Introduction

The crop protection industry develops plant protection products (PPP) for farmers that contribute to producing good quality food in an efficient and sustainable way. While remaining exposed to the chemicals and biologicals in those PPPs to humans and the environment. From the industry commercial viewpoint there is a desire to develop and market the PPPs to farmers to ensure a good return on investment. Issues must be identified early in the development process to reduce the risk of adverse findings becoming apparent later on.

The discovery, development, and approval processes leading to commercially successful active substances (a.s.) and PPPs has always been a long, costly, and challenging process. Newer chemistries or novel modes of action are only discovered by the plant protection industry about every 10–15 years. As scientific knowledge and technological understanding increase, new opportunities are opened for post-market protection, but not far behind comes the development of legal regulation and legislation to ensure the safety of that technology. The regulatory burden needs to balance the safety of a new a.s. continue to increase in all major global markets driven by consumer demand that the food we eat is safe and produced in a way that does not negatively impact the environment.

Approval of a new a.s. comes down to the basic question: Can the risks identified for the a.s. be adequately managed? In managing these risks authorities will consider the hazard presented by the a.s. and the potential for exposure to that a.s. The emphasis that global authorities put on these elements of the risk equation varies and this influences the decision-making process. Further, different global authorities will, to different extents, consider the benefits that a.s. will bring to its farmers.

The costs of research and development continue to increase at a rate of Ca. 4% p.a. The biggest increased in costs (approximately 44%) is expected to come in the development phase (Phillips & Dougall, 2016). It can take 7-15 years to develop and bring to market a PPP containing a new a.s. Crop protection companies generally have a global view and, if possible, will look to gain approval for a new a.s. in all the major global markets. However, the political landscape and regulatory burden of gaining approval can impact the development plans for any new a.s. For example, whilst the European Union (EU) is a valuable market for PPPs the regulatory hurdles and additional development and regulatory costs are high. Furthermore, there is a high degree of uncertainty and unpredictability about timelines and outcomes of the EU regulatory process. This has resulted in a trend in recent years for companies developing new a.s. to seek approval in other markets such as the USA and Japan, more looking closely at approval and commercialization in the EU. The number of new a.s. being approved annually now in Europe is in single figures. This is against a background of a declining number of existing a.s. being re-approved. Since 2013, 12 new a.s. have been submitted, ten have been approved, one not approved and nine are still pending (Purja, 2018). It is clear that innovation is being hindered in Europe not only for chemical a.s. but also for biocides, some of which can clearly be identified as low risk.

Tiered Early Stage Screening

So where does tiered early stage safety screening fit into the R&D process? At Envigo we see this being at that interface between the research and development phases of new a.s.s.

Biological research has taken place and continues to demonstrate efficacy. The potential value of use patterns has probably been identified, commercial and market potential evaluations are ongoing, manufacturing and formulation costs and methods are being evaluated.

The aim of early stage safety screening is to:

- Help cost-effective decision making on major development projects
- Reduce the risk of issues emerging late on
- Improve confidence to proceed to full development
- Potentially reduce the time for the full development program and improve time to market

The important point is any program, and even individual tests are bespoke and designed to answer key development questions, e.g.

- Pre-screening of development analogues for registrability
- Key issue management for chemical class / mode of action
- Early stage assessment of key EU hazard criteria: PBT, POP, toxic, ED, or substitution criteria
- Identify ‘red flags’ or challenges for future registrability

Safety screening of development candidates can be approached in a tiered fashion:

1. Tier 1: Initial assessment – where there is little or no existing data
2. Tier 2: More advanced screening programmes, building on Tier 1 data

Tier 1 Screening Approaches

Use of quantitative structure-activity relationships (QSARs)

- Physical/chemical properties (MP, BP, Log Kow, etc.)
- Environmental fate (bioaccumulation, biodegradation, etc.)
- Ecotoxicity
- Toxicity (dermal, oral, aquatic, invertebrates, etc.)

However, it should be remembered that QSAR is a scientific assessment and requires understanding of the model used and the science being assessed (Fluent et al., 2017). The use of QSARs is a reasonably new driver of the scientific and regulatory landscape and the need to interpret the results properly is crucial. Therefore, the use of QSARs is important but should be approached with caution.

Tier 2 Screening Approaches

Use of full pre-screening programs (PSAPs)

- Toxicity (toxicology, ecotoxicology, environmental fate, etc.)
- Environmental fate (biodegradation, decomposition, etc.)
- Ecotoxicity
- Toxicity (dermal, oral, aquatic, invertebrates, etc.)

It is important to keep in mind the limitations of the QSARs and the need for additional testing.

Case studies

Case study 1: Pre-screening for early hazard identification

Figure 1: Early stage safety screening program

- Acute fish
- Low Kow
- Water solubility
- Water toxicity
- Acute Daphnia
- Acute algae
- Chronic algae
- Chronic fish
- Chronic invertebrates
- Sensitivity tests

- Some responses:
  - Persistent in soil (DT50 >180 days)
  - Chronic toxicity to Daphnia, <0.01 mg/L
  - Acute invertebrates and algae toxicity
  - EU = Candidate for substitution

- Success will depend on:
  - Efficacy
  - Place in resistance strategies
- Registration gained in USA and Japan
- Evaluation eventually completed in EU with acceptable risk and safe uses identified

Case study 2: Candidate fungicide of a known chemical class

- Customer already had some data
- There were concerns about fungicidal activity

A series of toxicity studies were run:

- Rat (MPF) 28-day toxicity (showed maximum tolerated dose)
- Maternal toxicity – helpful to dose range for third study
- Reproduction toxicity (generation prem.)
- Studies did show indications of endocrine disrupting activity

Outcome:

- Proposals for further in vivo and in vitro testing were subsequently made.

Case study 3:

- This case involved screening an analogue of an existing herbicide with a known mode of action
- Existing a known to different extents to be persistent in soil and affect reproductive performance
- Water solubility and log Kow
- Moderate to toxic to fish and Daphnia
- Highly toxic to green algae and Lemma but less toxic than some other analogs
- Regulatory acceptable concentration (RAC) estimated
- Preliminary aquatic risk assessments indicated higher tier species testing was needed to refine the RAC
- Further aquatic fate testing to refine endpoints
- Some adverse findings in reproduction toxicity study indicated possible toxicological hazard classification

Outcome:

- Extended and introduced a prioritized list of further studies in a second more extensive screening program.

Conclusions

Finding an effective safe new crop protection agent is extremely challenging.

But with population growth and ever decreasing land area on which to grow global demand and market opportunity for chemical and biological based PPPs will continue.

Core data requirements for registration will be similar and costs of development similar for example in EU and USA. However, in recent years a number of factors:

- Predictability of the evaluation timelines
- Registration costs and fees
- Use of a risk vs. hazard based approaches
- Focus on metabolites and groundwater limits in EU, application of new guidance etc.

The above factors have all contributed to more applicants seeking approval in the USA first before considering the EU. If a candidate molecule is discovered and selected as a potential new a.s. the development and regulatory approval up to commercialisation is costly and timely process.

In a world where the regulatory hurdles have and will continue to become ever more stringent the development process is not without risk of adverse findings that will impact the registrability of the a.s.

Whatever the final shape of an early development screening program the main aim is to give decision makers more confidence and information for their decision-making processes.

Potentially such safety screening programs can reduce the time for the full development program and improve time to market which ultimately means a quicker return on investment.

References: