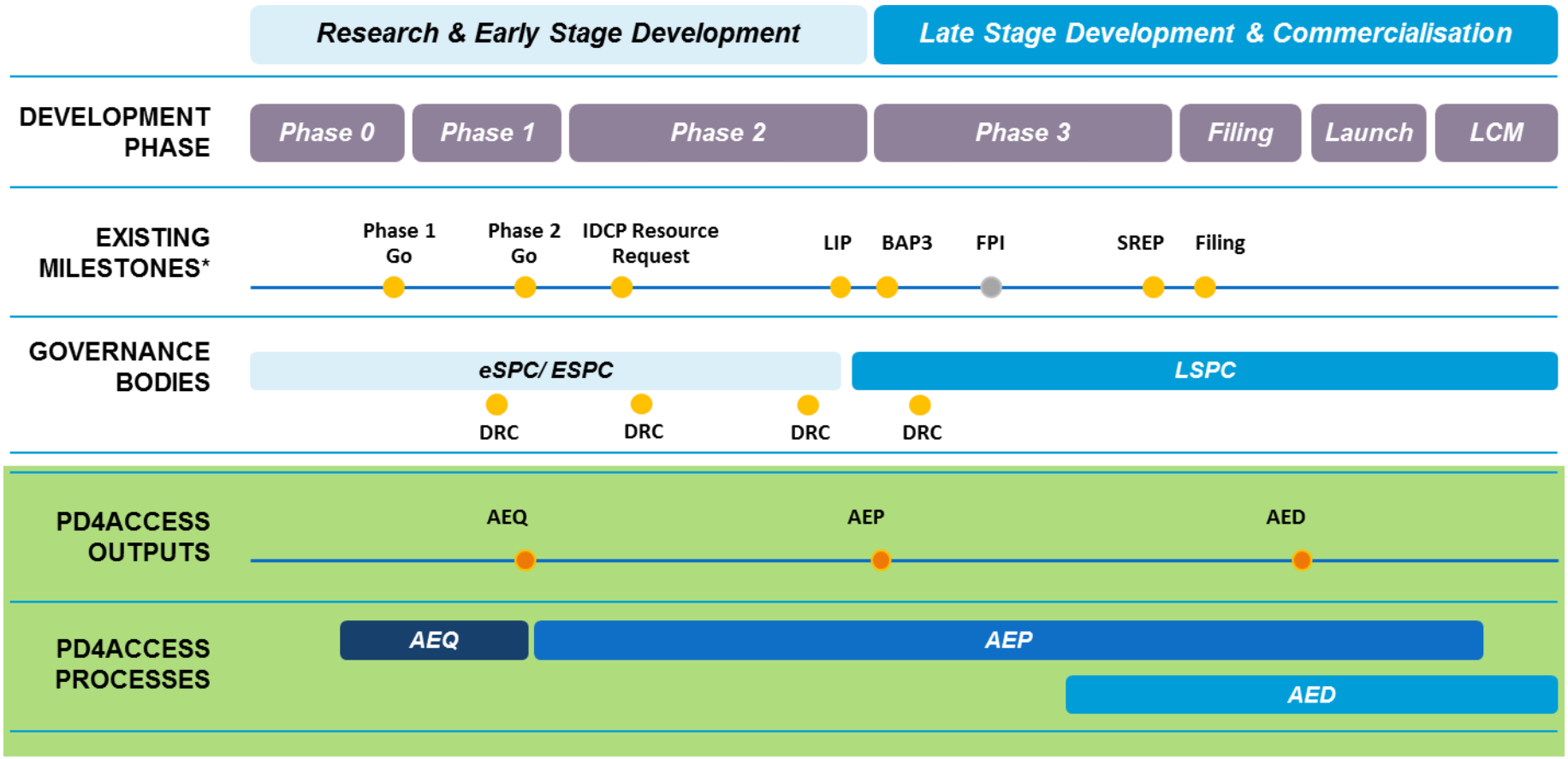
- Real World Evidence data
- *Pay for performance* arrangements

EMA: European Medicines Agency; FDA: Food and Drug Administration

Requirements: FDA/EMA versus HTA

REGULATORS (EMA, FDA)	PAYERS (HTA)
Risk/Benefit profile	**Value compared to existing alternatives**
Surrogate / Intermediate are usually primary endpoints in clinical research	**Final outcome first (mortality and quality of life)** Intermediate (avoided events) and surrogate afterwards
Economic impact not considered	Crucial role played by the **economic impact: value for money and budget impact**
Standard criteria	Different approaches across countries and sometimes within countries

New working models needed with more focus on Access Evidences throughout drug development



