HETA
Institute of Health Economics and Technology Assessment

Expert conference on rare diseases (EUPRES)

EU2022.CZ

3) Revision of the Orphan Drug and Pediatric Drug Regulations

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Disclaimer/conflict of interest

- O.P.S/NGO = non-profit, non-governmental organization
- Scientific projects
- EUnetHTA projects
- Education: health economics, outcomes research, market access
- Round tables: WTP, guidance, social and societal costs
- Building HTA capacity: new legislation assistance, guidance, experience from other countries

- LTD= commercial organization
- Services in: health economics, pharmacoeconomics, market access, RWE, non-intervantional research, drug registration (all in majority for pharmaceutical industry)
- Mainly preparing submissions to local HTA agency (SUKL)
- Currently, 30-40 of reimbursement submissions every year to SUKL

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Topics of Section 3

Topic of section 3)

3) Revision of the Orphan Drug and Paediatric Drug Regulations

In many ways, the Regulation on Orphan Medicinal Products implemented in 2000 proved to be a great success, leading to progress of care in many overlooked conditions. Despite this progress, concerns about remaining unmet needs, patient access, affordability, and sustainability of pharmaceutical spending have risen in the past few years. In particular, there are concerns related to the appropriateness of the current regulatory framework to attain the societal goal of reducing unmet needs while ensuring value-for-money.

The CZ PRES encourages the European Commission:

A. to use the opportunity of the upcoming revision of the Orphan Medicinal Products and Paediatric Regulation, together with the planned revision of General Pharmaceutical Legislation, to evolve the incentives framework to maintain predictability for sponsors while enhancing Europe's competitiveness. This needs to be the main focus of the European Action Plan on Rare Diseases.

In particular, the CZ PRES believes there is a unique opportunity to:

A. Define a model that is centred on the unmet needs of people living with a rare disease, and includes patient participation in its establishment and implementation;

B. Transform the European Research & Development for the rare disease ecosystem building upon advances of the past 20 years, for the next 20 years. This must reflect and connect developments across science, technology and policy;

C. Situate Europe as a global leader in research, development and access to diagnostics, treatment and care, through a regulation that is attractive and competitive globally. Reflections should be made in aligning with and maintaining competitiveness with the USA's FDA system;

D. Establish a European pathway, from development to access, to ensure innovation coupled with affordability and to gain that crucial strategic autonomy in research and development;

E. Ensure convergence and coherence of relevant existing as well as currently negotiated legislation.

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Czech background and new orphan legislation in force from 2022

