

Risk Mitigation / Minimization ... Suppression? and Medicinal Products

Meeting of the chairs
Scientific Committees involved
in Risk Assessment
Brussels, December 7-8, 2005

Daniel Brasseur
CHMP at the EMEA

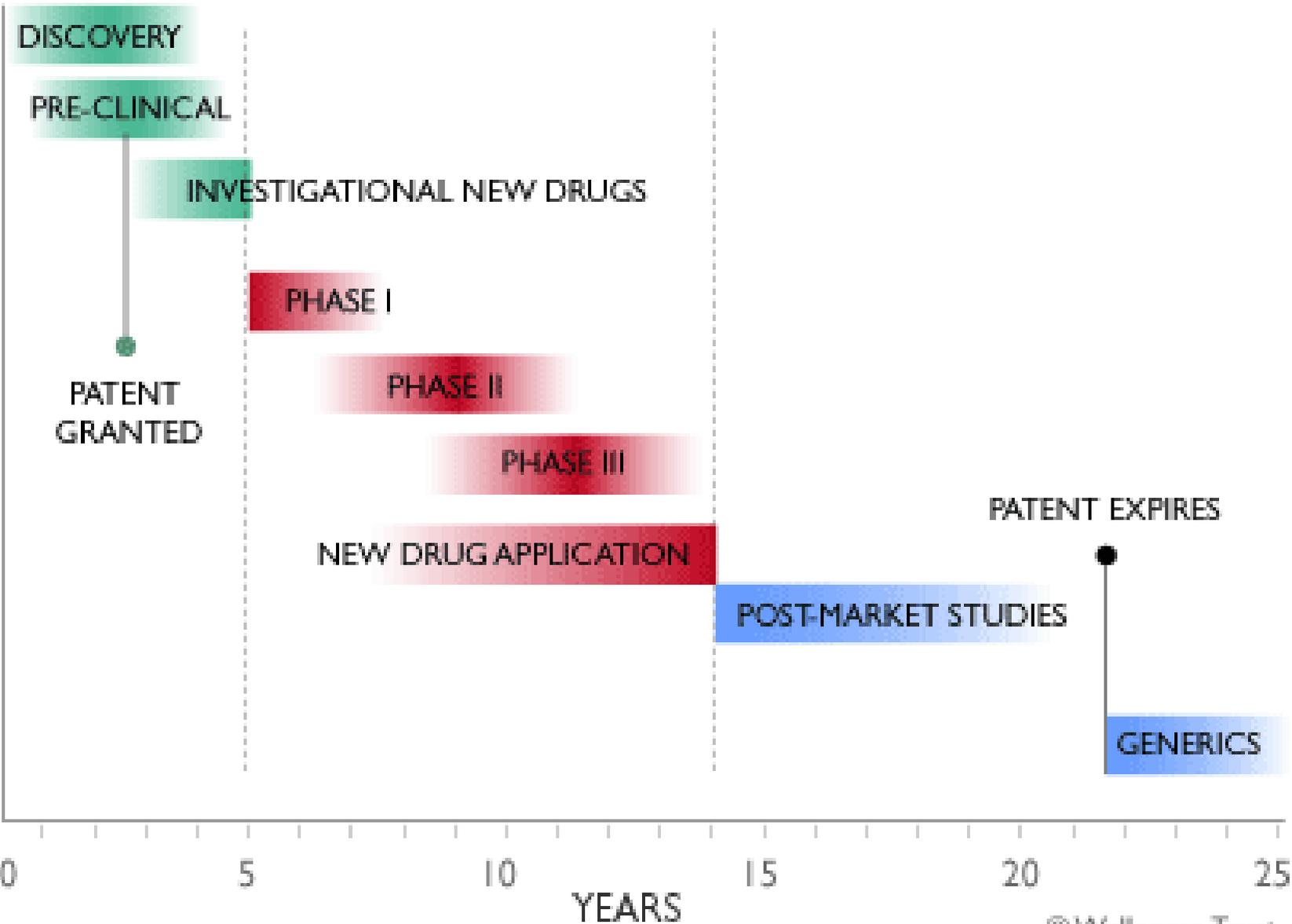
Plan

1. Drug Development
2. Pre Clinical Safety Information
3. Safety Database in CT
4. Safety Assessment
5. Risk Assessment Strategies
6. Novel Therapies
7. How to improve further,
Role of the EMEA
8. Conclusions

PRE-CLINICAL

CLINICAL

POST MARKET



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Pre-Clinical Safety Assessment

In Vitro models (cells, tissues...)

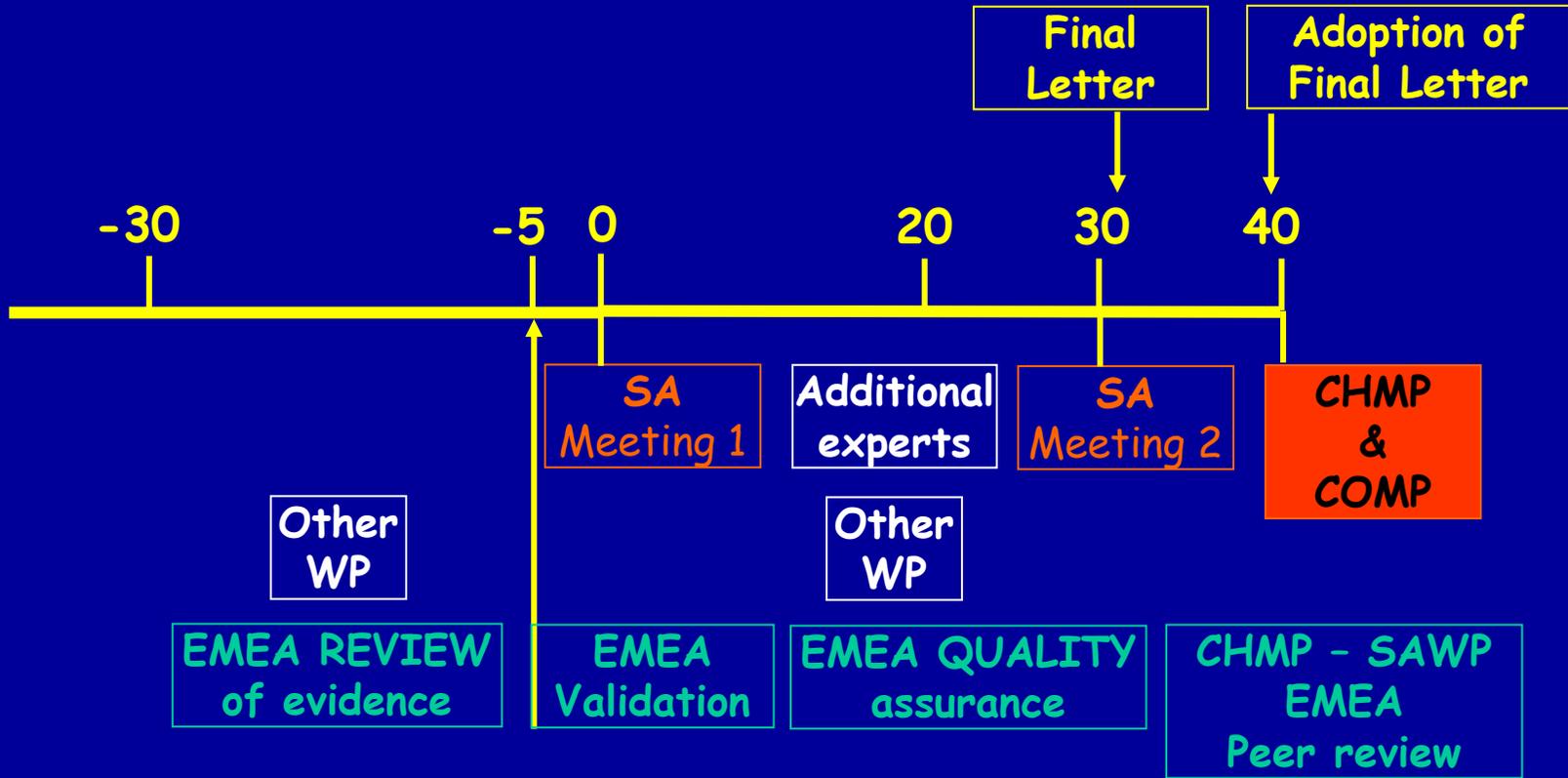
- Development of mechanistic models
- Validation (Reproducibility, reliability)
- Predictability