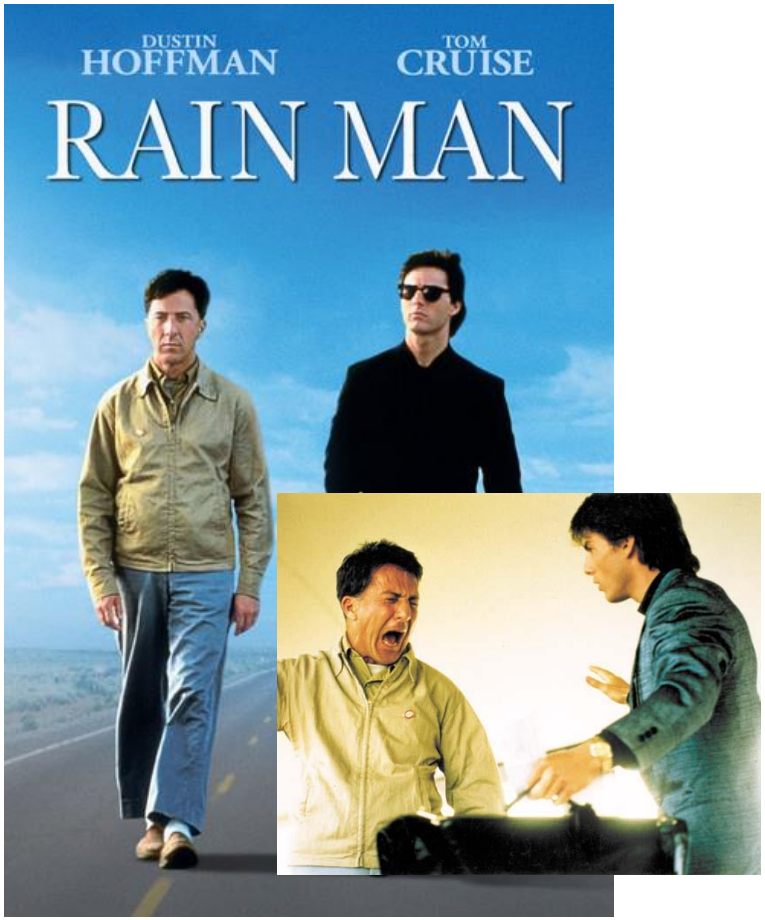
* Process shown for NMEs, principles will be applied similarly for major life cycle extensions

HTA and R&D

- Defining the value of a new product from the very beginning of the development process
- ***Challenges of early products from an HTA perspective***
- Product value and Market Access: Italian experience in outcome based managed entry agreements

Assessment of the challenges from a PAYER perspective

Autism



Globally, autism is estimated to affect **21.7 million people**

About 1.5% of children in the United States (one in 68) are diagnosed with ASD as of 2014, a 30% increase from one in 88 in 2012

The first drug to cure Autism

V1A modulates social behaviors associated to Autism

Vineland II Adaptive Behavior Composite Scale (VABS) *Measures 3 domains of adaptive behavior relevant to core symptoms of ASD*

Semi-structured interview to caregiver/parent by qualified rater (psychologist)

Standard scores: mean = 100; SD = 15 (for the typical population)

What is VABS II Composite?

Composite calculated from three separately measured domains:

Socialization Domain

The skills and behaviors that are needed to get along with others

Communication Domain

How an individual speaks, understands others and uses written language

Daily Living Skills Domain

The practical skills and behaviors that are needed to take care of oneself.

Comprising of questions in each of these areas

Autism: challenges from a payer perspective

No Drug is presently indicated for autistic patients and symtoms are treated with old molecules not effective on disease progression

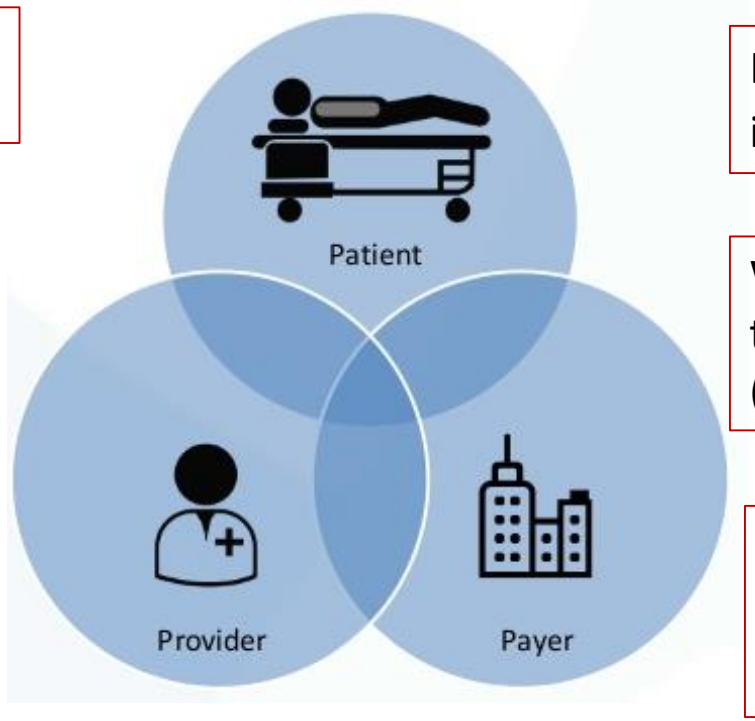
Which is the target population?