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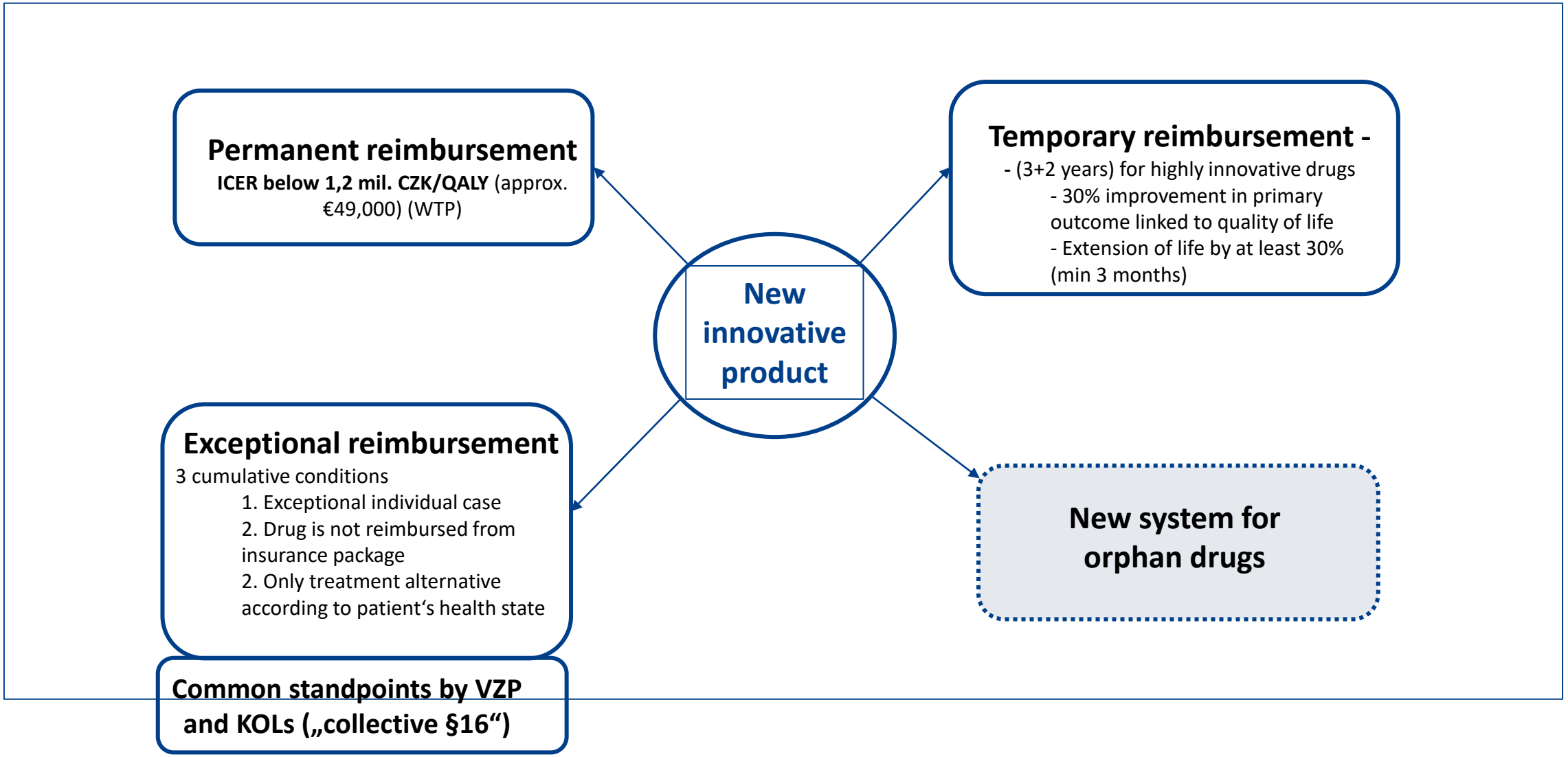
General description of price and reimbursement system

Reimbursement in the Czech republic



New orphan legislation in force from 2022

Usual limits of orphan/pediatric drugs (1/2)

1) Uncertainty in clinical data (small patient population, heterogeneity of patients, persistence of treatment effect, drop-out from treatment, long-term efficacy etc.)
2) Absence of comparative arm in the trials
3) Unclear/heterogenous comparative arm (sometimes bundled in „Standard of care" but nonetheless some important therapies might be excluded)
4) Off-label/unlicenced drugs as comparator with limited data but their comparison might be required during HTA process: difficult to conduct indirect tr. comparison
5) Short clinical trials relative to disease duration (often life-long)
6) Absence of long-term observational data of clinical history/course of disease, difficult to model long-term outcomes during HTA process
7) High costs due to small patients populations (Onakpoya et al. 2015)
8) Uncertainty in costs (treatment duration or re-treatments, combinations with other new therapies or treatment sequences)
9) Absence of quality of life data and sometimes no possibility to collect them in comparative arm (such as phenylketonuria without diet)

Onakpoya et al. (https://pubmed.ncbi.nlm.nih.gov/26109112/)

Usual limits of orphan/pediatric drugs (2/2)

10) No patient pathway/delegation within the healthcare system (or disease testing)

11) No established specialized treatment centers

12) No/low information about costs of usual care which might be costly

13) Comparators do not have robust clinical data but comparison with them might be required (plus absence of comparative arm from clinical trial) – problematic indirect treatment comaprison

14) No patient organization – hard to collect data from societal perspective

15) No long-term registry data of new drugs or low motivation to collect data in real clinical practice (uncertainty of the true drug effect in real practice will be worse than in clinical trials)

Onakpoya et al. (https://pubmed.ncbi.nlm.nih.gov/26109112/)

