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3Rs in drug development
- the regulatory perspective

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The role of the Swedish Medical Products Agency

Ensure the quality, safety and efficacy of medicinal products to safeguard public and animal health

act at national and EU/International level through (e.g.:)

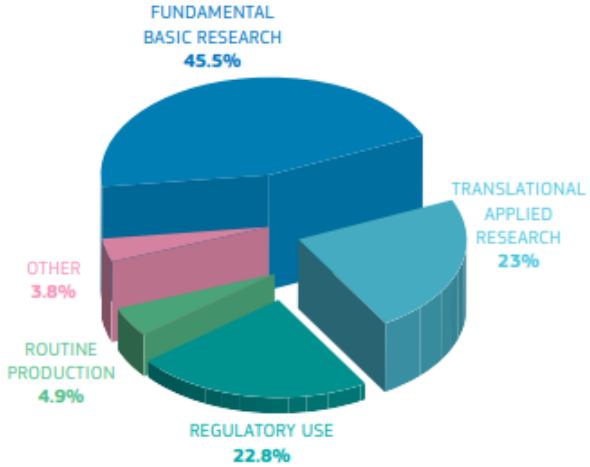
- **Assessment and approval of clinical trials and marketing authorization applications**
- **Scientific advice**

Requirements regulated by EU directives/regulations implemented in Swedish law (including Directive 2010/63/EU)

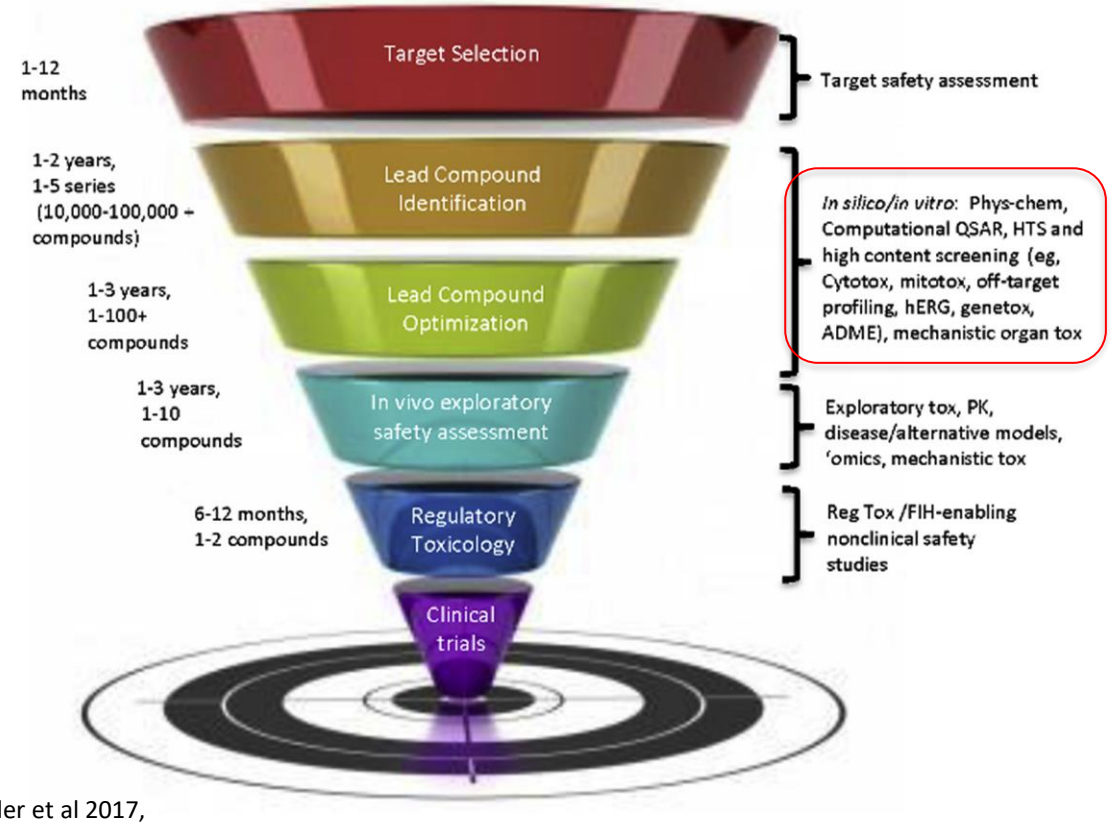
Ensure that changes in requirements do not impair the evaluation of efficacy and safety of a drug