Are there subgroups to prioritize?

Who is the responder?

Starting/stopping rules?

Which is the Clinically relevant & Tangible treatment benefit?



How much more to pay for a given improvement

How to measure improvement?

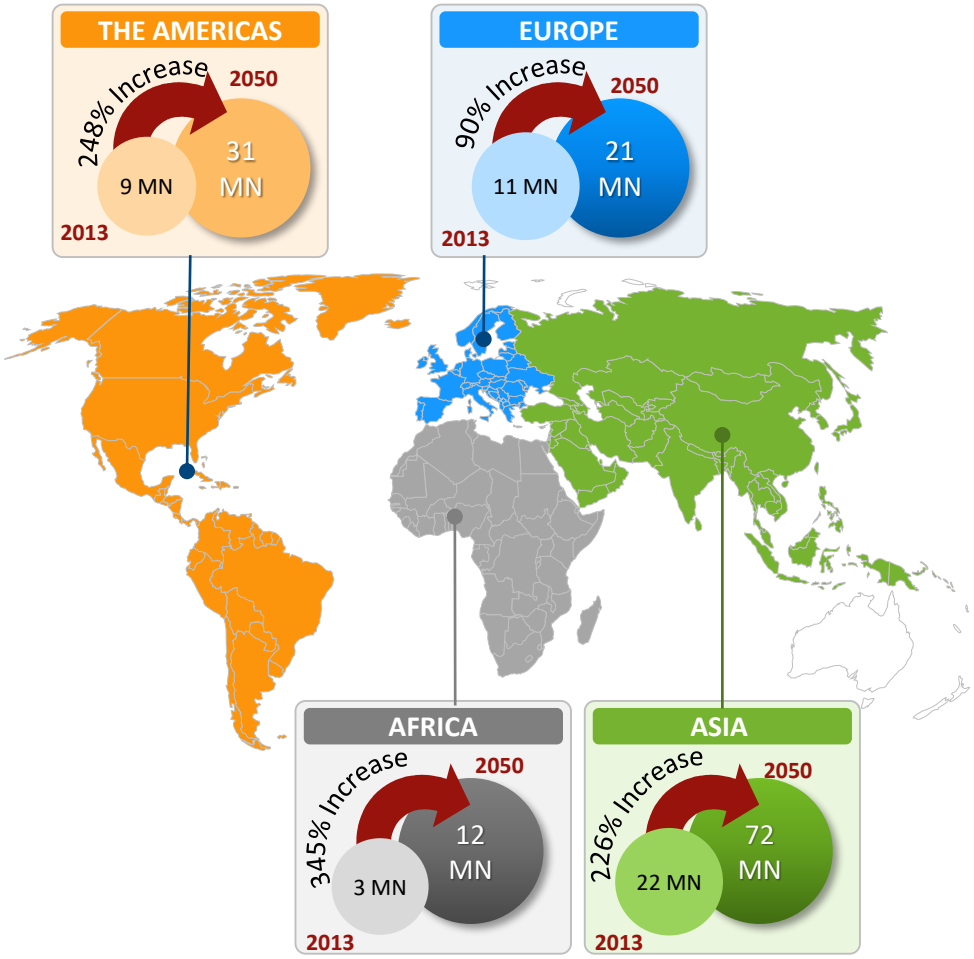
Which is the added therapeutic value (patient condition)?

Expected improvement of health care system (social impact)?

