Intelligent design for new fungicide

Iblon launch event

While discovering new active ingredients still requires extensive screening, digital tools are set to speed up the process, removing the element of luck. The launch of Bayer's new fungicide, Iblon, in London marked the first of these intelligently designed molecules.

By Lucy de la Pasture

Just like London buses, registrations of new fungicide molecules have been coming one behind the other over the past couple of years, after what has been a fairly long hiatus. So it was fitting that the UK's capital hosted the recent launch of isoflucypram, branded as Iblon, which also marked the first European regulatory approval.

Ironically, farmers in the European Union will have to wait at least another three years before they have access to the new wheat fungicide. The UK's Chemicals Regulation Division (CRD) acted as the Rapporteur Member State responsible for evaluating the active substance and producing a draft assessment report for its fellow member states, at that time, to consider. After Brexit, France took over that function and the decision was made to ignore the work done by CRD and start the evaluation process again, which is why they are so far behind the UK which accepted its own report.

The active substance belongs to the succinate dehydrogenase inhibitor (SDHI) group of chemistry and offers a step-change from Bayer's pioneering cereal SDHI, Aviator Xpro (bixafen+ prothioconazole) — first launched in the UK in 2011 and subsequently combined with SDHI active, fluopyram, as Ascra Xpro in 2016.

Unique structure

According to Michael Maue, Bayer's global project lead, the "unrivalled biological efficacy" of Iblon is due to its unique molecular structure. It has an N-cyclopropyl ring at its centre, and it's this that makes a difference at its target binding site in the pathogen. In the field this translates to efficacy on a range of diseases, notably septoria and rusts, and distinguishes the active as a new subclass of SDHI chemistry.

The structure of the isoflucypram molecule was a deliberate design process and the addition of the N-cyclopropyl ring transformed its efficacy, he added.

As well as Iblon's intrinsic activity, Michael highlighted the new fungicide's formulation as the second factor giving it good field performance. "A fungicide formulation needs to give the active ingredient the ability to penetrate the waxy leaf layer into the upper epidermis, so it's protected against environmental stresses — such as rain — and it's available for

> *"Stewardship is an individual responsibility for the collective good."*

Michael Maue described Iblon as having "unrivalled biological efficacy".

systemic transport in the leaf to better protect the plant. It should also have good spreadability on the leaf surface. These are both optimised in Iblon's formulation."

The regulatory requirements in the European Union — mirrored in the UK's own regulations since Brexit — have tightened under its hazard-based criteria, adopted in 2009. Active ingredients have been lost as their registrations come up for review and the flow of new molecules through the pipeline has slowed. Iblon's own journey began 15 years ago, and Michael described its development path as "complicated, with a few potential show-stoppers" which the Bayer team navigated by finding scientific answers to the regulatory questions posed.

In addition to Iblon's performance on many of the diseases that trouble wheat crops in the UK, the emphasis at the launch was as much about resistance management to preserve its efficacy for years to come.

SRUC's Professor Fiona Burnett welcomed the new chemistry and rated its performance as very similar to the other new fungicide actives on septoria. "The UK is very reliant on multiple applications of a limited palette of chemistry. Iblon is an exciting new tool, but let's think about how we steward it going forward," she said.

"Since the strobilurins [which totally succumbed to resistance in the 2003 season], we've developed much better ways of managing chemistry from a resistance perspective. Trials show that what is done on an individual farm really matters when it comes to pathogen shifts in sensitivity," she said.

"Dose is the ultimate choice to be made in the field — using appropriate balanced ▸

Iblon – the technical details

Initially, Iblon is only available in co-packs while approval of a co-formulation is awaited by CRD (predicted for 2025-26), said Rosalind O'Hare, Bayer campaign manager for combinable fungicides.

The Ion Iblon co-pack will contain Vimoy (isoflucypram) and Proline (prothioconazole), and Vimoy plus Jessico One (Inatreq) will also be available as a co-pack following a global agreement with Corteva Agriscience for Bayer registration of its active ingredient fenpicoxamid.

Vimoy can be used at rates of up to 1.5 l/ha (75g active substance/ha), with a minimum recommended rate of 1.0 l/ha (50g as/ha), and Proline at 0.5 l/ha, supplying 125g/ha of prothioconazole. Jessico One should be applied at 1.2 l/ha, supplying 60g/ha of Inatreq.

One of the main advantages of Iblon is its broad spectrum of disease control in wheat, with activity on septoria, rusts, and eyespot. Comparing its efficacy against septoria to new-generation triazole Revysol (mefentrifluconazole), and Quinone-inside Inhibitor Inatreq, Rosalind slots Iblon in between the two, with Inatreq acknowledged as having the edge.

"It also has good activity against both brown and yellow rust, performing at a similar level to the number one yellow rust fungicide, the SDHI Solatenol (benzovindiflupyr). Brown rust is Iblon's biggest strength, and it's at the top level of current best chemistry against the disease."

Eyespot activity is another string to Iblon's bow and it offers added control to the previous best option. "Prothioconazole is the benchmark for eyespot, with around 40% control of W- and R-types. Ascra offers a little extra activity, and Iblon adds a few percentage points more again. Mildew and fusarium are mostly covered by prothioconazole," she added.

The alternative Vimoy co-pack with Jessico One looks to be particularly suited to the T2 timing. "The combination of these two actives, with well-balanced efficacy on septoria, will provide the best possible anti-resistance strategy at the recommended dose rates. It's important to note that although both actives have strong activity against septoria, dose rates shouldn't be trimmed as this would be against the Fungicide Resistance Action Committee guidelines."