We are aware…

- 10,61 million animals used in research and testing (2019, ALURES statistical EU database)
- Progress is being made in early drug development phases



In vitro/in silico methods in early drug development



Butler et al 2017,
Reg Tox Pharm 87; S1-S15

Regulatory testing requirements

Animal testing still required to support quality and safety of medicines

- defined in EU directive **2001/83/EG annex I** and **European Pharmacopeia**
- **recommendations in EU/international guidelines**

Examples of nonclinical information needed to support administration to humans	Examples of type of studies required (according to ICH M3 (R2))
support for efficacy and dose selection	In vitro/in vivo **pharmacology** (study requirements not specified in guidelines)
uptake, distribution and fate of the active substance	**ADME** in test species (similarity to humans)
What are the potential acute and long-term risks (target organs)? Is observed toxicity reversible and monitorable? What are the margins of exposure to unwanted effects?	**Safety Pharmacology testing** *in vitro and in vivo testing* **Repeat-dose toxicity studies in two species** (rodent + non-rodent)
Information on risk not obtainable from clinical trials: Cancerogenic potential Potenital risks for the off-spring and fertile population?	**Genotoxicity** screening (in vitro + in vivo) and **cancerogenicity** studies in rodents **Evaluation of reproductive toxicity** (e.g. embryofetaltoxicity studies in rodent + non-rodent species)

How do the regulatory agencies support 3Rs?

Replace

Reduce

Refine

- 3Rs considered in revisions of EU/international guidelines, for example
  - *reducing the need for testing in two species*
  - *optimization to address several safety aspects in one study*
  - *ethical aspects taken into account*
  - *opening up for use of (qualified) alternative methods*
- e.g. ICH S5(R2) reproductive toxicity testing
- ICH S1B addendum on carcinogenicity testing
- *Requirements for abnormal toxicity and pyrogenicity removed (quality). Requirements for potency testing are being revised*
- 3Rs considered/promoted in assessments and scientific advies.
- EMA initiatives to support introduction of new approach methodologies

EMA strategies and initiatives for 3Rs

EMA Regulatory Science to 2025' includes strategies to enforce 3Rs:

- **raise awareness on 3Rs** and start discussing/defining context of use, endpoints and reference compounds
- **Providing qualification of 3Rs methods**
- engaging with stakeholders to establish a good **European regulatory network**

-> **early dialogue on 3R with Innovation Task Force** on regulatory acceptance of new approach methodologies

-> **qualification advice**

-> EMA group for 3Rs - CHMP/CVMP Joint 3Rs Working Party
advice to EMA committees
prepare/review concept papers and guidelines
engage with stakeholders
provide training and workshops to assessors

Guideline on the principles of regulatory acceptance of 3Rs testing approaches

EMA/CHMP/CVMP/JEG-3Rs/450091/2012

Regulatory acceptance

- incorporation of a new 3R testing approach into regulatory guideline
- on a case-by-case basis: acceptance by regulatory authorities of new approaches not (yet) incorporated in guidelines but used for regulatory decision making

Criteria for testing approaches

- Defined test methodology (protocol, endpoints)
- Relevance within a particular context of use (including accuracy)
- Context of use (including limitations).
- Reliability/robustness
- Safe harbour

Procedure: submission to EMA for qualification (Guideline on Qualification of Novel Methodologies for Drug Development *(EMA/CHMP/SAWP/72894/2008 Rev. 4)*

Summarizing the regulatory perspective:

- **Drugs are developed in a global context -> important to reach global harmonization for progress in the field**
  - European Regulatory Network open to discuss 3R testing approaches and to collaborate internationally with stakeholders
- **EMA encourage submission of data** multiple pathways possible
- The new **CHMP/CVMP J3RsWP** aims to foster regulatory acceptance of 3Rs
- **Training** (of regulators) is important
- **European regulatory network need to be included in new method development:**
  - New methods of interest must answer regulatory questions
  - Regulators can provide insight in the tools that are needs or identify gaps
- Specific **areas for regulatory input**: qualification criteria / context of use, reference compounds, performance standards
- **Replacing *in vivo* tests with NAMs must not lead to impaired risk evaluation**


Thank you!