Global burden of Alzheimer's Disease

- Prevalence ITALY **1,7mil pts** (950prod+450mild+300mod)

World dementia prevalence

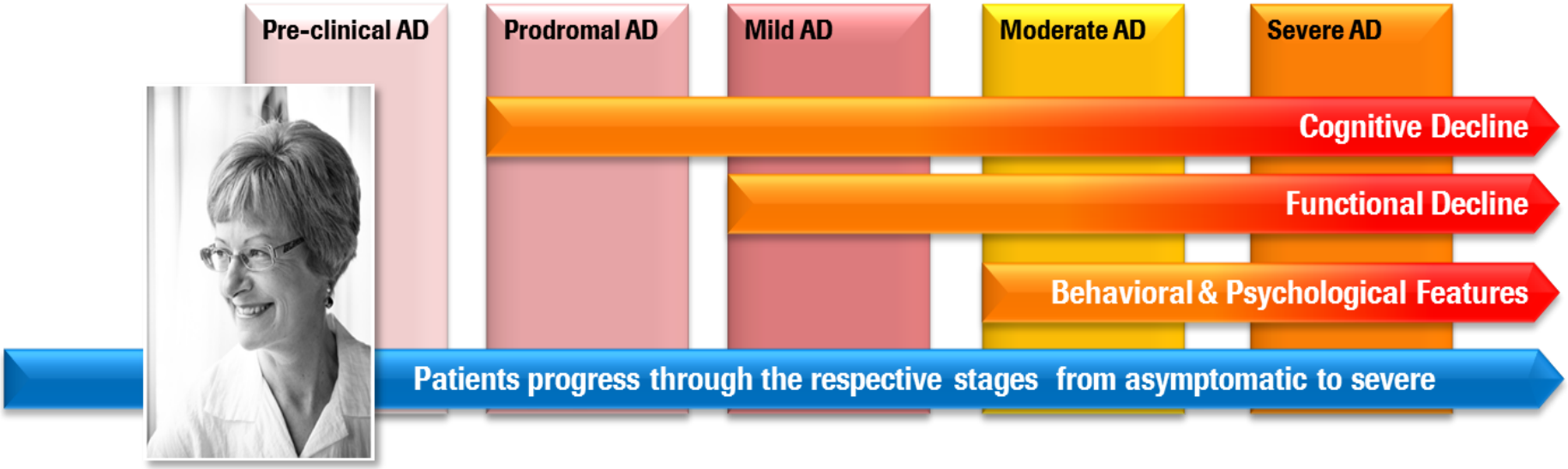


Profound unmet need
for patients, caregivers and societies

- Global **dementia prevalence to triple** from 45M in 2015 to **130M in 2050**
- **AD** accounts for **60-80% of all dementia**
- AD will become **leading cause of death** in many developed countries in next ten years
- **Global costs** will rise from ~$800 billion in 2015 to **$2T by 2030**, equivalent to the current size of the economy of India
- Caregivers also carry a huge direct burden. The average **caregiver** in the US provides **22hrs/wk of active support with $5k/yr additional out of pocket expenses**

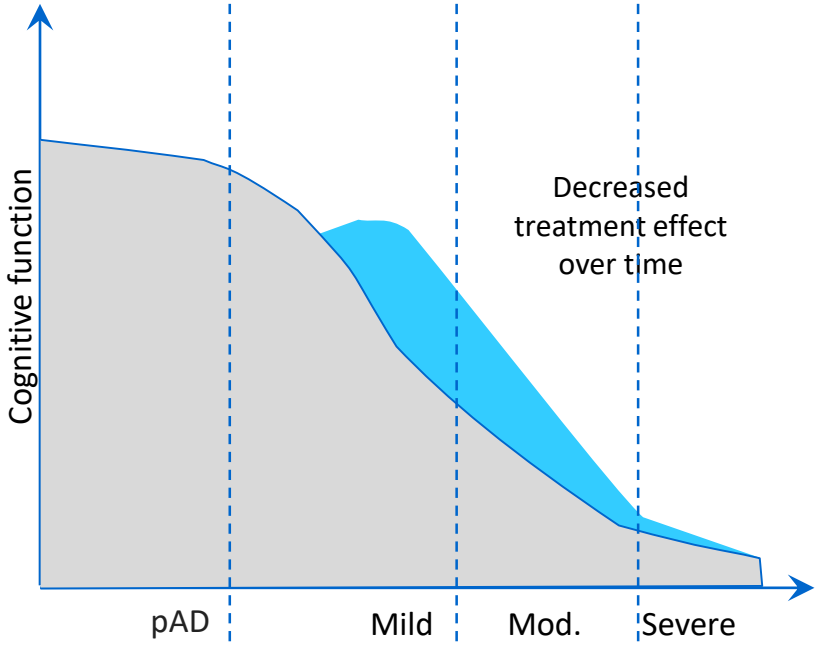
AD is a progressive and fatal neurodegenerative disease

Alzheimer's disease is a continuum: individuals move through a spectrum from pre-symptomatic to cognitive impairment, and dementia

