Prioritising non-animal methods to improve environmental risk assessment for pharmaceuticals and promote innovation in the EU

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Key Policy Events

2001 — EU pharmaceutical legislation enters into force (Directive 2001/83/EC)

2006 — ERA for new APIs becomes mandatory

→ First EMA ERA guidance for medicinal products

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April 2023 — Proposal for revision of the EU pharmaceutical legislation[1,2]

Draft provisions:
- Transition from animal testing to non-animal methods
- Mandatory ERA of legacy pharmaceuticals

July 2023 — EU Commission roadmap to phase out animal testing in chemical safety assessments[3]

September 2024 — First revision of ERA guidance for medicinal products become effective[4]

? — Revised EU pharmaceutical legislation enters into force

? New revision of the EMA ERA guidance for medicinal products

Path forward: enhancing ERA with non-animal methods and innovation

EMA recently adopted the first revision of its guidance on ERA of medicinal products for human use to become effective in September 2024. Here, we present recommendations on how the latest EMA guidance on ERA can be improved further by prioritising non-animal methods and aligning with broader initiatives, enabling the EU to take the lead in fostering innovation.

Chronic fish toxicity

When a Phase II risk assessment is triggered (PEC is ≥ 0.01 µg/L), the **FELS test** (OECD TG 210) **is mandatory**. Current guidance acknowledges justified use of alternative methods but does not provide examples of suitable adaptations.

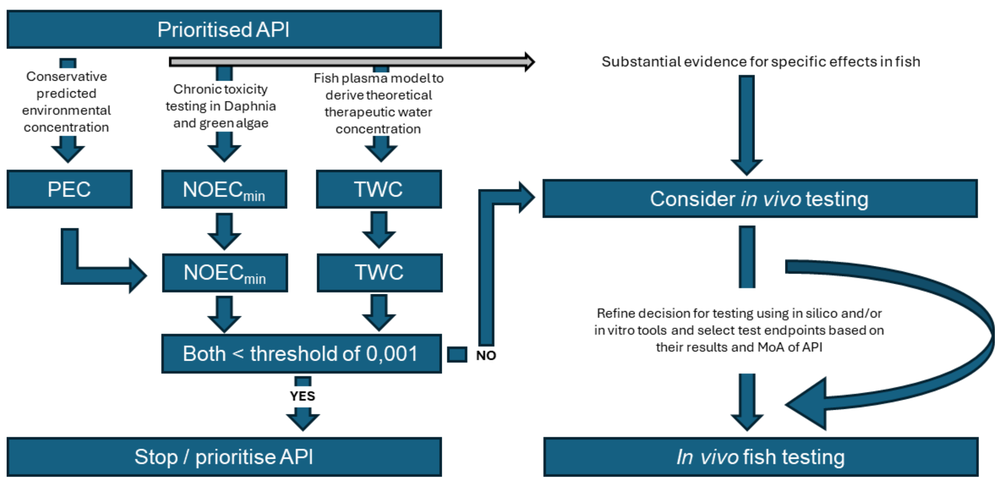

Figure 1. Scheme of the proposed decision tree from Coors et al. 2023[6]

Recommendation

It's likely that the revised EU pharmaceutical legislation will **mandate ERA for legacy pharmaceuticals** (authorised before 2006).

Consider **adapting data requirements** to explicitly allow **IATAs** and **WoE** approaches.

Development of **AOPs** and ***in vitro* systems**, such as **EcoToxChip**, which has the potential to prioritise chemicals for management and further testing of the effects of pharmaceuticals on growth, survival and reproduction of fish (or amphibians and birds).[5]

Implement the decision tree developed in the **PREMIER Project** (see Fig. 1). This can be used to **reduce the requirement for testing on fish** by approximately 35% **without compromising environmental protection**.[6]

Bioaccumulation

When a Phase II risk assessment is triggered and the log Kow for the active substance is ≥3, an **OECD TG 305** study is **required** for the determination of a BCF to evaluate the **potential for secondary poisoning**. This will involve the use of approximately 110 to 240 juvenile fish per substance.

When the BCF_{FISH} is ≥100 L/kg, the potential for secondary poisoning should be further assessed.

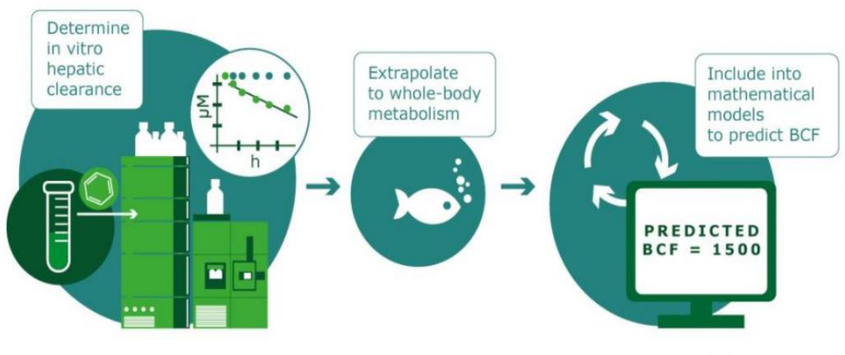

Figure 2. *In vitro* hepatic clearance to predict BCF values © EU,2018[8-10]

Recommendation

Several non-animal methods are now **available to predict bioaccumulation**, e.g. OECD TGs 319A and B on the assessment of ***in vitro* intrinsic clearance using cryopreserved rainbow trout hepatocytes**[8] and **rainbow trout liver S9 subcellular fraction**[9], and the associated guidance document.[10]

Liver intrinsic clearance values can be used either for **physiologically based toxicokinetic models** for fish bioaccumulation or **for extrapolation to an *in vivo* biotransformation rate**. The latter can be used with *in silico* models for the prediction of BCFs (see Fig. 2).

Although TG 319A and 319B use primary cells, they help reduce the use of live fish in OECD TG 305 studies.

SeqAPASS has **the potential to replace testing for secondary poisoning** by using predictive computational methods that could **reduce testing on terrestrial animals** while improving ecological protection.[11]

Duplication of studies

To prevent repetition of animal studies, the applicant should provide a complete literature review and marketing authorisation holders are encouraged to share data with the applicant.

However, there is **currently no provision in the pharmaceutical legislation preventing companies from conducting animal tests in parallel.**

Recommendation

EMA must play an active **coordinating role** in facilitating data sharing, similar to the **SIEFs under REACH**, which would prevent duplication of studies.

Abbreviation	Definition				
AOP	Adverse Outcome Pathway	IATA	Integrated Approaches to Testing and Assessment	PEC	Predicted Environmental Concentration
API	Active Pharmaceutical Ingredient	ITF	Innovation Task Force	SeqAPASS	Sequence Alignment to Predict Across-Species Susceptibility
BCF	Bioconcentration Factor	Kow	n-octanol-water partition coefficient	SIEF	Substance Information Exchange Forum
EMA	European Medicines Agency	MoA	Mode of Action	TG	Test Guideline
ERA	Environmental Risk Assessment	NOEC	No Observed Effect Concentration	TWC	Therapeutic Water Concentration
FELS	Fish, Early-Life Stage	OECD	Organization for Economic Cooperation and Development	WOE	Weight Of Evidence

References