



The Analysis of Product Global Layout, and the Design of the Registration Strategy



➤ The Market Layout and Crop Application:

1. **Global Sales Revenue:** Normally, for generic producer, it is better to trace the MACRO newly off-patent molecules, instead of the low revenue molecule. (Exception: Elite Technology)
2. **Regional Sales Revenue:** The main sales region will determine the key countries of generic registrations, and future distribution.
3. **Crop line and application:** Focus on current crops, and relevant formulations. May consider the synergy with existing products.
4. **Annual Increase:** Consider the factors of Increase: The promotion of MNCs, Competition with similar molecules. Normally, we may utilize the trends.
5. **Price comparison:** Estimate the margin, and the competency against similar products. It will be helpful in designing primary pricing policy and promotion plan.

➤ TC Content, Formulation, Relevant Patents:

1. **Confirmation of TC Content:** Feasibility in manufacturing, and equivalence recognition in registrations.
2. **Formulation Type:** Focus on the diversity of formulations, and the applications of the mixture formulations. It will be helpful in designing the formulation, and achieve the synergy.
3. **Patent Situation:** Compound patent (including PCT), Formulation Patent, Synthesis pathway. Avoiding patent conflict, while utilize the patent information for Product development.



➤ **Registration Feasibility Analysis and Data Generation Plan:**

1. **Determination of TC Content:** Need to consider the registered TC content in EU, USA, Australia, and Brazil. Meanwhile, MNCs may change the registered TC content (Indoxacarb)
2. **Confirmation of equivalent impurities:** Major references:
 1. Toxicological concerned impurities in publications (EU, APVMA, EPA);
 2. Metabolites information in EPA records;
 3. Intermediates and side reactions in patent synthesis pathways
 4. AI metabolism pathways (to judge the potential metabolism of impurities, and its potential toxicological effects)
3. **Choice of formulations:** Focus on MNC formulations and mixture AIs, but need to consider the supply of the mixture AIs, and their registration status.
4. **GLP data generation:**
 1. 5 Batch: Determination of the impurities is the KEY concern, and need to consider the global acceptance of the report
 2. TC phy-chem, and tox: Comparison to reference data (pre-studies may needed)
 3. Formulation data: Consider the universal acceptance.
5. **Registration Plan:** Normally, the feasibility of the key markets has high priority, then the synergy with other markets. Focus on data barrier, and data compensation. And need to categorize the target countries by registration requirements.

➤ **Overall Consideration based on Market, Technology, and Registrations**

➤ Overall Market Situation:

1. **History:** Target crop and Spectrum, Competitive products, Key markets
2. **Development Trends:** Primary understanding of countries, target crops, competition, and formulation diversity.
3. **Domestic/Oversea synergy:** Consider the product launch in both China/Abroad.
4. **Patent Situation:** Patent status: Compound, Crystal type, Synthesis, Formulations

➤ Overview of Pyraclostrobin Market:

1. **Launch history:** Discover by BASF in 1993, launch in 2001 (Azoxystrobin in 1996). Now in the quick development period. (Increase rate higher than Azoxystrobin)
2. **Development Trend:** Wide layout on crops, diversity in formulations, concentrate on several key crops (Cereal, soybean and F&V);
3. **Synergy:** Off-patent. Chinese manufacturers can apply for TC/FP regs. May apply for domestic/oversea registrations simultaneously

4. Patent Status:

PCT/EU Patent: Compound Patent: [2-[(dihydro)pyrazolyl-3'-oxymethyl anilides, their preparation and use, EP0804421, Expire on June 21st, 2015; (Chinese patent CN1154692/CN1308065 expires in the same time)

Synthesis pathway patent: [Preparation of N-methoxy-N-[pyrazoloxymethyl] phenyl] carbamates and analogs as agrochemical fungicides and pesticides, DE4423612, Expire on July 6th, 2014

Formulation patents: Single formulation expires in end 2015, and mixture formulations patents will be expire till 2018, and all valid for present.