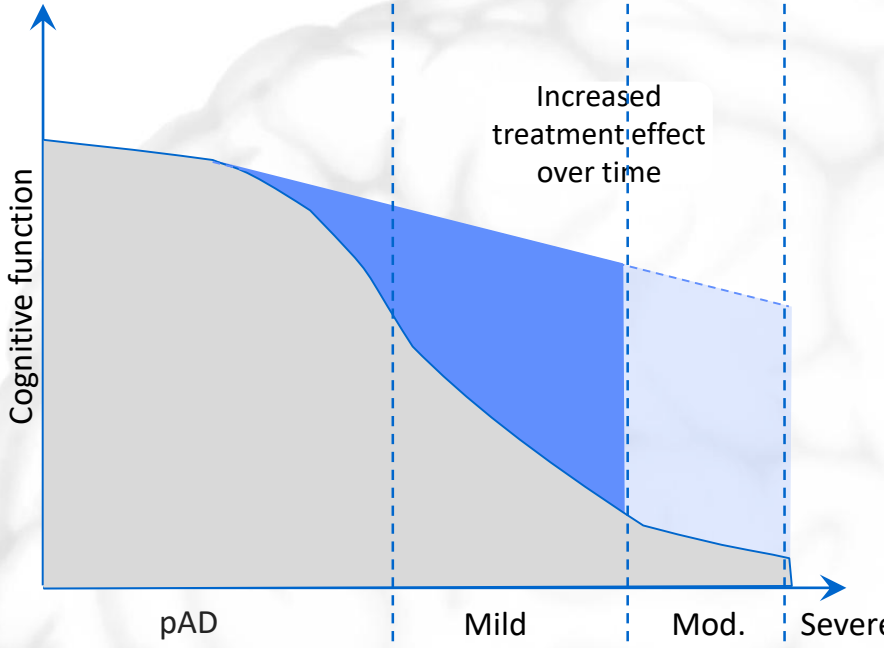


Unlike symptomatic therapies, DMTs are expected to substantially change the course of disease

Current symptomatic treatments might improve cognition, function and behavior, but do not modify disease



Only DMTs can potentially delay or halt progress of AD



Source: Primary Psychiatry 2013, http://primarypsychiatry.com/from-symptom-palliation-to-disease-modification-implications-for-dementia-care/; Roche

HTA with AIFA
HTA suggested evidence plan from a VALUE perspective

Feedback from AIFA

- **Biomarkers**
- **Value & added therapeutic value per subgroup (which patients for how long)**
- **Tangible benefit**
- **Medical need / appropriate patient for treatment (prioritization criteria)**
- **Starting/Stopping rules**
- **Burden of disease (real world data)**
- **Expected impact on health/social system (sustenibility)**

Source: Roche Italy (Sep. 2017)

HTA and R&D

- ***Defining the value of a new product from the very beginning of the development process***
- ***Challenges of early products from a market access perspective***
- ***Product value and Market Access: outcome based evaluation/managed entry agreements***

P&R Process in Italy

Roche

Market Authorisation

EMA/AIFA

AIFA

Technical-Scientific Commission (CTS)

Clinical evaluation and advice on reimbursement classifications

Pricing & Reimbursement Committee (CPR)

Evaluation of CTS assessment and economic data, price negotiations with company

AIFA Board of Directors

Ratification of pricing and reimbursement decision

Consultative Experts Committee

Provide expertise on specific area:

- Cardiology
- Neuroscience
- Endocrinology
- Pediatrics
- Primary Care
- Oncology

Months* 6

National Pharmaceutical Formulary

(Prontuario Farmaceutico Nazionale, PFN)

Class A (Retail), Class H (Hospital)
100% reimbursement

Official gazette publication

No reimbursement

Class C
No reimbursement

** In theory, the pricing and reimbursement process should take 6 months, while in practice it often takes longer*

AIFA, Agenzia Italiana del Farmaco = Italian Medicines Agency

CTS, Commissione Tecnico Scientifica = Technical-Scientific Commission
CPR, Comitato Prezzi e Rimborso = Pricing & Reimbursement Committee

PFN, Prontuario Farmaceutico Nazionale = National Pharmaceutical Formulary

Technical-Scientific Commission (CTS) Reimbursement Assessment

- CTS is responsible for scientific evaluation, place in the therapeutic strategy, therapeutic innovation and advice on reimbursement class for drugs
- CTS assessment is mainly based on the following criteria:

Disease criteria	Product profile	Economic criteria
– Severity of illness – Unmet needs	– Therapeutic value – Safety profile – Treatment alternative – Therapeutic innovation	– Cost-effectiveness – Budget impact

CTS: Commissione Tecnico Scientifica = Technical-Scientific Commission

IL DIRETTORE GENERALE

OGGETTO: Criteri per la classificazione dei farmaci innovativi e dei farmaci oncologici innovativi ai sensi dell'articolo 1, comma 402 della legge 11 dicembre 2016, n. 232.

Visto l'articolo 48 del decreto legge 30 settembre 2003 n. 269, recante "*Disposizioni urgenti per favorire lo sviluppo e per la correzione dell'andamento dei conti pubblici*", convertito, con modificazioni, dalla legge 24 novembre 2003 n. 326, che ha istituito l'Agenzia Italiana del Farmaco;

Visto il decreto 20 settembre 2004 n. 245 del Ministro della Salute, di concerto con i Ministri della Funzione Pubblica e dell'Economia e delle Finanze: "*Regolamento recante norme sull'organizzazione ed il funzionamento dell'Agenzia Italiana del Farmaco, a norma dell'articolo 48, comma 13, del decreto-legge 30 settembre 2003, n. 269, convertito, con modificazioni, dalla legge 24 novembre 2003, n. 326*", come modificato dal decreto 29 marzo 2012 n.53 del Ministro della Salute, di concerto con i Ministri per la Pubblica Amministrazione e la Semplificazione e dell'Economia e delle Finanze;

Visto il decreto del Ministro della Salute del 17 novembre 2016, vistato ai sensi dell'art. 5, comma 2, del d.lgs. 30 giugno 2011 n. 123 dall'Ufficio centrale del bilancio presso il Ministero della Salute in data 18 novembre 2016, al n. 1347, con cui è stato nominato Direttore generale dell'Agenzia italiana del farmaco il Prof. Mario Melazzini;

AIFA Criteria for the classification of innovative drugs and innovative oncology medicines

Therapeutic unmet need	maximum	high	moderate	poor	absent
Therapeutic added value	maximum	high	moderate	poor	absent
Clinical data robustness and power	high	moderate	low	very low	

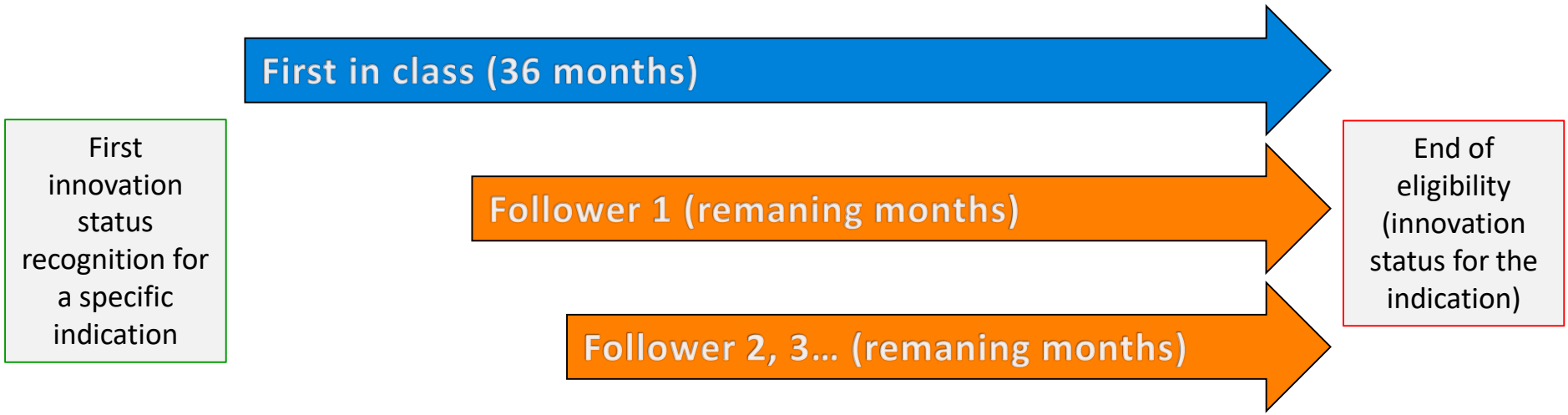
Recognition of innovation status

1) **The recognition of innovation** status will be associated with the inclusion in the **Innovative Medicines Fund (500 mil euro)** or the **Innovative Oncology Fund (500 mil euro) (**Article 1, paragraph 403, Law 11 December 2016, no. 232 - Budget Law 2017) and **inclusion into the Regional Therapeutic Formulary** within the terms of the current legislation (Chapter III, Article 10, paragraph 2, Law No 189 of 8 November 2012)

2) **The recognition of conditional (or potential) innovation status** only results in the **inclusion into the Regional Therapeutic Formulary** within the terms of the current legislation (Chapter III, Article 10, paragraph 2, Law No 189 of 8 November 2012)