In Vivo models (Animals)

- Avoiding (Replacing, reducing, refining)
- Transferability (Extrapolation to humans)
- Predictability (Duration/Dose levels)

Safety Aspects Systematically looked for during Drug Development

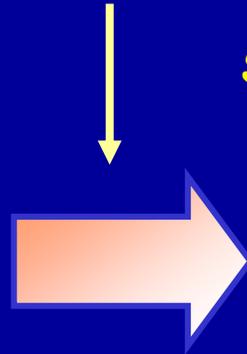
- QT prolongation
- Liver / Renal / Bone Marrow toxicity
- Drug-drug interaction
- Polymorphic metabolism
 - if clinical programme well defined/assessed
if not ... back to Scientific Advice
 - currently being further developed at the EMEA



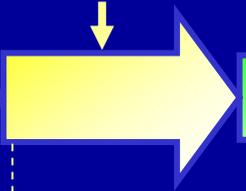
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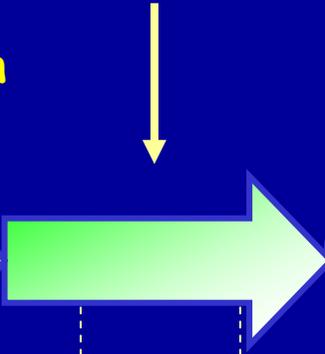
Exploration
Nomination



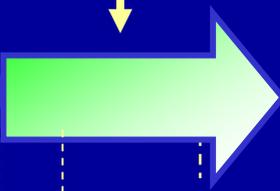
Submission
Validation



Primary
Evaluation



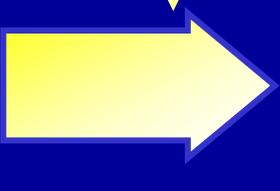
Secondary
Evaluation



Opinion
Decision



Product
Launched on
the market



D.0

D. 70
Rapp
Co-rapp
ARs

D.120
LOQ

D. 110
CPMP
comments

D.121

D. 150
Joint AR

D. 180
hearing?

D.210

D.330

Safety Database of CT

Quality & Completeness of the DB

Terminology (different CT, investigators reporting)

Particular evaluation of patients « leaving » CT

- drop outs
- deaths

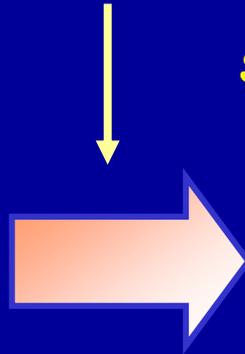
Continuation of safety monitoring of CT Patients

- Events rate
- Attrition of Adverse Events

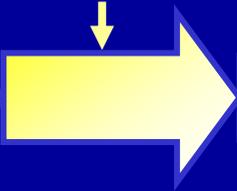
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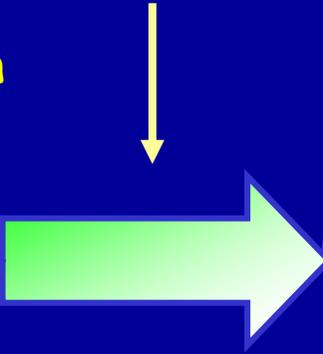
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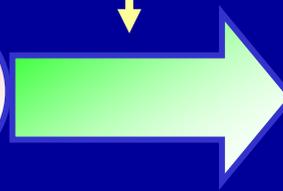


Primary
Evaluation



Stop
Clock

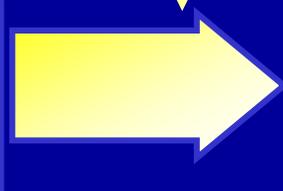
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Review

MSU
Q

WP

Ph Vig

Expert

SAG
Clinical
Relevance
Risk
Assessment



SAG
Risk
Management

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Safety Assessment Interactions

