Overview of a Conceptual Framework for Assessing the Hazards of Human Pharmaceuticals in the Environment*

Gerald Ankley (USA), Marsha Black (USA),
Jeanne Garric (France), Thomas Hutchinson (UK),
Taisen Iguchi (Japan)

*From a SETAC Pellston Workshop (July, 2003)

Historical ERAs for Human Active Pharmaceutical Ingredients (API)

- Prediction of potential environmental concentrations (PEC)
- Short-term lethality assays with algae, cladoceran and fish conducted if some threshold (e.g., 1 ppm) exceeded
- Little/no consideration of potential long-term toxicity, secondary impacts (e.g., via bioaccumulation), effects of metabolites, etc.

Little emphasis on possible ecological effects

Relevant Properties of APIs

- Present at low, often constant concentrations in water bodies
- Comprised of chemicals representative of relatively few MOA classes
- Usually designed not to be highly lethal
- Target specific biochemical pathways that can be highly conserved

Suggests potential for chronic (not acute) toxicity

Examples of Acute:Chronic Ratios (ACR) for APIs

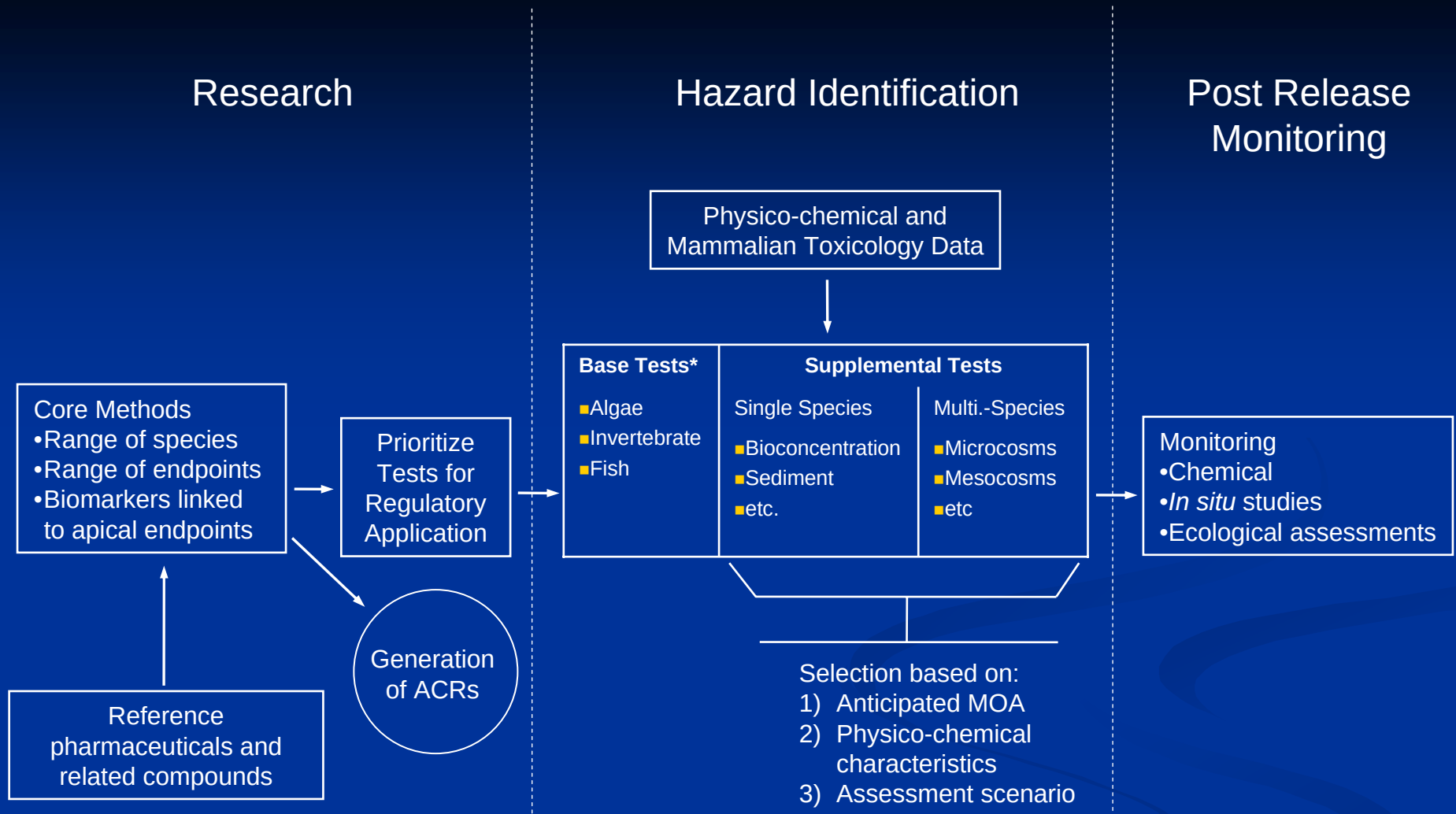
- Ethynylestradiol
  - Copepod: 10.2 (Breitholz et al. 2001)
  - Fish: 150,000 (Hutchinson et al. 2003)
- Propranolol
  - Amphipod: 59.6 (Huggett et al. 2002)
  - Fish: >48,500 (Huggett et al. 2002)