3) **The lack of recognition of innovation status**

The final application report will be communicated to the applicant, who may submit observations on the report within 10 days. At the end of the process, the final outcome and the Scientific Technical Commission **assessment will be made public** on the AIFA portal. The applicant, when completing the form, may request omission from the publication of any sensitive data. As established by Article 1, paragraph 402, of Law 11 December 2016, no. 232 (Budget Law 2017), **the recognition of innovation and the resulting benefits have a maximum duration of thirty-six months for the overall indication.**



Therapeutic unmet need

- **Maximum**: **no therapeutic options** for the specific indication
- **High**: **There are therapeutic alternatives** for the specific indication, but **do not produce any impact on clinically relevant and validated outcomes** for the disease
- **Moderate**: **presence of therapeutic alternatives** for specific indication with a **measurable limited impact** on recognized clinically relevant outcomes and / or with an **uncertain or unsatisfactory safety profile**
- **Poor**: presence of one or more **therapeutic alternatives** for specific indication with **measurable impact** as high on outcomes recognized as clinically relevant and with a favorable safety profile
- **Absent**: **presence of therapeutic options for the specific indication** that can alter the natural history of the disease and with a favorable safety profile.

Therapeutic added value

- **Maximum**: **greater efficacy than therapeutic alternatives (if available) demonstrated on clinically relevant outcomes.** The drug is able to **heal the disease or to significantly alter its natural history**
- **High**: **increased efficacy on clinically relevant outcomes**, or ability to reduce the risk of disabling or potentially fatal complications, or better risk/benefit ratio than alternatives, or ability to avoid the use of high clinical procedures risk. **The drug modifies the natural history of the disease in a subpopulation of patients, or there is a clinically relevant benefit** (for example in terms of quality of life and disease-free interval compared to the available therapeutic alternatives)
- **Moderate**: **moderate efficacy improvement in some** subpopulations of patients or surrogate outcomes, with limited effects on the quality of life. For diseases where the absence of a comparator is possible and there are evidences of better clinical efficacy and risk/benefit profile than available therapeutic alternatives
- **Poor**: increased effectiveness which has been shown to be **clinically non-relevant or is of little magnitude**. Lower level of benefits (for example, more favorable route of administration) than available therapeutic alternatives
- **Absent**: **no additional clinical benefit than the available therapeutic alternatives**.

Clinical data robustness and power

Proper evaluation of the innovative potential of a drug depends on the **quality of the scientific evidence** brought to support the request.

For the assessment of this parameter, AIFA decides to adopt the **GRADE method (Grading of Recommendations Assessment, Development and Evaluation)**

Table: GRADE's approach to rating quality of evidence (aka confidence in effect estimates)

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1. Establish initial level of confidence		2. Consider lowering or raising level of confidence		3. Final level of confidence rating
Study design	*Initial confidence in an estimate of effect*	*Reasons for considering lowering or raising confidence*		*Confidence in an estimate of effect across those considerations*
		↓ Lower if	↑ Higher if*	
Randomized trials →	High confidence	Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias • would reduce a demonstrated effect or • would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies →	Low confidence			Low ⊕⊕◯◯
				Very low ⊕◯◯◯

*upgrading criteria are usually applicable to observational studies only.

http://www.jclinepi.com/content/jce-GRADE-Series.

INNOVATIVI NON ONCOLOGICI 1/2

FARMACO	PRINCIPIO ATTIVO	Indicazioni	CLASSE	DATA EFFICACIA	DATA SCADENZA
SOVALDI	sofosbuvir	epatite C cronica (chronic hepatitis C, CHC) negli adulti	A **Classe C – a partire dalla data del 02/06/17**	20/12/2014	01/06/2017
OLYSIO	simeprevir	epatite C cronica (chronic hepatitis C, CHC) negli adulti	A	27/06/2015	23/02/2018
VIEKIRAX	ombitasvir, aritaprevir, ritonavir	epatite C cronica (chronic hepatitis C, CHC) negli adulti	A	24/05/2015	23/05/2018
EXVIERA	dasabuvir	epatite C cronica (chronic hepatitis C, CHC) negli adulti	A	24/05/2015	23/05/2018
DAKLINZA	daclatasvir	epatite C cronica (chronic hepatitis C, CHC) negli adulti	A	05/05/2015	04/05/2018
KALYDECO	ivacaftor	Kalydeco 150 mg compresse rivestite con film: trattamento di pazienti affetti da fibrosi cistica (FC), di età pari o superiore a 6 anni e di peso pari o superiore a 25 kg, che hanno una delle seguenti mutazioni di gating (di classe III) nel gene CFTR: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N o S549R. Trattamento di pazienti affetti da fibrosi cistica (FC), di età pari o superiore a 18 anni, che hanno una mutazione R117H nel gene CFTR" Kalydeco 50mg e 75mg: fibrosi cistica (FC), in pazienti di età pari e superiore a 2 anni e di peso inferiore a 25 kg, che hanno una delle seguenti mutazioni di gating (di classe III) nel gene CFTR: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N o S549R.	A	05/05/2015	04/05/2018