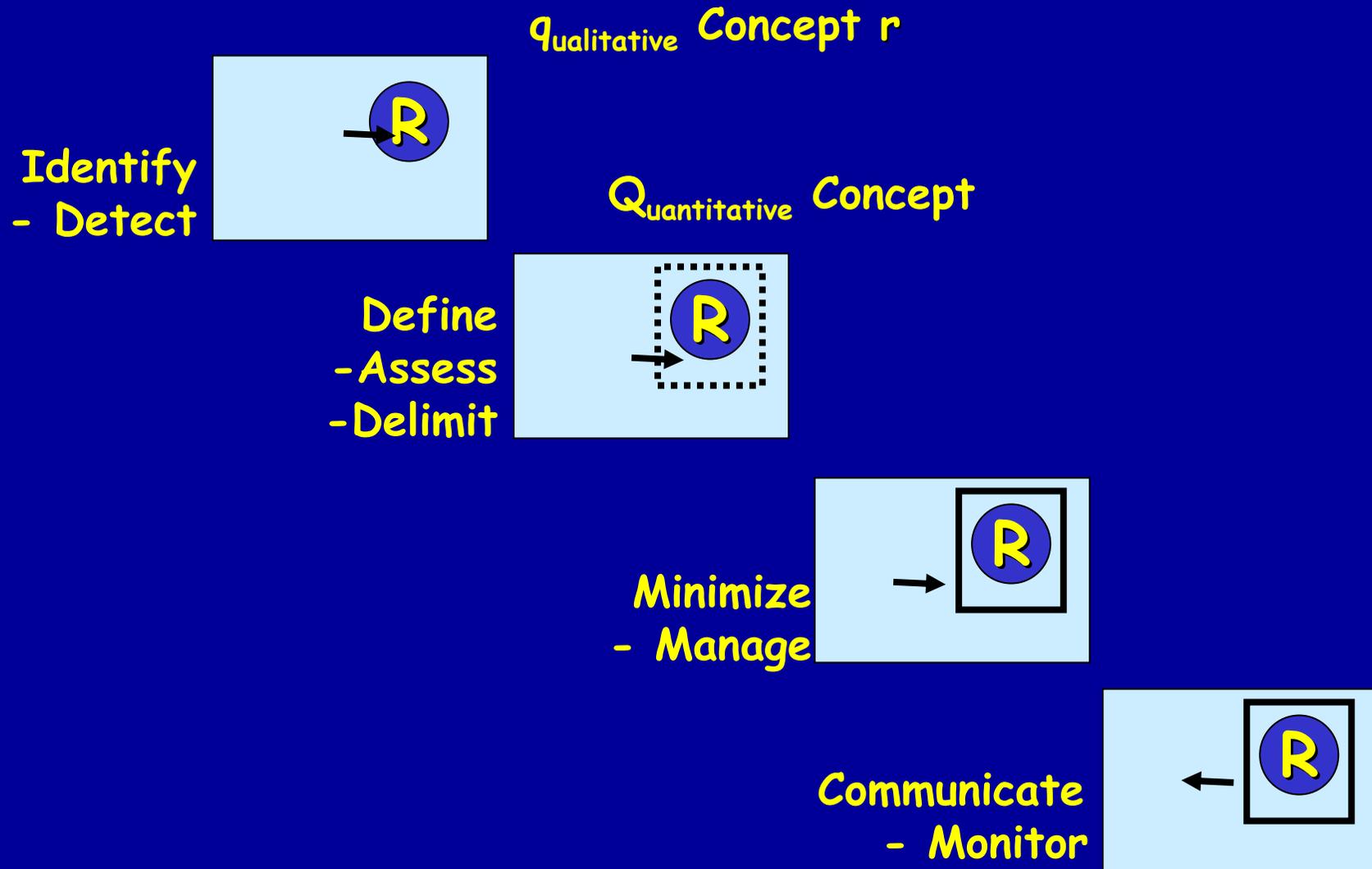
- Drug-drug interactions
Metabolic pathways (« CYP system », ...)
- Demographic relationships
Age, Gender, Race....
- Disease interactions
Stages of ...(NY-Heart Failure, Scale MS)
- Dietary interactions
Food, fat...(Anti HIV)

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Signal Detection

Risk ?



Results: numbers expected: Pv_i

Age distribution SUDI (1999-2001) and DTPa-HiB combination vaccines (1997-1998) Germany



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Safety Aspects of Novel Therapies

Biologicals (cytokines, Antibodies...)

- Immuno Genicity + binding antibody formation

Gene

- Transfection of non-target cells
- Transmissibility to close contacts
- Gene stability

Cell

- Distribution/Migration/Growth beyond the intended administration (long term...)
- Specific Scientific Advice on case by case basis

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**Beyond the scientific assessment
How to improve further?
Role of the EMEA (1)**

Top Quality scientific Assessment

- **High-quality expertise/resources**
- **Increase Number of experts in NCA**
- **Facilitate Educational Tracks in Academia**
- **Benchmarking with other Authorities**
- **Establishment of centres of assessment**

Regulation 726 / 2004
Pharmaco-Vigilance
Risk Management
New provisions
art. 59

Collaboration with other Agencies & Bodies

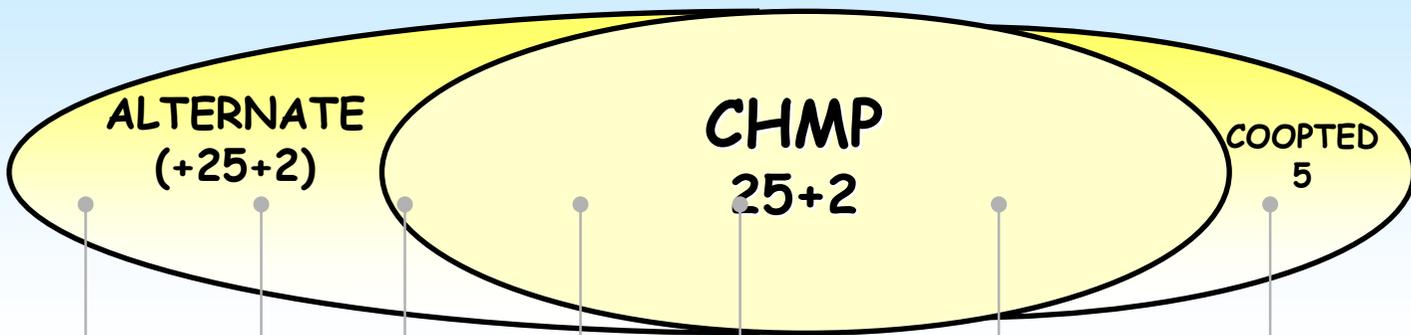
- Food chain and AB residues
- Yeasts/Bacteria.. in Food and Health Claims/Disease Indications?
- Environmental risk
 - *GMO* vaccine for Cholera vaccines
 - Estrogens patch for contraception
 - Miconazole in "cosmetics"
 -

Beyond the scientific assessment

How to improve further?

Role of the EMEA (2)

- Building on the current architecture (networking model between NCA and EMEA) which has already provided substantial benefits
- Allowing to a better use of (limited) resources
- Sharing the pre/post-authorization work
- after having defined harmonized/agreed approaches