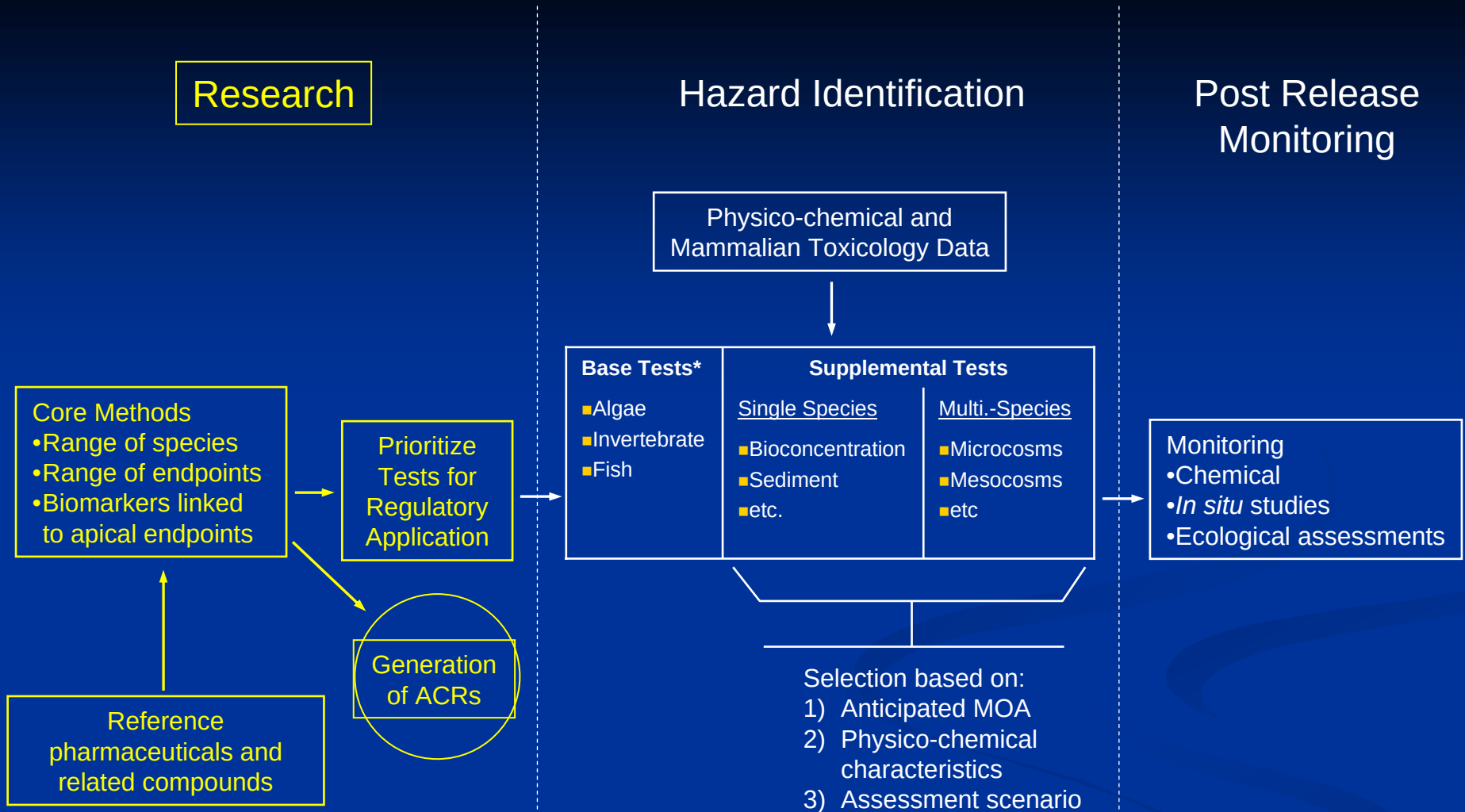
The Challenge

- Dealing with (potentially) 100s to1000s of chemicals, some that could have significant chronic toxicity
- Trying to protect all microbial, plant and animal species, with uncertainty about most sensitive phyla

The Proposed Solution

- Test a set of reference APIs with defined MOA
  - Microbes, plants, and animals representative of phyla of concern
- Define logical suites of tests for untested APIs to estimate risk
- Conduct post hoc environmental monitoring to assess robustness of risk prediction


Research
Hazard Identification
Post Release Monitoring
Physico-chemical and Mammalian Toxicology Data
Core Methods
•Range of species
•Range of endpoints
•Biomarkers linked to apical endpoints
Prioritize Tests for Regulatory Application
