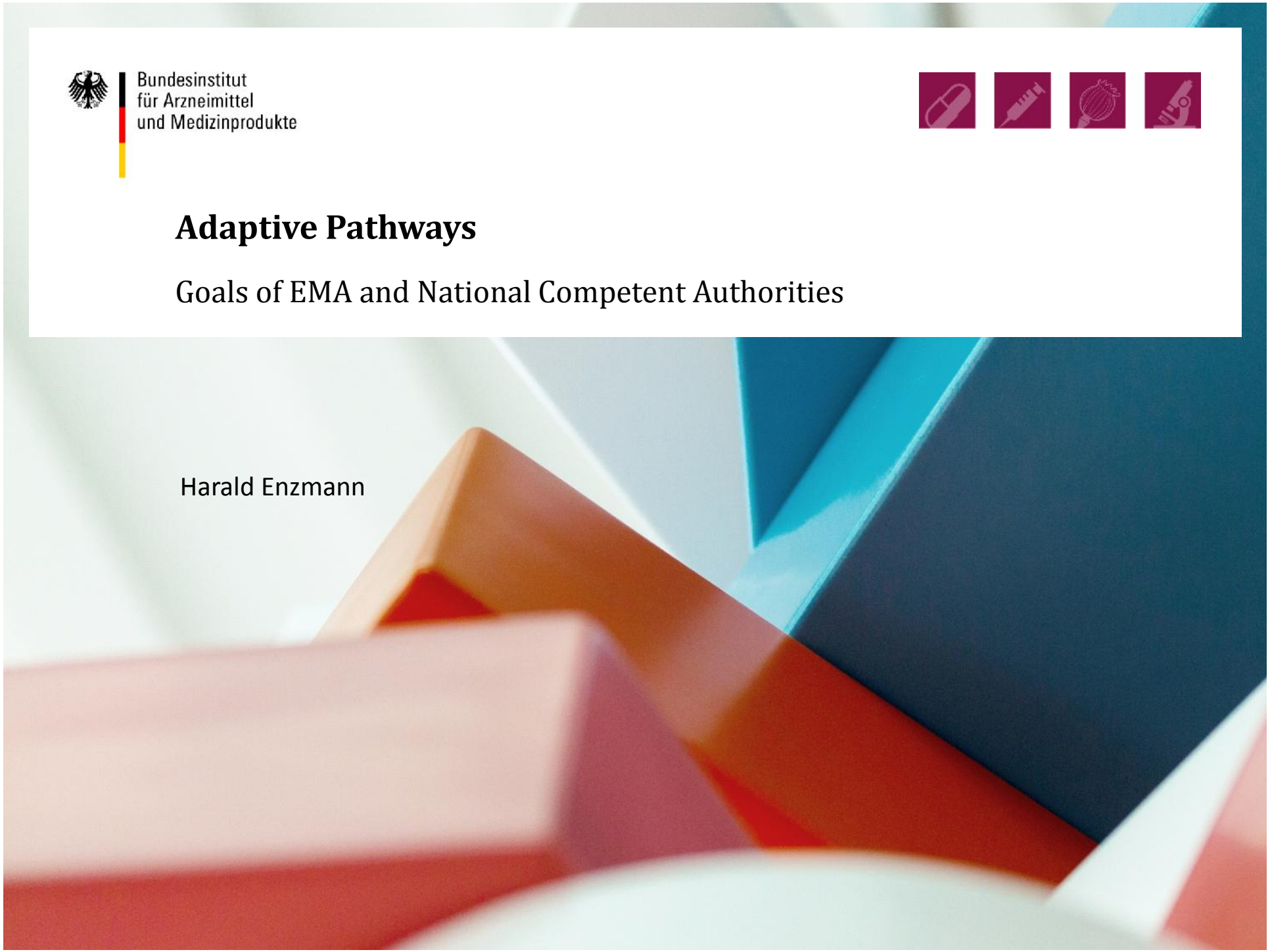
Bundesinstitut
für Arzneimittel
und Medizinprodukte

Adaptive Pathways

Goals of EMA and National Competent Authorities

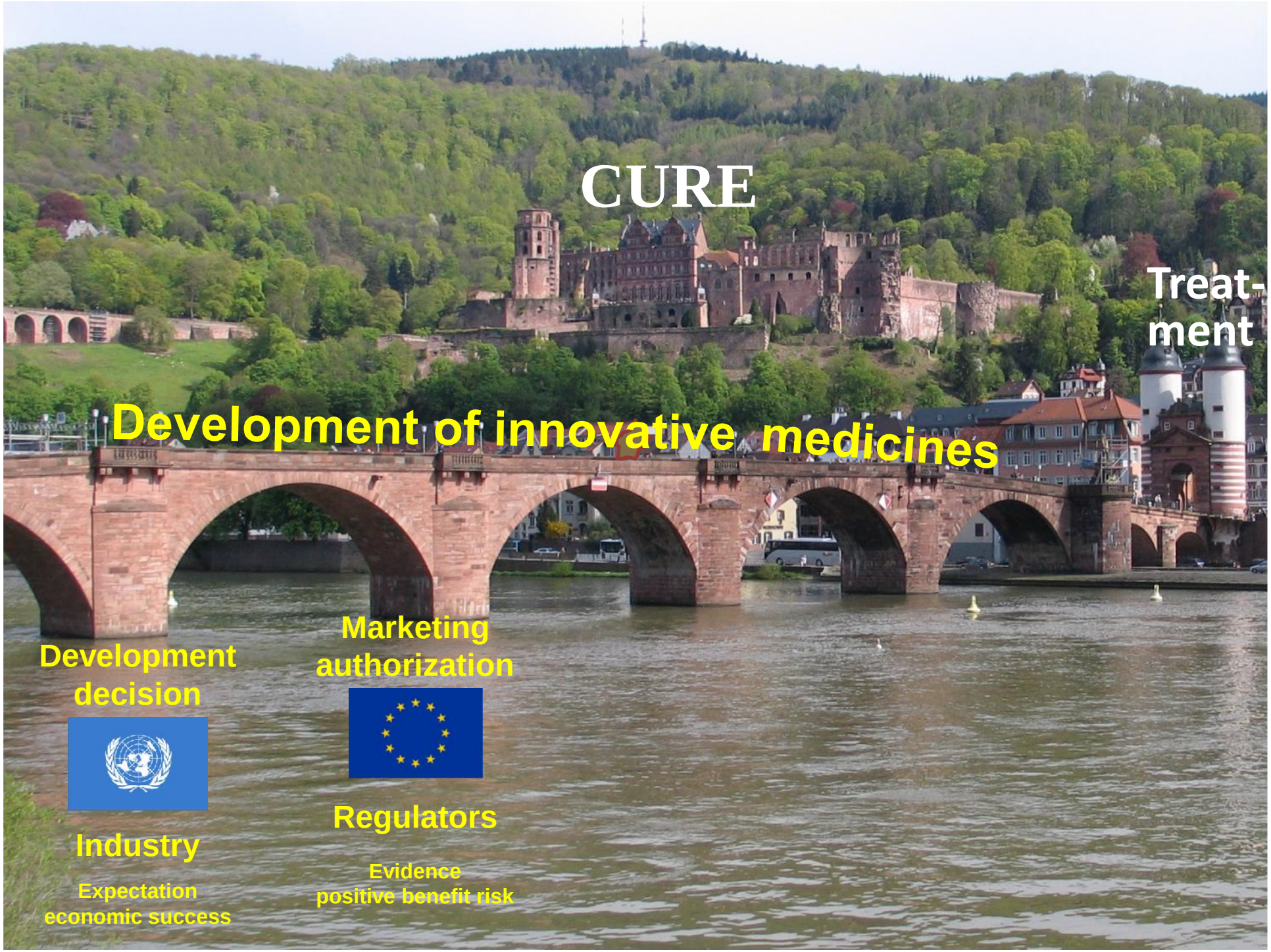
Harald Enzmann



Setting the Scene


CURE
Treat-
ment
Development of innovative medicines
Heidelberg am Neckar


CURE
Treat-
ment
Development of innovative medicines
Development
decision
Industry
Expectation
economic success