Rosalind has a similar warning for Vimoy in Ion Iblon. "One of the regulatory hurdles Iblon had to navigate was the environmental fate of its metabolites, and this resulted in an approval restriction that only 75g/ha of Iblon can be applied to a field every two years. It's really important not to reduce or split the Iblon dose to try and get around this."

Bayer is currently collecting data to submit to CRD to show one of the new fungicide's metabolites doesn't accumulate in the soil and hopes to get this restriction lifted in due course.

As well as the disease control it offers, Iblon has a second ring in its molecular structure — pyrazole-4-carboxamide — and this brings a physiological benefit by way of a greening effect. In Bayer trials, this has extended the green area duration for eight days compared with untreated plants, and three days longer than when the crop has been treated with Ascra.

"Pyrazole carboxamide encourages the upregulation of nitrogen reductase, so more nitrogen uptake equates to more chlorophyll, increased levels of photosynthesis and therefore more energy for the plant. It also contributes to an increase in antioxidant enzymes, making plants more resilient to stress," explained Rosalind.

"Plants are reliant on hormones to control their physiology and pyrazole carboxamide also supports hormonal balance. A reduction in ethylene production delays senescence, enabling plants extra time to capture sunlight, which translates to 0.15t/ha yield per extra day of greening."

Rosalind O'Hare slots Iblon in between Revystar and Inatreq in terms of septoria efficacy, with Inatreq acknowledged as having the edge. Iblon will be available in a co-pack with Inatreq in 2024.

Product details for 2024

Co-Pack Name	Contents	Active ingredient	Recommended rate	Restrictions
Ion Iblon	Vimoy	Isoflucypram (50g/l)	1.0 l/ha (50g)	• Max 75 g/ha in two years
	Proline	Prothioconazole (250g/l)	0.5 l/ha (125g)	• 5m aquatic buffer zone
Unnamed	Vimoy	Isoflucypram (50 g/l) (50 g/l)	1.0 l/ha (50g)	• Max 75 g/ha in two years
	Jessico One	Fenpicoxamid	1.2l/ha (60g)	• 12m aquatic buffer zone

Source: Bayer

Fiona Burnett warned that the actions of individuals would ultimately decide the longevity of the new fungicide products available to them.

▸ mixtures, alternating and mixing fungicide modes of action, and reducing but not splitting fungicide doses. Diversifying, with a new SDHI to add to programmes, brings benefits," she said.

Fiona warned that its time for individuals to take responsibility as it's their actions that will ultimately decide the longevity of the products available to them. "Stewardship is an individual responsibility for the collective good," she emphasised.

New Zealand farmers were the first to benefit from Bayer's new fungicide chemistry, with its regulatory authorities granting approval for use in the 2019-2020 season.

Bringing his experience of Iblon to the launch, NZ farmer Eric Watson outlined his farming system on the Canterbury Plains and amazing video footage brought this to life with the Southern Alps forming a stunning backdrop.

New Zealand farmer Eric Watson has been impressed with what he's seen of Iblon on his own farm over the past few seasons.

Digital tools to enhance innovation

According to Michael Maue, the development of Iblon reflects "a move away from advanced trial and error [in the discovery process], to really designing a molecule with desired features".

This intelligent design is made possible by the advancement of digital technologies such as deep learning, machine learning, artificial intelligence, big data generation and analysis. "All of these tools help us to actually find specific molecules more quickly than before," said Michael.

A technology that is already being used in Bayer R&D is deep learning. "This helps our chemists to synthesise molecules in a faster and better way. And for this, we treat it as a system or a training system with millions of reactions from internal as well as external databases. And the system is then able to suggest a synthesis route, taking parameters like sustainability or cost of goods into account."

Another technology being developed is the digital twin — a technology that has been used by Formula One (F1) race teams to build a digital replica of a race car by adding hundreds of sensors to F1 cars and capturing all the information during races. With that, they are able to generate a digital twin of the race car where they can predict and simulate how it would behave under certain conditions, as well as set up changes the teams haven't tried before in real life."

Bayer is drawing on innovation in Formula One and aims to create digital twins of farmers' fields.

Bayer's idea is to have a digital twin for every field a farmer has and simulate different parameters, including weather conditions, to achieve optimum yield. "This approach will take many years because the parameters and variables are just mind blowing," said Michael. "It's much more complicated than for a F1 racing car, but I think it's too compelling not to give it a shot."

Eric's appetite to regain his Guiness World Record for wheat yield, snatched from him last year by UK grower Tim Lamyman, was evident. With two world records already under his belt — recording 17.398 t/ha in 2020, beating his previous record of 16.791 t/ha in 2017 — Eric believes Iblon will be instrumental in his next attempt to regain the record he covets. To beat his UK rival, he said, it just needs the right amount of sun, at the right time… ■

Predictive disease management

A crystal ball would come in handy when making fungicide recommendations — the weather, latent disease, and evolving pathogen populations can make a fool of the best agronomist. But help may soon be at hand to provide future insights into whether and when to apply fungicides.

Talking at the launch event, Fabrice Houdebert, Bayer cluster lead for NW Europe, said the company is working hard to invent a prescriptive disease management tool for wheat, called PreDiMa. The new tool will be customised for the UK, France, and Germany and early versions of the model have already been tested in the UK.

"PreDiMa is a methodology to predict what to apply, if you need to apply, and on which field you need to apply with high precision. This is the power of digital agriculture and data ingestion that we are putting in motion to bring forward this new service.

Fabrice Houdebert described the company's commitment to integrate crop protection, seeds, crop nutrition, and digital farming to become a holistic system that's more productive and more sustainable.

"It's an example of our commitment and the stimuli to bring together crop protection, seeds, crop nutrition, and digital farming to become a holistic system that's more productive, more sustainable, more regenerative."