INNOVATIVI NON ONCOLOGICI 2/2

FARMACO	PRINCIPIO ATTIVO	Indicazioni	CLASSE	DATA EFFICACIA	DATA SCADENZA
SPINRAZA	nusinersen	Trattamento dell'atrofia muscolare spinale 5q	H	28/09/2017	27/09/2020
MAVIRET	glecaprevir/pibrentasvir	trattamento dell'infezione cronica da virus dell'epatite C (HCV) negli adulti	A	28/09/2017	26/04/2020
HARVONI	ledipasvir + Sofosbuvir	epatite C cronica (chronic hepatitis C, CHC) negli adulti	A **Classe C – a partire dalla data del 02/06/17**	14/05/2015	01/06/2017
EPCLUSA	sofosbuvir/velpatasvir	epatite C cronica (chronic hepatitis C, CHC) negli adulti	A	27/04/2017	26/04/2020
ZEPATIER	elbasvir/grazoprevir	epatite C cronica (chronic hepatitis C, CHC) negli adulti	A	04/02/2017	03/02/2020
STRIMVELIS	cellule autologhe CD34+	immunodeficienza grave combinata da deficit di adenosina deaminasi (ADA– SCID)	H	16/08/2016	15/08/2019

Tali elenchi saranno aggiornati dall' AIFA con cadenza mensile, sulla base dei successivi pareri resi dalla CTS

INNOVATIVI ONCOLOGICI

FARMACO	PRINCIPIO ATTIVO	INDICAZIONI	CLASSE	DATA EFFICACIA	DATA SCADENZA
PERJETA	pertuzumab	carcinoma mammario HER2 positivo, non operabile, metastatico o localmente recidivato, non trattati in precedenza con terapia anti–HER2 o chemioterapia per la malattia metastatica	H	08/07/2014	07/07/2017
ABRAXANE	Nab paclitaxel	trattamento di prima linea adenocarcinoma metastatico del pancreas	H	21/02/2015	20/02/2018
ZYDELIG	idelalisib	leucemia linfatica cronica (chronic lymphocytic leukaemia, CLL) che hanno ricevuto almeno una terapia precedente , o come trattamento di prima linea in presenza di delezione 17p o mutazione TP53 in pazienti non idonei ad altre terapie linfoma follicolare (follicular lymphoma, FL) refrattario a due precedenti linee di trattamento	H	11/09/2015	10/09/2018
IMBRUVICA	ibrutinib	linfoma mantellare (MCL) recidivato o refrattario CLL che hanno ricevuto almeno una precedente terapia, o in prima linea in presenza della delezione del 17p o della mutazione TP53 per i quali una chemio- immunoterapia non è appropriata Imacroglobulinemia di Waldenström (WM) che hanno ricevuto almeno una precedente terapia, o in prima linea per i pazienti per i quali una chemio–immunoterapia non è appropriata	H	05/01/2016	04/01/2019
OPDIVO	nivolumab	melanoma avanzato (non resecabile o metastatico) negli adulti. carcinoma polmonare non a piccole cellule (NSCLC) localmente avanzato o metastatico dopo una precedente chemioterapia negli adulti carcinoma a cellule renali avanzato dopo precedente terapia negli adulti	H	25/03/2016	24/03/2019
KEYTRUDA	pembrolizumab	melanoma avanzato (non resecabile o metastatico) nei pazienti adulti prima linea del carcinoma polmonare non a piccole cellule (NSCLC) metastatico negli adulti il cui tumore esprime PD–L1 con tumour proportion score (TPS) ≥ 50 % in assenza di tumore positivo per mutazione di EGFR o per ALK NSCLC localmente avanzato o metastatico negli adulti il cui tumore esprime PD–L1 con TPS ≥ 1 % e che hanno ricevuto almeno un precedente trattamento chemioterapico. I pazienti con tumore positivo per mutazione di EGFR o per ALK devono anche avere ricevuto una terapia mirata prima di ricevere KEYTRUDA	H	11/05/2016	10/05/2019

Take home messages

- **FDA/EMA and HTA requirements are diverging not converging. Traditional development paradigm with regulatory focus necessary but not sufficient.**

- **A Value based strategy must be defined from the start of a drug development to address HTA requirements. Product perceived value will 'drive' Market Access.**

- **AIFA Criteria for innovation will be a model of product evaluation for any new applicants. The 'NEW' must have a measurable value in term of improving patient condition and healthcare system quality.**

Doing now what patients need next