CURE
Treat-
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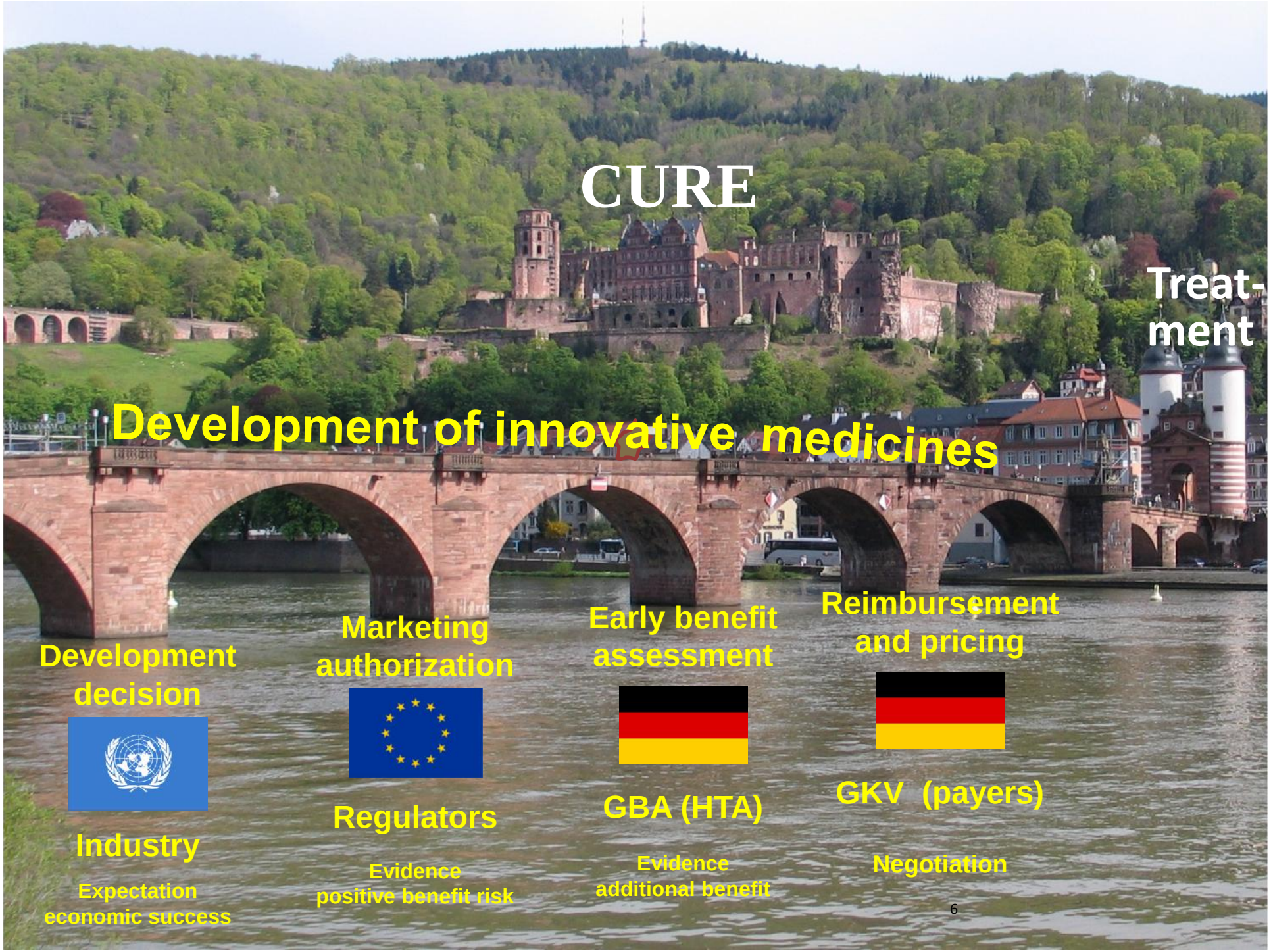
Development of innovative medicines
Development
decision
Marketing
authorization
Industry
Regulators
Expectation
economic success
Evidence
positive benefit risk


CURE
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Marketing authorization
Regulators
Evidence positive benefit risk
Early benefit assessment
GBA (HTA)
Evidence additional benefit
Reimbursement and pricing
GKV (payers)
Negotiation

CURE

Treat-
ment

Development of innovative medicines

Development decision

Industry

Expectation
economic success

Marketing authorization

Regulators

Evidence
positive benefit risk

Early benefit assessment

GBA (HTA)

Evidence
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Reimbursement and pricing

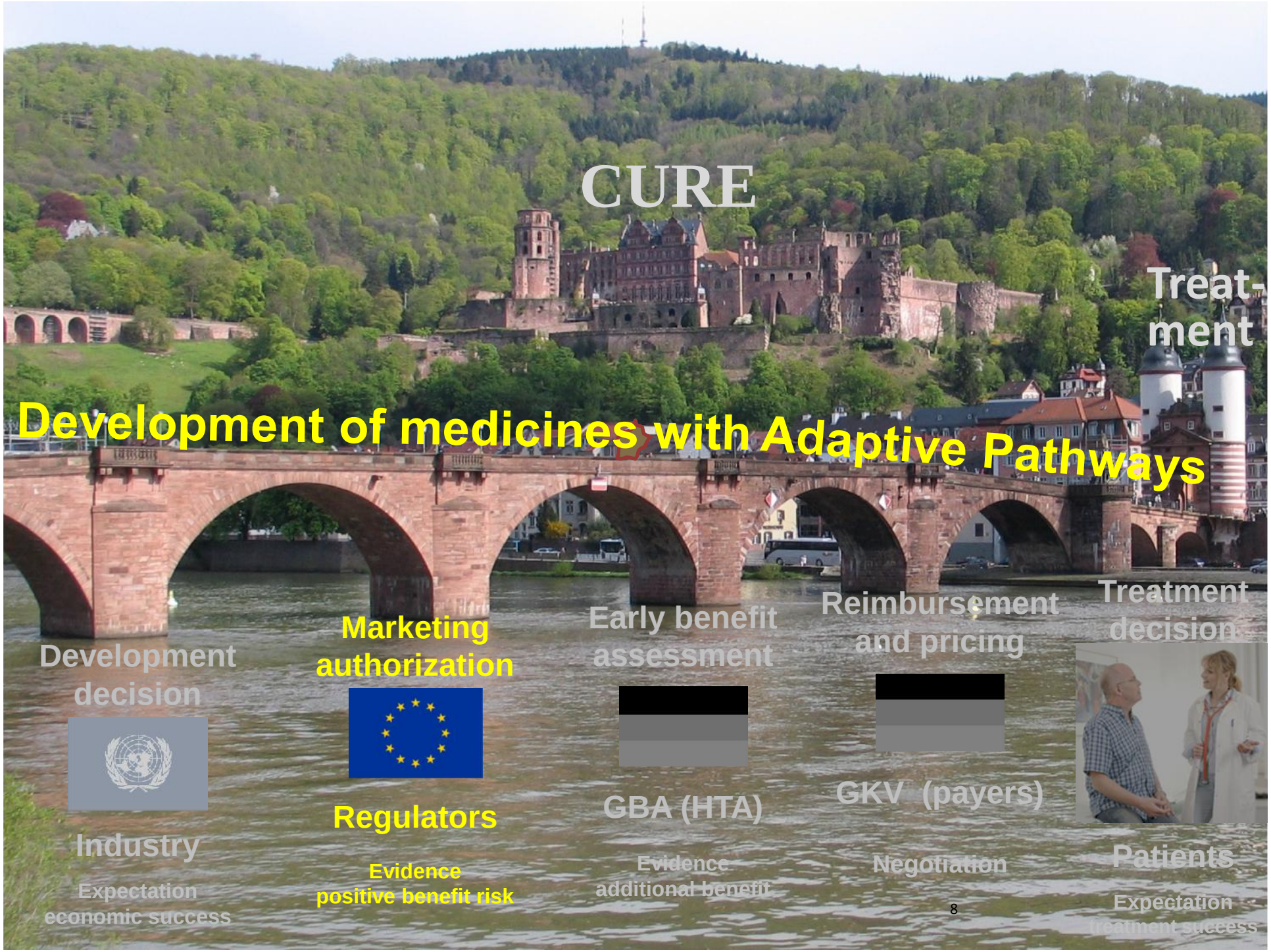
GKV (payers)

Negotiation

Treatment decision

Patients

Expectation
treatment success


CURE
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Development of medicines with Adaptive Pathways
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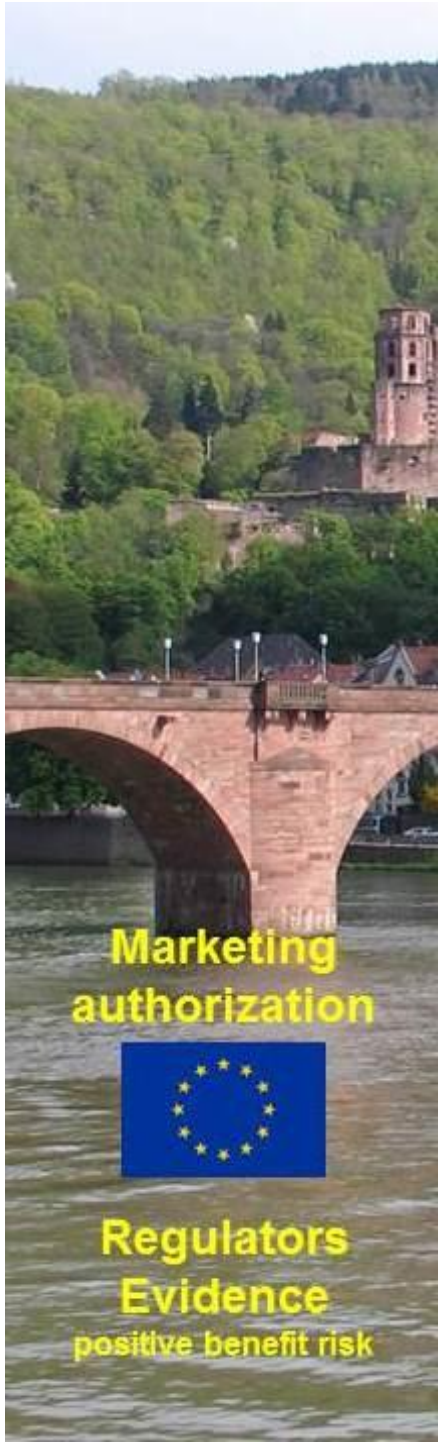


STATE OF THE ART

nature publishing group

Open

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garner[8,9], P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke[16], E Pezalla[17], D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsch[2]

Clinical Pharmacology & Therapeutics (2012); 91 3, 426–437

HMA
Heads of Medicines Agencies

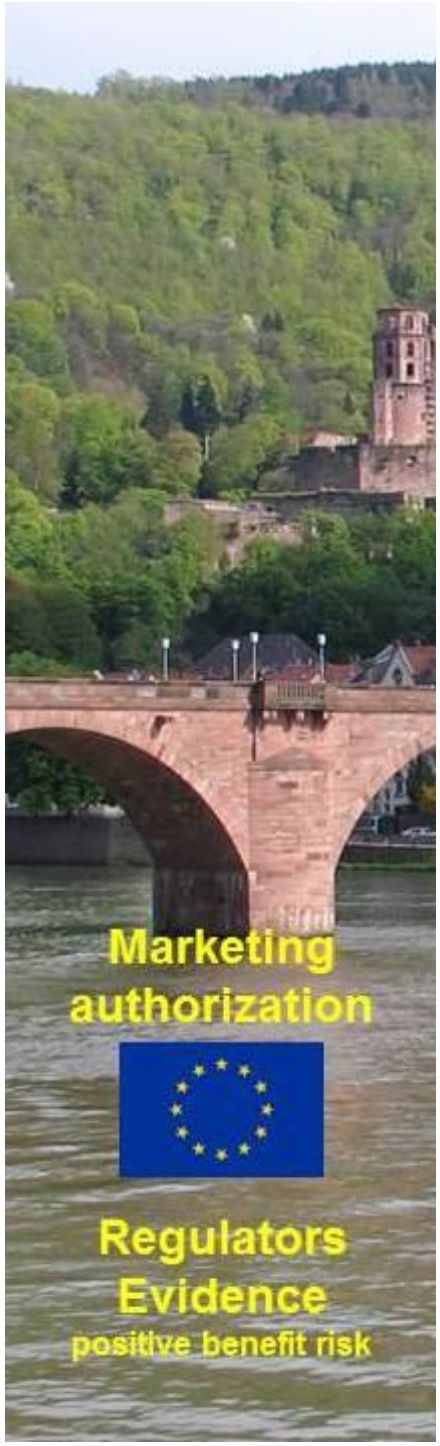
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/MB/151414/2015

EU Medicines Agencies Network Strategy to 2020

Working together to improve health

… get appropriate medicines to patients more quickly … , by taking forward the concept of adaptive pathways…



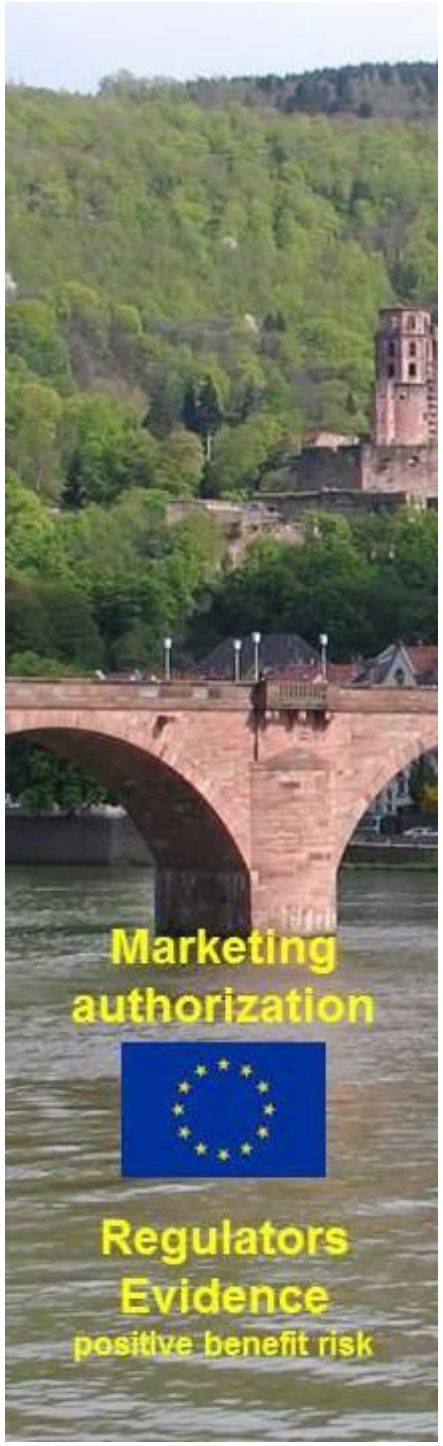
Adaptive Pathways

A scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine

Adaptive pathways is based on three principles:

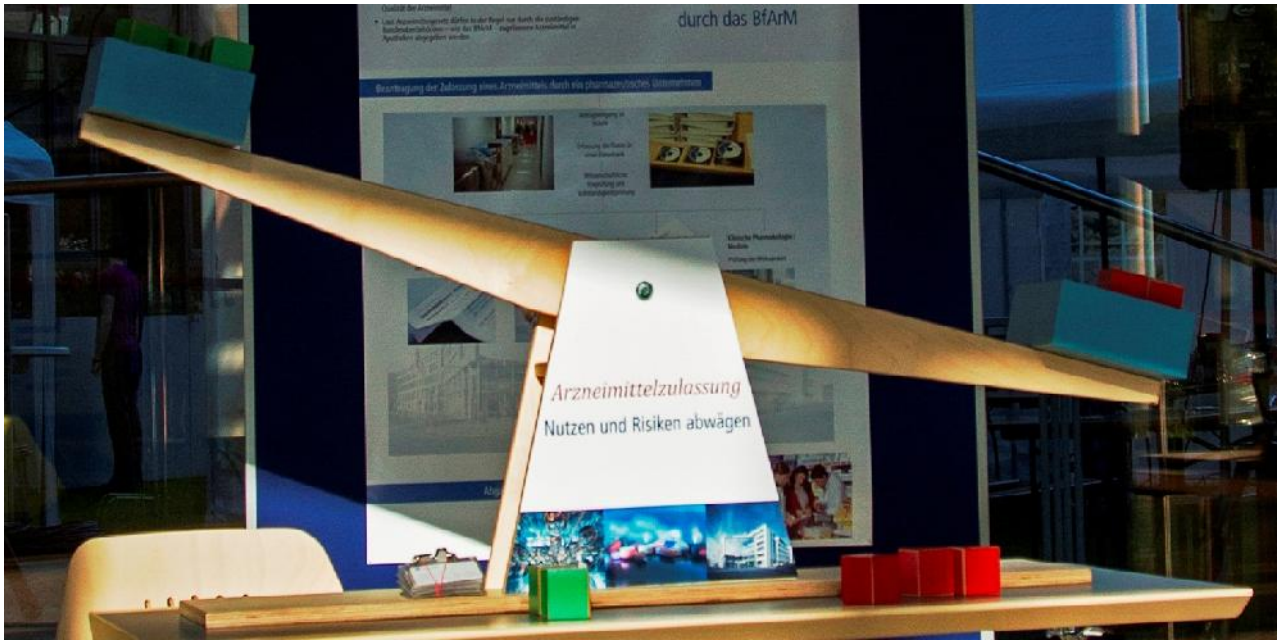
- **iterative development, which either means:**
  - **approval in stages**, beginning with a restricted patient population then expanding to wider patient populations;
  - confirming the benefit-risk balance of a product, following a **conditional approval** based on early data (using surrogate endpoints) considered predictive of important clinical outcomes;
- **gathering evidence through real-life use to supplement clinical trial data;**
- **early involvement of patients and health-technology-assessment bodies in discussions on a medicine's development;**

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

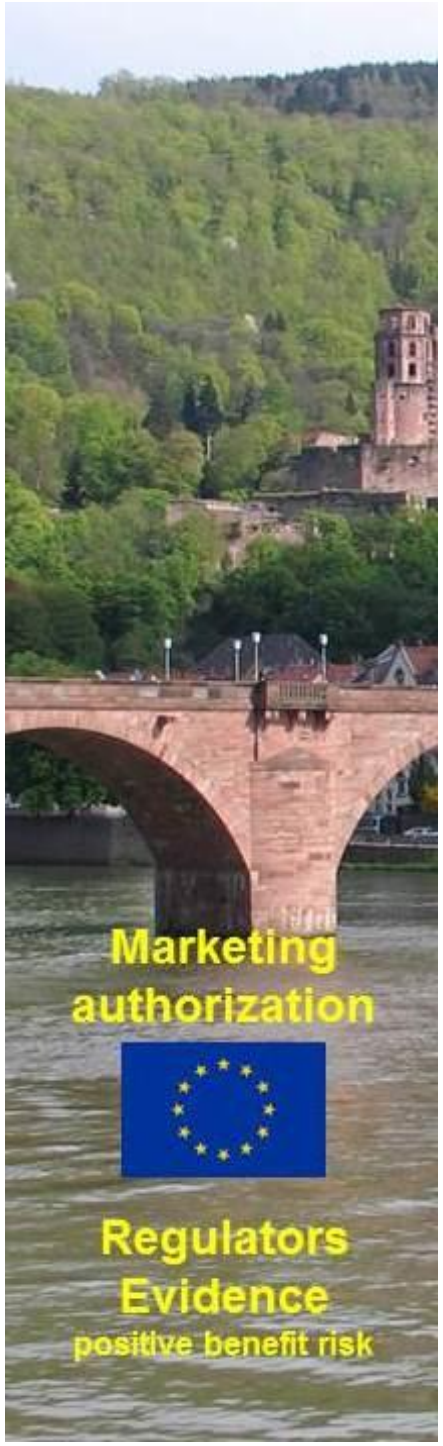


Benefit Risk Balance in Adaptive Pathways

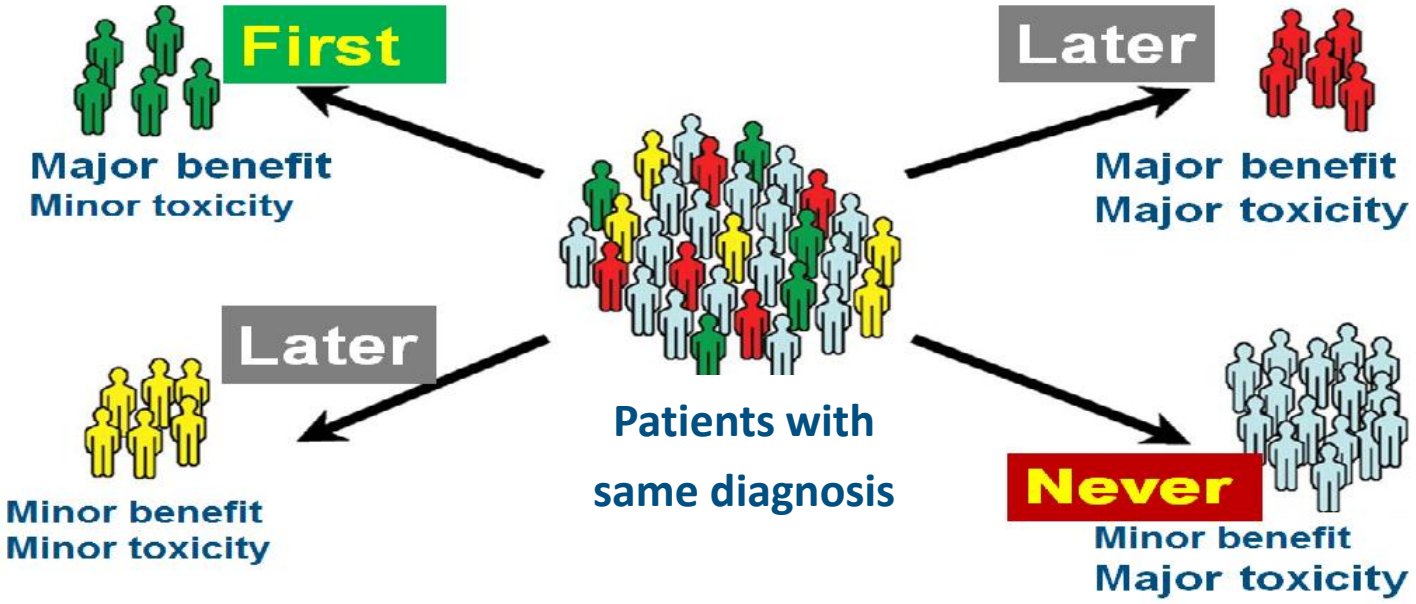
still defined as favourable effects (benefits) versus unfavourable effects (risks)



Positive benefit risk balance
= more benefits than risks
= “net” benefit of the medicine



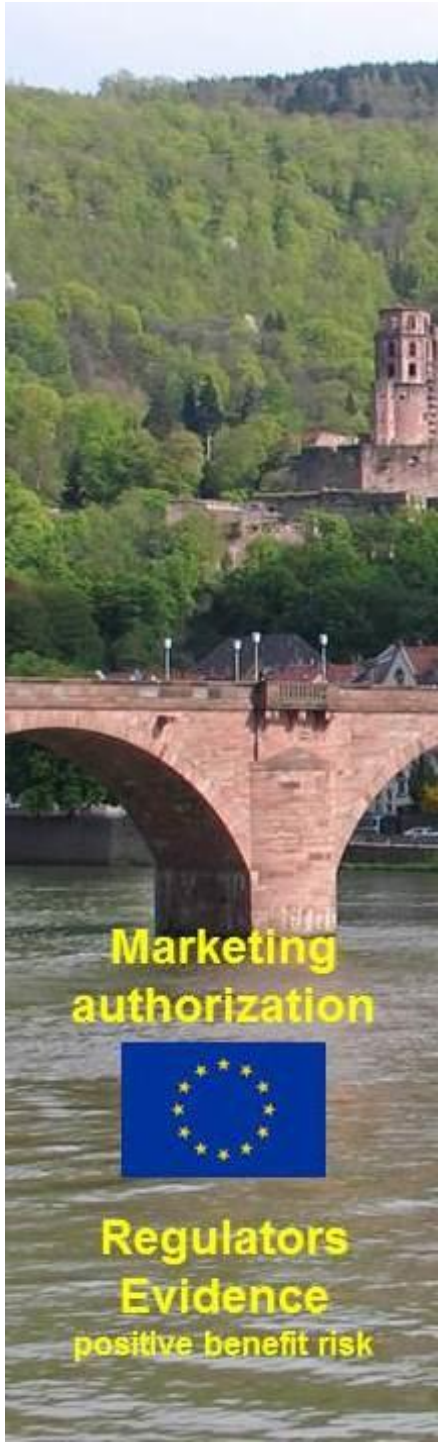
Adaptive Pathways: approval in stages



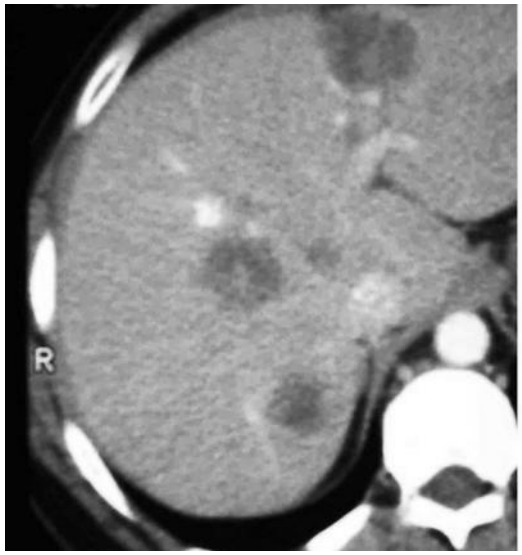
Start with well-defined “best” subpopulation

High “added benefit” receives high reimbursement price

Extend indication later



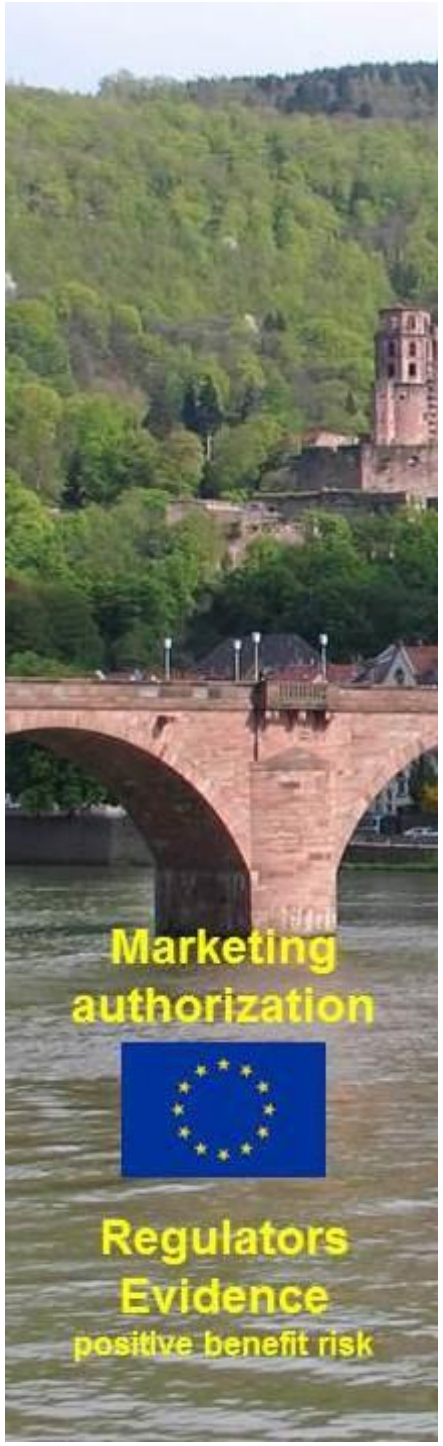
Adaptive Pathways: confirming the benefit-risk balance … following a conditional approval



Surrogate endpoint

Final outcome

- Start with surrogate endpoints
- Later confirm important clinical outcome



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EU Medicines Agencies Network Strategy to 2020

Working together to improve health

Objective 2 Human Medicines:

The network will review ways to ensure timely access to novel medicines, ensuring that existing flexibilities to get appropriate medicines to patients more quickly are used to their maximum potential, by taking forward the concept of adaptive pathways and strengthening the collaboration with Health Technology Assessment (HTA)/pricing and reimbursement bodies and healthcare professionals and patient representative bodies.


