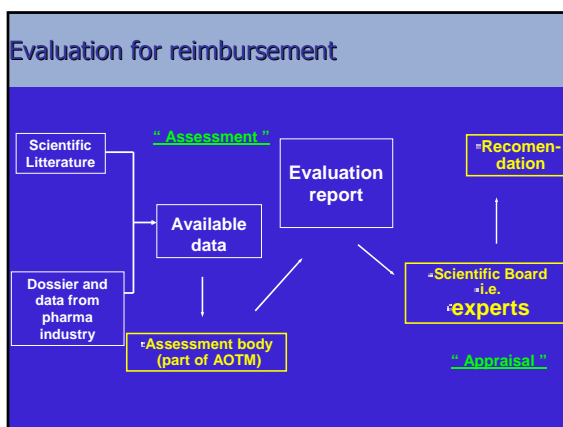
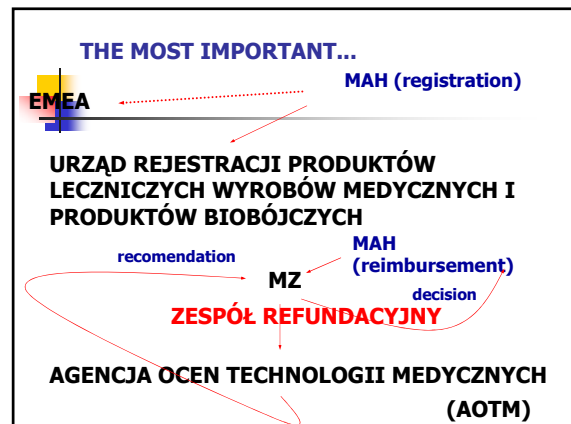


Innovative medicine in the light of guideline of HTA preparation

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- ## HOW IT IS DONE ?
- Key activities:**
- Main points in assessment:
- Evaluation of clinical benefit, will determine the reimbursement rate of a technology
 - It takes into account the severity of the illness, the clinical efficacy and safety, the existence of therapeutic alternatives and the impact in terms of public health.
 - The “added therapeutic value” of a medical technology in comparison with alternatives - ? (see below)
 - The size of the target population

ADDED THERAPEUTIC VALUE

„Added therapeutic value” paradigm not introduced, yet. It is directly connected to the understanding of „innovation” – term still under discussion at EU forum

In order to show added therapeutic value:

- comparison with existing alternative(s) – in case of drugs, head-to-head trial
- methods of comparison depend on the definitions

MANDATE OF PHARMACEUTICAL FORUM

Created by Ph Forum working group of Relative Effectiveness was asked to:

„...clarifying views on the value of innovation, taking account of national health systems in order to establish a sound basis for further discussion between different stakeholders”..

Following 1.5 year discussion the only output was a list of variety (more than 20 kinds) of innovations.

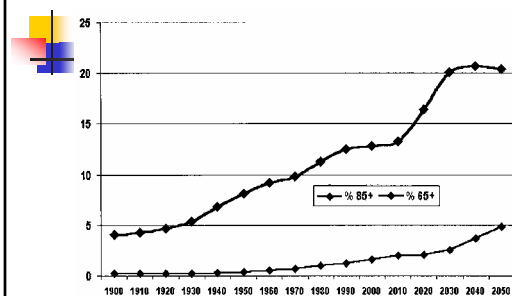
IMPORTANT QUESTIONS

- What is valuable innovation ?
- Who is judging the innovation ?
- Who is the addressee of innovation?
- How to identify and measure innovation ?
- When and how to reward and to provide incentive for innovation ?

THERAPEUTIC INNOVATION: WHY?

- Patients !! Mostly because of diseases of great zone
- Number of new, innovative drugs decline
- Industry is concentrating on "me-too" drugs
- Decision makers are not happy because progress in treatment is slowing
- Industry pipeline are drying
- Vigorous activity of governments, academia, and drug registration agencies is needed

DANGEROUS FUTURE: gray zone



DISEASES OF GRAY ZONE

- Alzheimer's disease – available treatment improves the ability to solve puzzles
- Parkinson's disease – treatment is only partially effective and with time is more dangerous than disease
- Rheumatoid diseases – symptomatic treatment (NSAIDs) and limited DMARDs
- Depression in old age: following treatment, recurrence in 50-90% !
- Grey zone inhabitants poorly exercise – INNOVATIVE drugs are necessary

WHAT IS REALLY IMPORTANT

- Goal of health care system is not only managing budget but firstly to improve pt's health outcome – not easy in elderly pts
- Real value of drug therapy is determined only by the degree to which pt's health improves
- What is the societal cost of limiting drugs supply in the elderly ?
- Health care system is not taking seriously „grey zone" inhabitants

SEVERAL KINDS OF INNOVATIONS

- Commercial innovation: "new drug belonging to known therapeutic class, without significant difference in efficacy and safety though difference in kinetics and mechanism of action possible"
- Technological innovation: "new formulation, new means of production, new isomer or metabolite"
- Therapeutic innovation: "scientifically proven advantage in efficacy, and/or safety, and/or quality of life in comparison with the best available medicine (reference drug)"

CATEGORIES OF INNOVATIONS

- Therapeutic innovation:
 - no other treatment
 - extension of therapeutic effect
„Scientifically proven advantage in efficacy, tested in randomized, controlled trial against the best reference drug“
 - resistance to treatment
- Efficacy: typical hard end-points plus, if not available, surrogates with established link to hard end-points

CATEGORIES OF INNOVATION

- Patient's utility innovation
 - important:
effect of drug on quality of life determined by the presence of serious adverse reactions, acc. to EMEA classification, i.e. death, life-threatening, requiring hospitalization, persistent or significant disability or incapacity (e.g. NSAID devoid of GI ulceration, antiemetics used with cytostatics, etc)
 - minor:
moderate effect on quality of life, e.g. effect on compliance (non-inferiority trial acceptable)

WHAT IS NOT THERAPEUTIC INNOVATION

- Efficacy based on surrogate (secondary) end points
- "Me-too" drugs
- Safety: difference in minor, not major, AE

These end-points may constitute the basis for clinical trial but the drug with positive outcome in such trial **does not** constitute therapeutic progress.

However, these drugs are also valuable and sometimes more important than therapeutic innovation.

FEW WORDS ON METHODOLOGY

The essence of non-inferiority trial:
„new drug is good because it is not bad“

(Blackwelder 2002)

In this trial the null hypothesis is tested that new drug is inferior to standard (reference) and when the results are similar this hypothesis is rejected and alternative (new is not inferior) accepted

Non-inferiority design *is not good for evaluation of therapeutic added value!*

Solution: guidelines CPMP „on inferiority margin“

CPMP GUIDELINES (on the choice of the non-inferiority margin)

This guideline allows to use superiority type of trial with increased significance level (i.e. $P < 0.1$)

In such trial increased risk of false positive results must be balanced against the risk of rejecting a drug with efficacy valuable advantage

It is recognised that certain delta is hidden in increased alpha level

The results of NI trial may be recalculated according to superiority with alpha < 0.1