Opinion to Decision

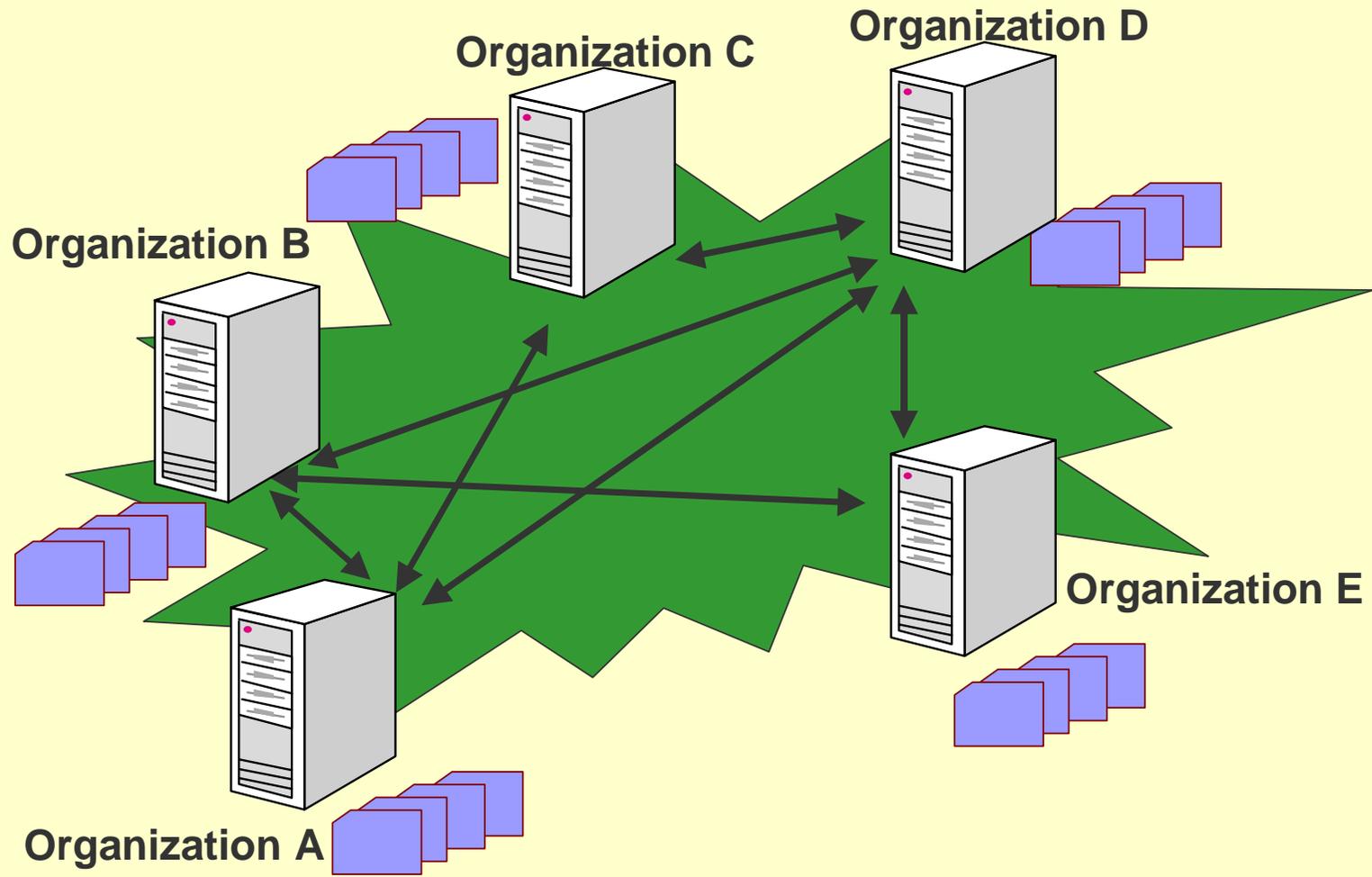


Guidance to R & D



Experience to Assessment

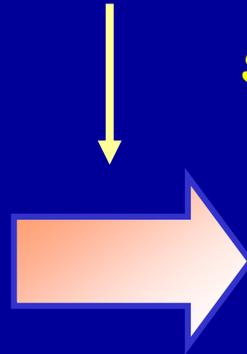
Message Routing



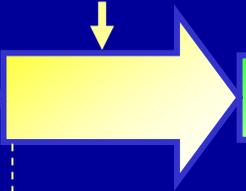
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How to improve further?
Role of the EMEA (3)

- Specific Expert/Rapporteurs looking at the Safety in the Evaluation Period
- Inspection of source data!

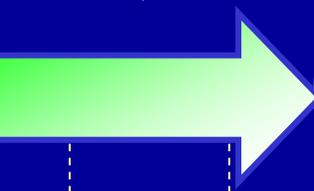
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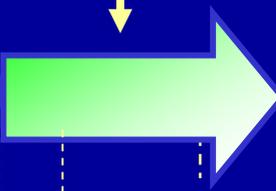
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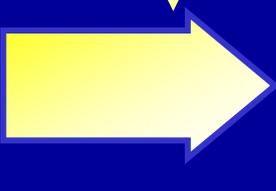
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Transparency

Role of the EMEA (5)

Before launch:

- Contribution of patient groups/Consumers
- Expl. Thalidomide (ENL/ Multiple Myeloma)

« Sharing of the risk in full awareness »

Conclusions

Advanced therapies

More effective/Risky drugs

Faster Access to the patients

but Improved Understanding/Knowledge

New legal Tools

Earlier intervention

Extensive collaboration

Fast communication

so move in managing the risk from a

Reactive → ProActive

Approach

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