Treat-
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Industry
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and pricing
GKV (payers)
Negotiation
Treatment
decision
Patients
Expectation
treatment success

Collaboration with HTA bodies

Limitations of Regulators' benefit risk assessment

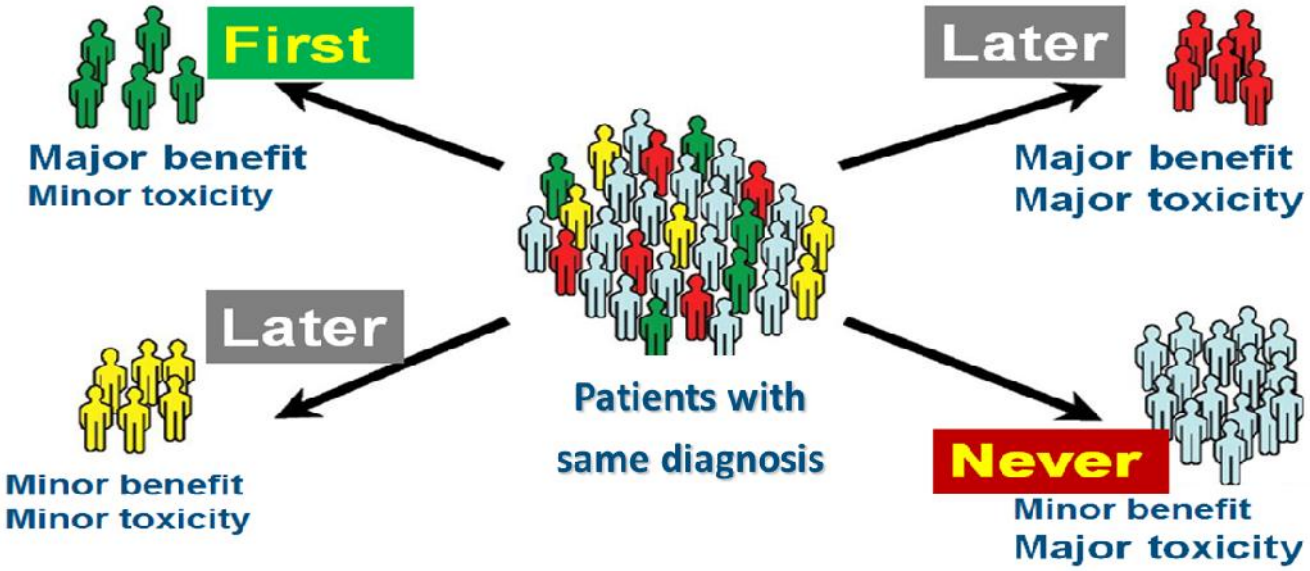
Primarily absolut benefit risk, relative benefit risk optional

Place in therapy may depend on national situation

Inferiority to other treatment options not necessarily prohibitive (availability?)

Collaboration with HTA bodies

Limitations of the approval in stages

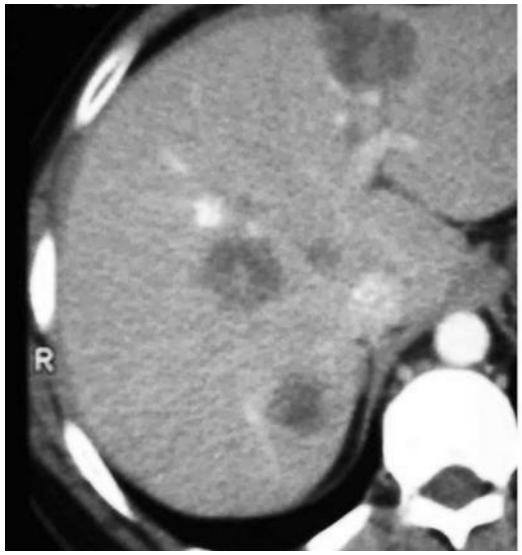


Start with well-defined subpopulation and extend indication later

- **Best benefit risk balance in first group - highest additional benefit**
- **Extension of indication (possibly repeatedly)**
- **For newly included patients group, benefit risk balance less impressive**

Collaboration with HTA bodies

Limitations of conditional approval based on surrogates



Surrogate acceptable for HTA bodies / payers at all?

Clinical outcome confirmative, but more / less favourable than surrogate?

Collaboration with HTA bodies
Common ground

- **G-BA Principles:**
- **Additional benefit over the appropriate comparator regarding patient-relevant endpoints**

- **Appropriate comparator**
  - G-BA: „Standard of care“
  - Regulators: three arm studies welcome
- **Patient-relevant endpoints**
  - G-BA: mortality, morbidity, adverse events, health-related quality of life
  - Regulators: all welcome

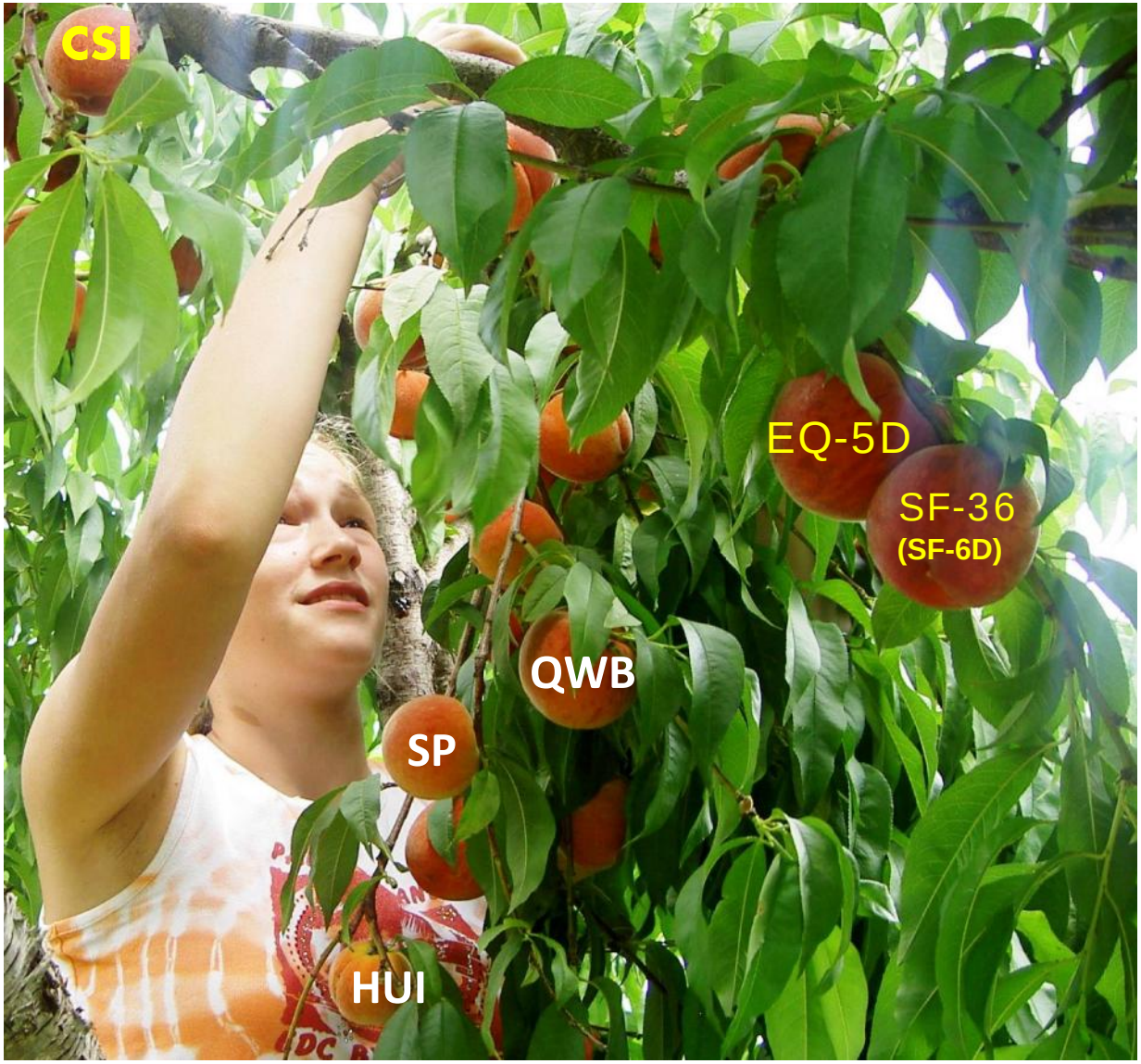
Collaboration with HTA bodies

Common ground and opportunities?