Base Tests*
Algae
Invertebrate
Fish
Supplemental Tests
Single Species
Bioconcentration
Sediment
etc.
Multi.-Species
Microcosms
Mesocosms
etc
Monitoring
•Chemical
•In situ studies
•Ecological assessments
Generation of ACRs
Reference pharmaceuticals and related compounds
Selection based on:
1) Anticipated MOA
2) Physico-chemical characteristics
3) Assessment scenario
*Proposed pending research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Test Design(s) and Endpoints

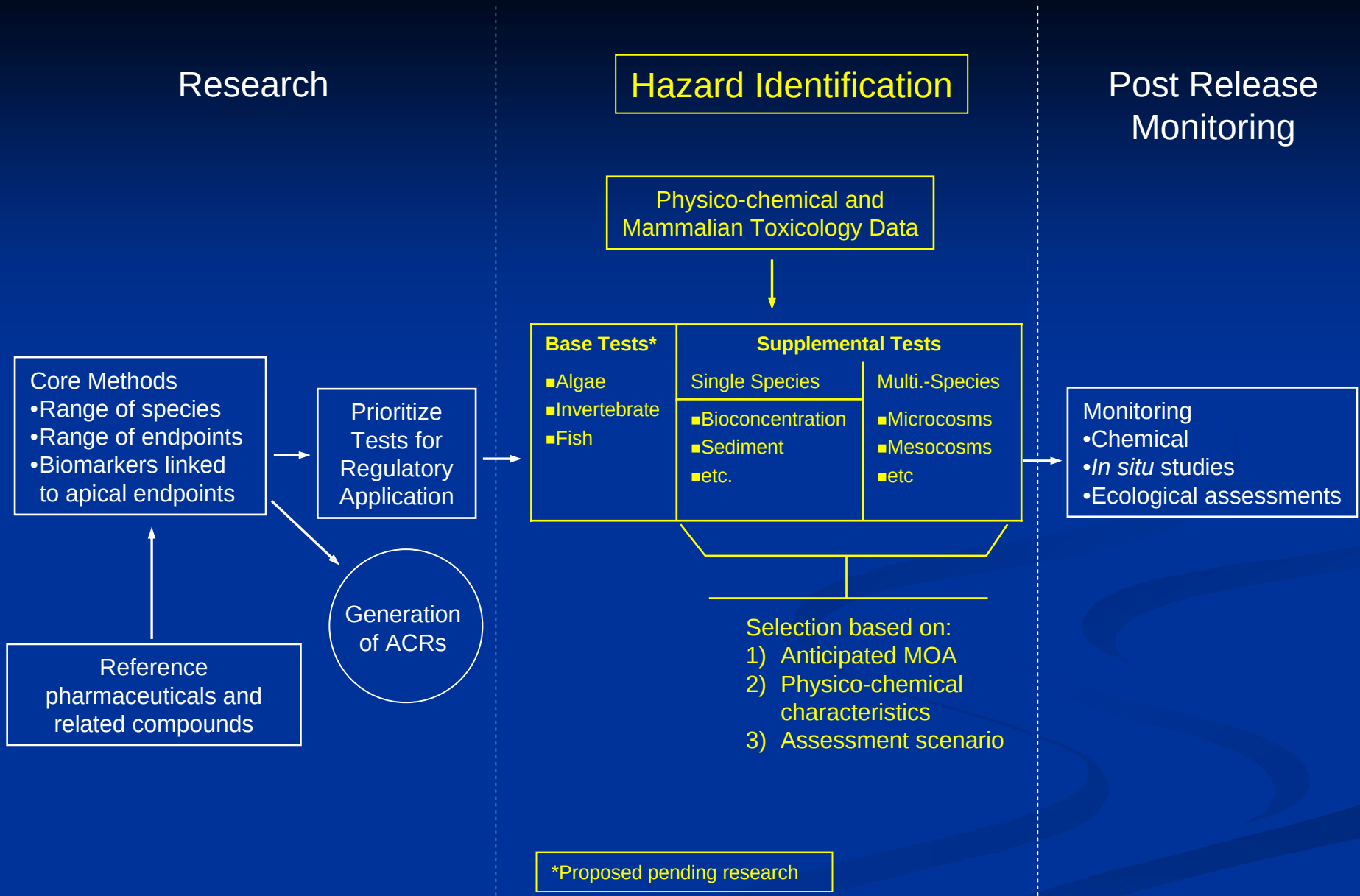
- Use existing methods with easily-tested species
- Conduct short-term and partial- or full-life cycle tests
- Focus on “traditional” whole-animal endpoints germane to risk assessments
- Supplement with diagnostic (“biomarker”) endpoints that reflect MOA