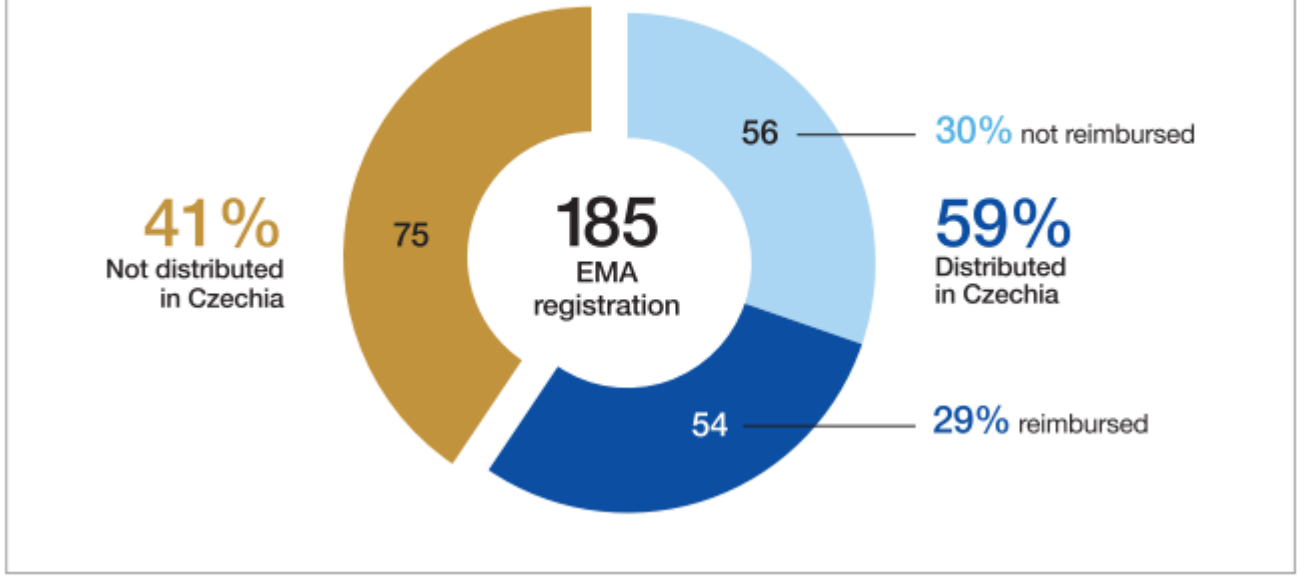
New Czech reimbursement legislation as of January 22‘: background

Why it is important? Why there was a need for new legislation for orphans in CZ?

Low availability of OMPs and this proportion was steadily **decreasing** over time

Majority of orphans were reimbursed via **exceptions/individual approval**, non-systemic approach with a very high uncertainty/unpredictability and unstability for patients, physicians, budgets

Figure 1. Availability of OMP (2015–2021)



Decker, Mlcoch, Doležal et al.: NOVEL APPROACH TO DECISION MAKING FOR ORPHAN DRUGS. ISPOR Europe conference 2022.

New Czech reimbursement legislation as of January 22‘: what is assessed

Criteria and parameters for OMP assessment

Necessity of valid orphan status at EMA (slightly discriminatory for some drugs)

Table 1. Criteria and parameters for OMP assessment
(according to Order n. 53/2021 from the Minister of Health)

Evaluated criteria	Methodology	Criteria for decision
a) Therapeutic effectiveness (1) and safety (2)	(1) Effect on survival, morbidity, quality of life, or other significant clinical outcomes (2) Severe adverse events profile, the occurrence of adverse events leading to treatment discontinuation	(1) Prioritize OMP with significant efficacy on major clinical outcomes (survival, QoL, complications, hospitalizations, long-term disability), with regard to the level of clinical evidence (incl. RWE) and corresponding level of uncertainty (2) Prioritize OMP with significant improvement in safety profile in case SoC toxicity is a major limitation
b) Severity of disease	Expected life expectancy without treatment, QoL, incidence of (irreversible) complications	Prioritize OMP for diseases that severely decrease life expectancy and/or QoL without treatment
c) Reimbursed treatment alternatives	Description of the current treatment algorithm	Prioritize OMP indicated for rare diseases with no treatment alternative
d) Societal impact	(1) Costs assessed from the societal perspective, including loss of productivity (2) Dependency of others – family, caregivers, need for home-care, long-term hospitalization, or institutionalization	(1) Prioritize OMP reducing costs from the societal perspective, including indirect costs (loss of productivity, social care costs) (2) Prioritize OMP, decreasing family/ caregiver/societal burden
e) Quality of life (QoL)	Treatment effect on the patient’s QoL	Prioritize OMP with robust evidence, ideally measured in clinical studies
f) Network of specialized medical centers	Existing network of healthcare providers and diagnostic tools	Provision of effective continuous care delivered by qualified healthcare professionals
g) Clinical guidelines	Nationally and internationally recognized clinical guidelines relevant for the OMP	Prioritize treatment included in the guidelines, with a high level of evidence and/or grade of recommendation
h) Managed entry agreements (MEAs) with payers	Proposed managed entry scheme (simple discount, budget cap, and pay-back, price-volume or outcomes-based agreement)	Prioritize outcome-based models where the manufacturer covers costs associated with ineffective treatment (outcome guarantees)
i) Cost-effectiveness	Costs per QALY critically assessed by the Institute, absolute QALYs gain	
j) Budget impact	Healthcare payers costs using a 5-year time horizon	Prioritize OMP delivering high benefit with acceptable budget impact

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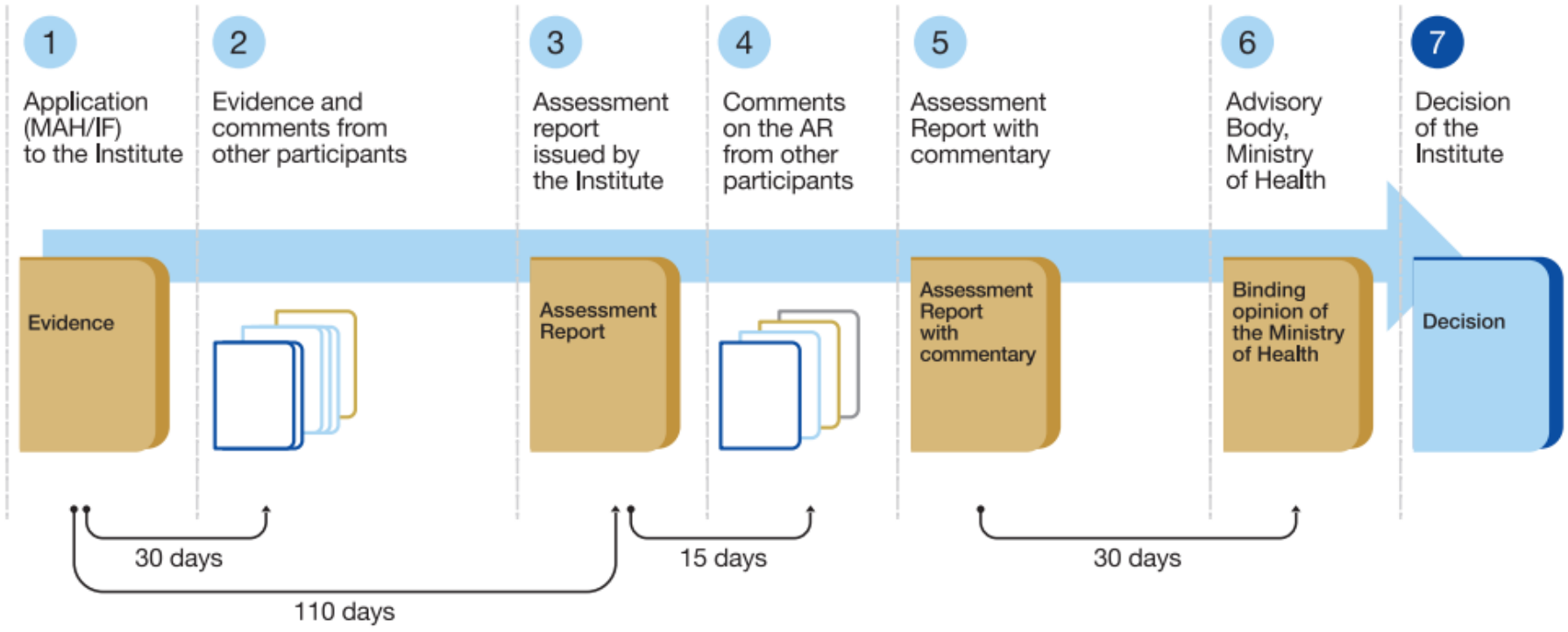
New Czech reimbursement legislation as of January 22‘: procedures

Procedures of administative proceeding

SUKL (State Institute for Drug Control) = **assessment**

Advisory body (Ministry of Health) = **decision**

Figure 2. Schematic of the administrative procedure



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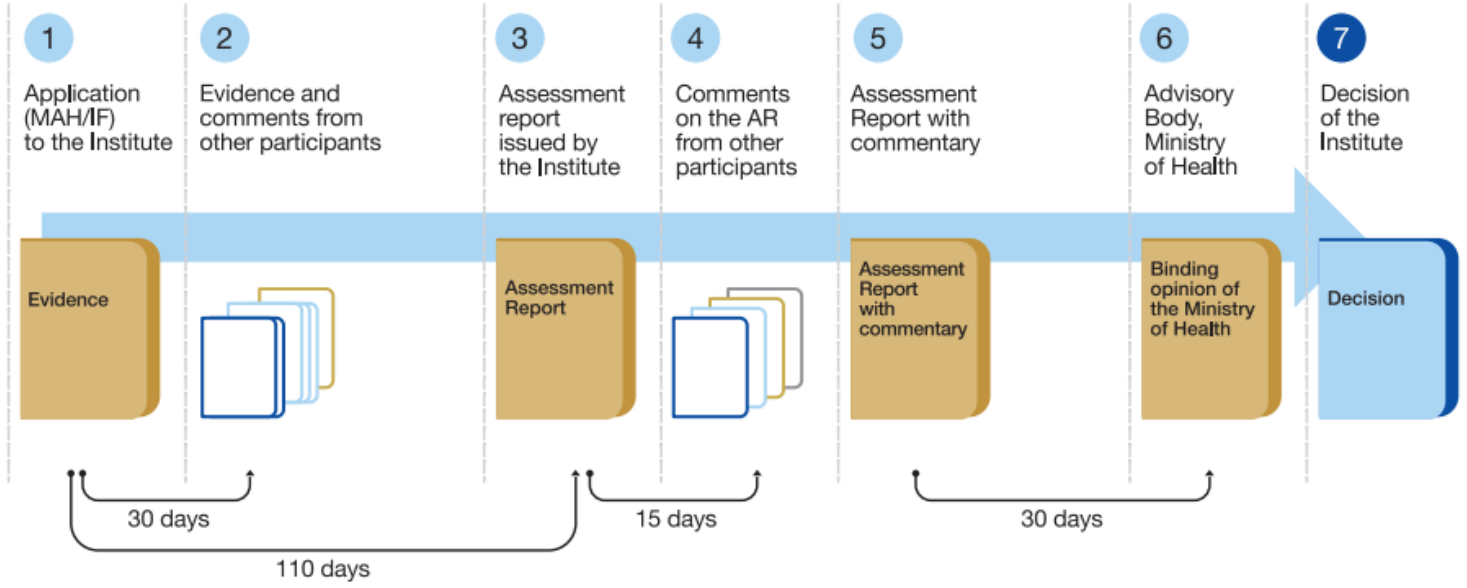

1. The application (containing clinical evidence, cost-effectiveness analysis, budget impact analysis, impact on patients and relevant patient access scheme) is submitted to the governmental HTA agency (the State Institute for Drug Control) by the Marketing Authorization Holder or a Health Insurance Fund.
2. Relevant professional associations and patients organizations as well as health insurance funds are entitled to present evidence and make comments during the 30 days after the initiation of administrative proceedings. This ensures the essential involvement of all key stakeholders in the P&R process.
3. The Institute performs the assessment/appraisal of the evidence. Within 110 days from the initiation of the proceedings, it publishes the Assessment Report summarizing available information.
4. All the participants have the right to comment on the Assessment Report within 15 days from its publication.
5. The Institute then publishes the final Assessment Report and forwards it to the Ministry of Health and its Advisory Body. The Advisory body consists of four stakeholders: [1] patients (not with the given disease), [2] clinical experts (not from the given disease area), [3] public health insurance funds, and [4] the State.
6. The Advisory body critically evaluates the documents and (within 30 days) issues a binding opinion based on the decision-making criteria that are summarized in **Table 1**.
7. The binding opinion is then forwarded back to the Institute, which then issues a final Decision on the P&R in line with the opinion.

Decker, Mlcoch, Doležal et al.: NOVEL APPROACH TO DECISION MAKING FOR ORPHAN DRUGS. ISPOR Europe conference 2022.

What is unique in the Czech orphan system?

1) **Advisory body** which decides about reimbursement
   - 8 members: 2 physicians and 2 patients (not from given diagnosis; from Professional medical society and Patient organization listed at Ministry), 2 health insurance funds and 2 from „State“ (Ministry of Health or other institutions)
   - Majority decides
   - If there is a equality of votes: then Minister of Health decides
2) Patients are **directly involved in the decision making process** with vote – unique internationally
3) **Division** of assessment and decision making process
4) **Societal perspective data and their inclusion into the cost-effectiveness and budget impact analysis** (i.e. impact on other than health care costs (social (disability pension, social benefits), patient (out-of-pocket payments), impact on caregivers, time burden of patients, disease burden etc)

New Czech reimbursement legislation as of January 22‘: goal

The goal of new orphan legislation has been following:

Increase availability of orphan drugs

Avoid non-systemic, individual reimbursement of orphans

Reduce non-systemic approach and try to regulate orphans with widely known and predictable rules

Make reimbursement process more attractive for orphans which are not possible to reach WTP threshold (in Czechia equal to 1.2 mil CZK/QALY ≈ €49,000/QALY)

Predictable budget management for orphans for health insurance funds

Avoidance of unnecessary „medialisation“ of individual cases and medial pressure from patients

Questions for panelists/discussion

1) How to improve orphan drug and pediatric drug access (regulatory perspective)

1) How to improve orphan drug and pediatric drug access and at the same time does not risk to bring any harm in terms of safety or entrance of a drug with lower efficacy than expected/submitted

- Fast access based on phase II trials with ongoing data collection
- Conditional approvals based on interim clinical data with ongoing update of data collection
    - How many drugs were initially approved and then refused based on additional data collection
- Mandatory data collections and registries for orphan/pediatric drugs
- Mandatory publication of overall survival data of later data cut-offs in oncologic trials – key for health economic analyses because there is not always proven PFS-OS relationship

2) How to improve orphan drug and pediatric market access with known data limitations

- 2a) How to cope with higher prices of these drugs (different willingness-to-pay thresholds, different pathways for orphans/pediatric indications)
- 2b) How to deal with imbalance in the systems between orphan/pediatric drugs vs. „other/usual drugs“
  - Most systems use cost/QALY approach and we know that 1 QALY = 1 QALY
  - Is it ethical/effective to give an advantage to some and not to others with high burden of disease, limited treatment options etc. and at the same time do not „signal“ a negative incentive that we can „reimbursed“ everything if this is labelled as orphan/pediatric drug with no limits compared to standard drugs

Questions

3) How to motivate/incentivise to invest into the orphan/pediatric indications and drugs?

4) How to lower costs of the orphan/pediatric drugs?

5) How to solve a situation with multiple indication drug with only one being orphan/pediatric? The reimbursement systems then cluster this drug as non-orphan, non-pediatric which might bring much lower incentives to invest into new orphan/pediatric indications with current drugs without orphan designation. Companies do not have much incentives to run new clinical trials with their drug if they receive the same price as in original large indication.

Question for „million dollars“

6) If you could somehow change/improve our systems for orphans/pediatric patients:

what would be your advice or recommendation in ideal world?

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