- **G-BA Principles:**
- **Additional benefit over the appropriate comparator regarding patient-relevant endpoints**

- **Appropriate comparator**
  - G-BA: „Standard of care“
  - Regulators: three arm studies welcome
- **Patient-relevant endpoints**
  - G-BA: mortality, morbidity, adverse events, health-related quality of life
    - **Highly welcome for regulators**
    - **But methodological challenges**

Low hanging fruit for applicants?



Choose your HRQL method, set standards

First Choice:

Generic HRQL Indexes

The SF-6D / SF-36

The EuroQoL-5D

Quality of Well Being Scale (QWB)

The Health Utilities Index(HUI)

Second Choice:

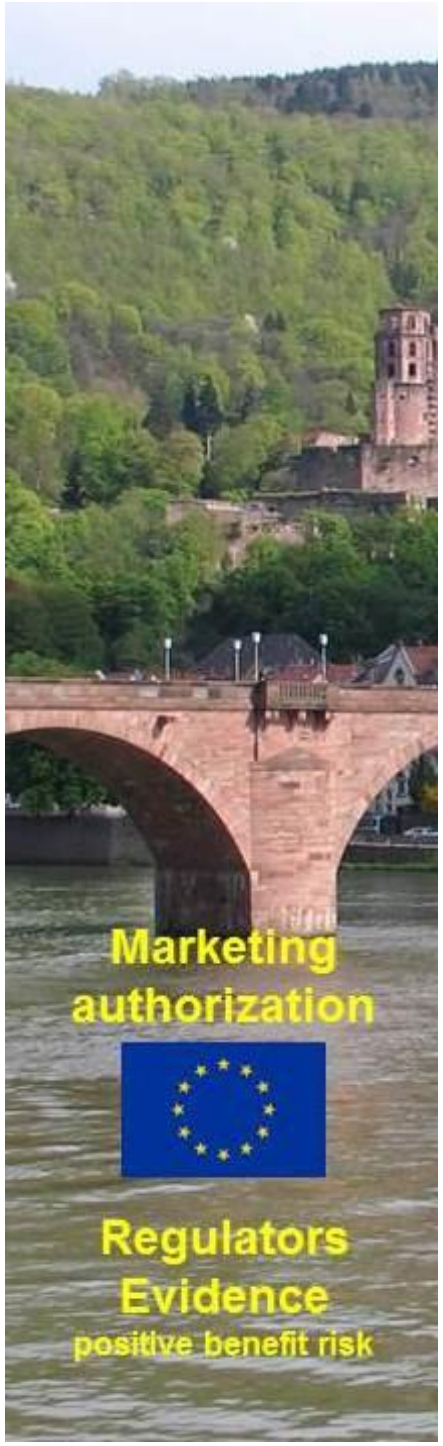
Condition-specific instrument (CSI)

Special populations

Different stakeholders may prefer different HRQL methodologies

If given a choice

take both!



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Patients‘ involvement in the assessment in the centralized procedure

Start day 1
Phase 1

Draft AR day80
Optional involvement through Rapporteurs (national level)

OMS comments day 100

LoQ day 120

Response document
CLOCK STOP up to 6 months

Restart day121
Phase 2

Always in Scient. Advisory Groups

Draft AR day 157

OMS comments day 170
Alle

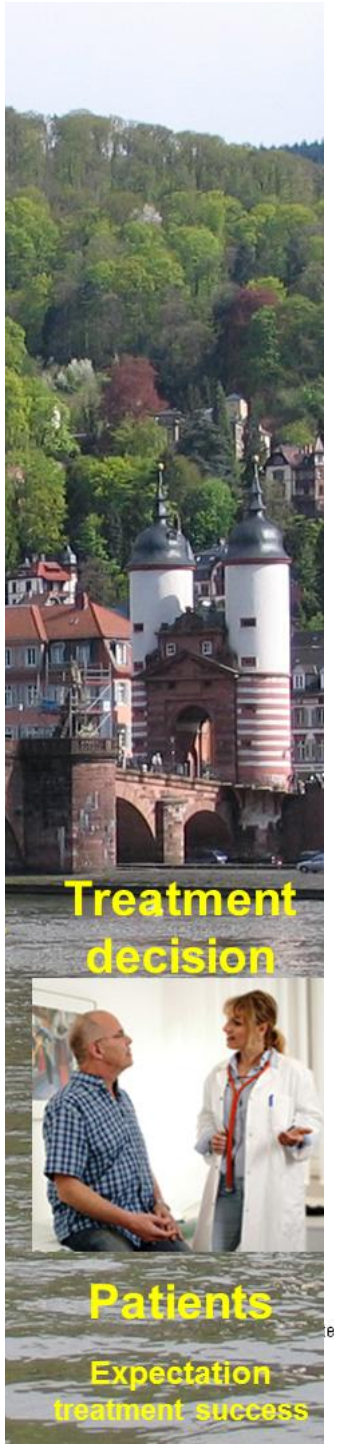
LoI day 180

Optional participation in OE

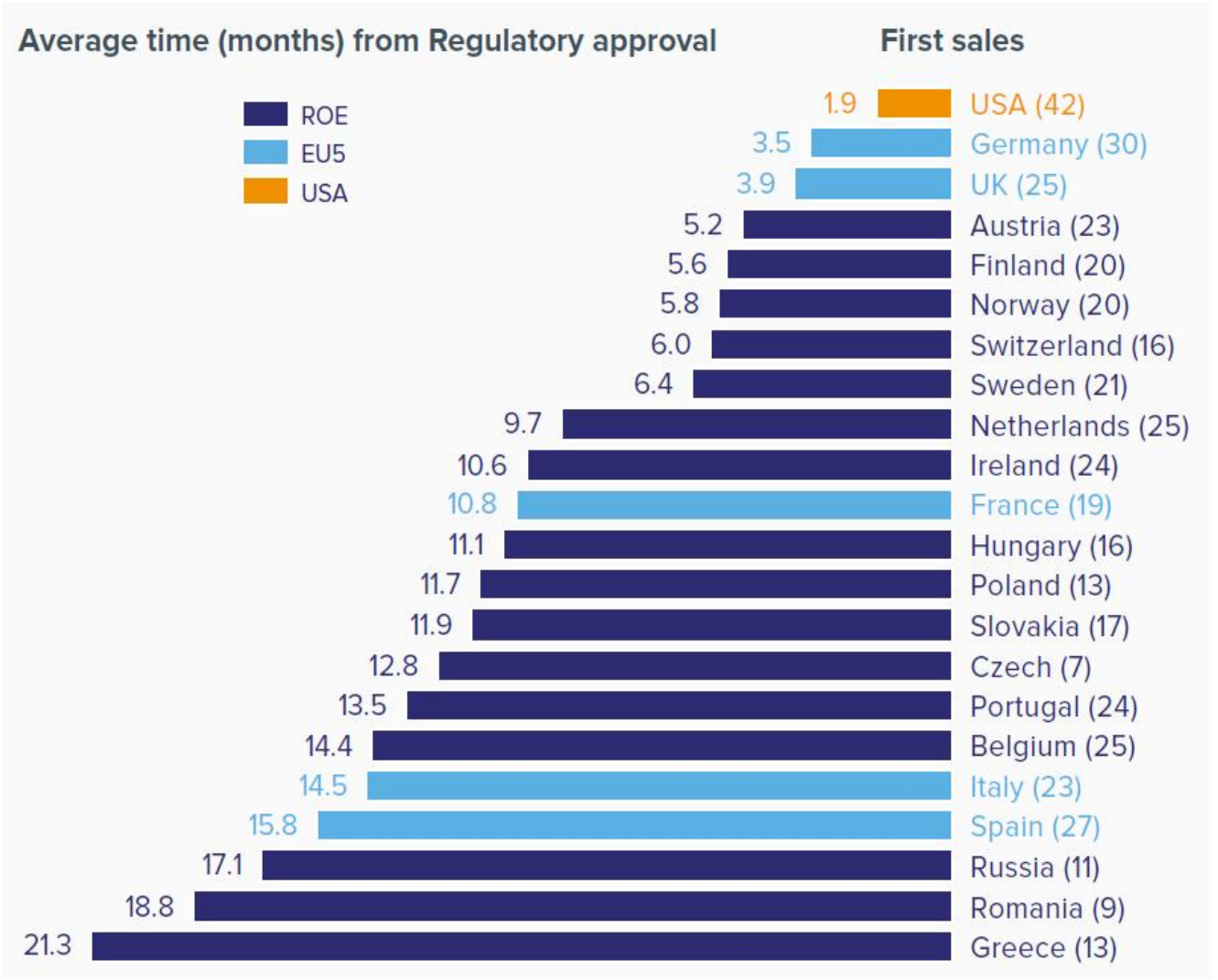
CHMP Opinion day 210

day 277 Commission decision

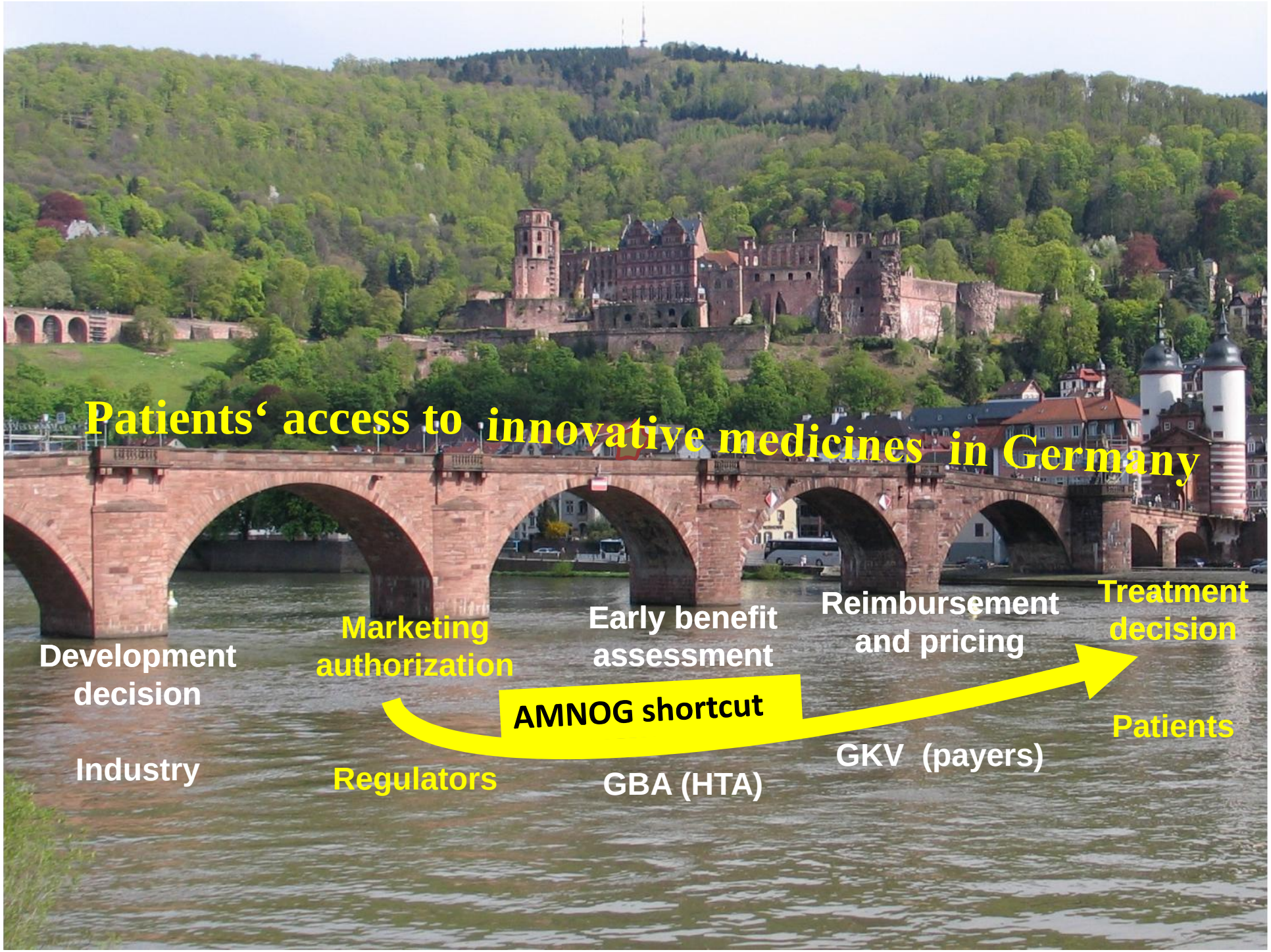
Patients‘ involvement in assessement of MAA



Important for Patients: Timely Access



IMS Pricing & Market Access Outlook, 2015/2016 Edition, ims consulting group.
https://www.imshealth.com/files/web/Global/Services/P&MA_2015.pdf


Patients‘ access to innovative medicines in Germany
Development decision
Industry
Marketing authorization
Regulators
Early benefit assessment
GBA (HTA)
AMNOG shortcut
Reimbursement and pricing
GKV (payers)
Treatment decision
Patients


Earlier marketing authorization with Adaptive Pathways will directly translate into earlier access
Patients‘ access to innovative medicines in Germany
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Summary:
Goals of EMA and National Competent Authorities

The End:

- **Innovative medicines to patients more quickly**

The Means:

- **Iterative development in adaptive pathways**
  - **Approval in stages beginning with a “best” patients, expanding to wider patient populations later**
  - **Conditional approval (using surrogate endpoints), confirming with clinical outcome data later**
  - **Evidence from real-life supplementing clinical trial data**
  - **Collaboration with Health Technology Assessment and reimbursement bodies**
  - **Collaboration with patient representative bodies**

Thank you very much for your attention!

Contact

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