Relevant Phyla for API Testing

- Bacteria
- Algae
- Higher plants
- Cnidarians
- Molluscs
- Annelids
- Crustaceans
- Insects
- Echinoderms
- Fish
- Amphibians

Examples of Reference APIs

- Acetaminophen (analgesic)
- Diazepam (anti-epileptic)
- Ethynylestradiol (estrogen agonist)
- Fluoxetine (SSRI)
- Flutamide (androgen antagonist)
- Lovastatin (lipid metabolism)
- Mitomycin C (cytotoxin -- anti-cancer)
- Propranolol (beta (B2) blocker)
- Tetracycline (antibiotic)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Test Selection

- Conduct “base test suite” to provide common baseline for APIs of potential ecological concern
  - Algal growth (72 h)
  - Cladoceran reproduction (7-21 d)
  - Fish partial-life cycle (7-10 d or 30-60 d)

Test Selection

- Conduct “supplemental” tests selected based on chemical-specific considerations
  - Sensitive species/endpoints identified in MOA-based testing program
  - Unique physico-chemical characteristics
    - Kow, photo-reactivity, etc.
  - Assessment scenario

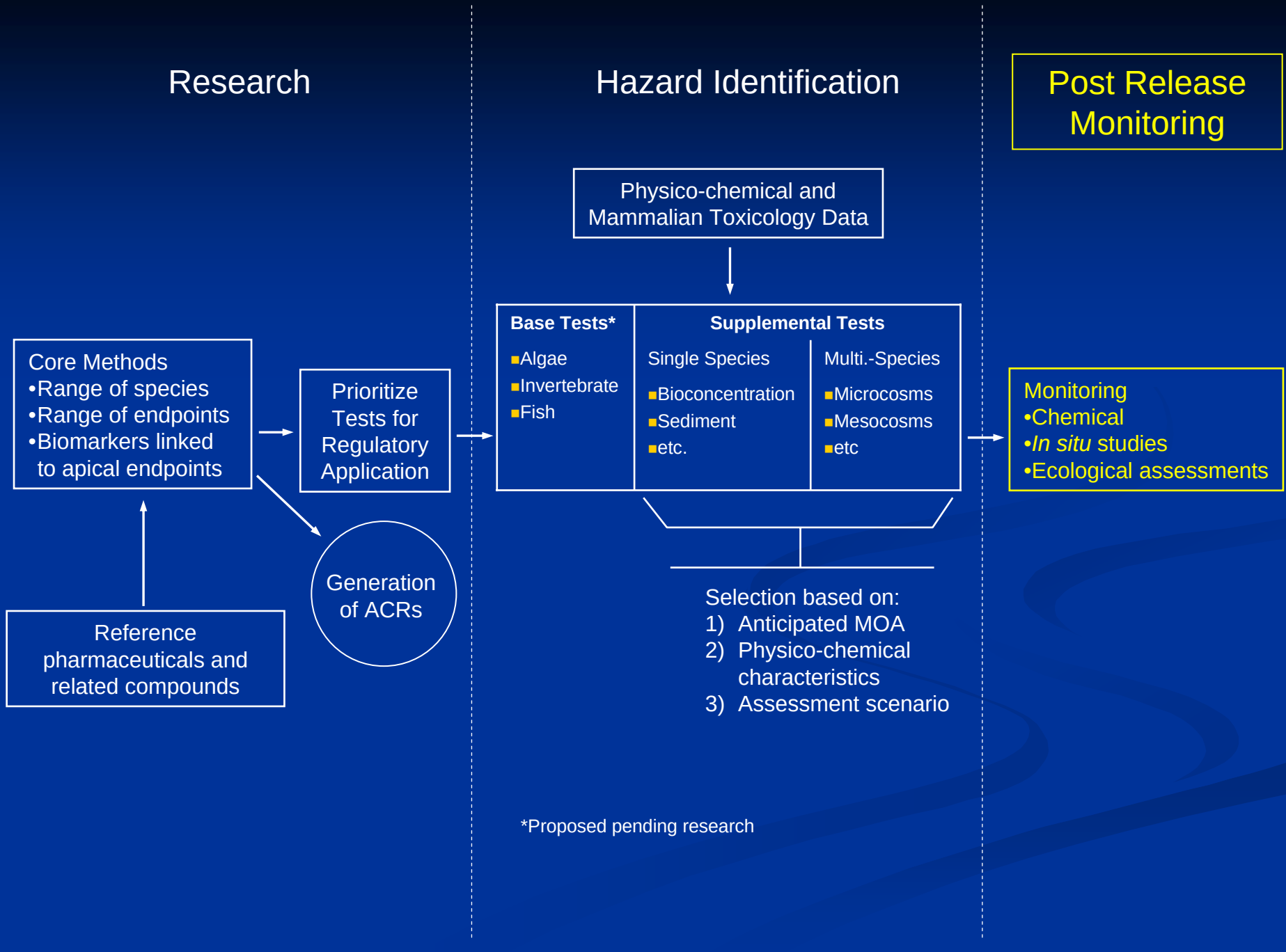
Test Selection

- Use data from drug registration process to help identify supplemental tests.

- Examples of data collected include:
  - Primary and secondary MOA
  - Pharmacokinetics/dynamics
  - Stability
  - Biotic and abiotic metabolites

Examples of Supplemental Tests

- Fish reproduction for estrogen agonists
- Amphibian metamorphosis for thyroid-active APIs
- Blue-green algal tests for antibiotics
- Bioconcentration and/or sediment tests for chemicals with high Kow
- Assays with marine species for chemicals discharged into marine environments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Post Release Monitoring

- Ascertain that exposure predictions (PEC) are accurate
- Document lack of (or degree of) impacts
- May employ techniques/endpoints developed as part of original testing

Basic Field Monitoring Approaches

- Target chemical monitoring
  - Parent and/or metabolites in water and/or biota
- *In situ* biological monitoring
  - Caged animals (fish, mollusks), with both apical and biomarker endpoints
- Ecological monitoring
  - Evaluates condition potentially at cellular to community levels

Summary

- Focused, technically-rigorous approach emphasizes on testing based on MOA
  - Identification of test “tool box” (species, endpoints) using model APIs/diverse phyla
  - Selection of chemical-specific test suites based on physico-chemical properties and assessment scenario
  - Application of routine follow-up monitoring

Acknowledgements

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