3. Case Study: Pyraclostrobin—Global Layout

Region	Cereal (\$m)	Corn (\$m)	Rice (\$m)	Soybean (\$m)	Rape (\$m)	Cotton (\$m)	Sugar beet (\$m)	Sugar cane (\$m)	Potato (\$m)	Vine (\$m)	Pome fruit (\$m)	F&V (\$m)	Non crop (\$m)	Total (\$m)
Asia	0.53		8.05						0.08	4.3	5.37	16.4	3.34	38.06
Europe	68.4	1.54		0.19			0.62		1.14	7.36	6.17	7.18	1.25	93.85
Latin A.	25.8	28.79	1.27	228.12		6.27		2.36	4.33	2.24	1.59	38.3	23.46	362.52
Afr. Middle East		2.41				0.01			0.14	2.47	0.22	0.66	0.76	6.67
North A.	32.88	34.8		51.99	16.34		3.96		4.73	4.99	1.43	17.9	39.28	208.3
Unallocated	8.15	4.31	0.6	17.9	1.04					1.36	0.94	5.14	51.16	90.6
Total:	135.76	71.84	9.92	298.2	17.38	6.28	4.58	2.36	10.43	22.72	15.72	85.58	119.24	800

From above sheet, the main regions of Pyraclostrobin is:

Latin America: Mainly Brazil, Argentine, Total: 362.52 M USD

North America: Total: 208.3 M USD

Europe: Total: 93.85 M USD

Asia: Mainly China, Vietnam, Korea, 38.06 M USD

From the crop layout, the application of Pyraclostrobin focus on:

Soybean: 298.2 M USD

Cereal: 135.76 M USD

Corn: 71.84 USD

F&V: 85.58 M USD (Mainly Asia and Latin America)

Vine: 22.72 M USD

Rapseed: 17.38 M USD (Mainly in North America)

➤ BASF formulations in Europe

1. boscalid 252 g/kg + pyraclostrobin 128 g/kg WDG
2. pyraclostrobin 5%+ metiram 55% WG
3. Pyraclostrobin 6.7%+Dimethomorph 12% WDG
4. Pyraclostrobin + Epoxiconazole 26+16% SC

Country	Crop	Treated Area (1000 ha.)	% Crop Area	Revenue (Mio. USD)	% in Products	Rank	Ave. Price (TC USD/kg)
France	Cereal	1077	3.16%	21.26	4.77%	8	314.73
UK	Cereal	1131	3.91%	12.70	5.96%	6	141.20
Denmark	Cereal	790.39	14.1%	7.15	14.8%	4	262.8
Romania	Corn	29.27	3.24%	0.98	68.4%	1	243.8
Spain	Pome fruit	88.99	8.12%	3.30	13.98%	2	791.37

➤ Major Trends in the Market:

1. The market shares of Pyraclostrobin differ in main cereal markets. And due to the differences in formulation type, the TC prices also have huge differences.
2. The main reason of price difference lies in the differences in combination AIs. (like in UK, with Boscalid and in France with epoxiconazole), and the monopoly in market (like UK and Denmark)
3. The pricing of Pyraclostrobin in niche markets are significantly higher than field crops. (like in Spain, the same formulation used on Pome fruit is much higher than in other market.)

➤ BASF formulation in Latin America

In Brazil, Argentine and Uruguay, the same FP: Opera (Epoconazole / Pyraclostrobin 16%+26%)

Country	Crop	Treated Area (1000 ha.)	% Crop Area	Revenue (Mio. USD)	% in Products	Rank	Ave. Price (TC USD/kg)
Brazil	Cereal	1299.57	9.22%	13.01	13.91%	3	<u>250.3</u>
Brazil	Corn	2455.76	5.28%	27.19	17.4%	2	<u>140.18</u>
Brazil	Soybean	19385.52	9.9%	199	15.93%	2	<u>156.96</u>
Argentine	Cereal	362.32	2.16%	6.16	10.79%	4	<u>130.79</u>
Argentine	Soybean	1627.2	3.56%	13.50	9.19%	5	<u>130.89</u>
Uruguay	Cereal	426.11	19.45%	4.08	34.31%	1	<u>120.89</u>
France	Cereal	1077	3.16%	21.26	4.77%	8	<u>314.73</u>
UK	Cereal	1131	3.91%	12.70	5.96%	6	<u>141.20</u>
Denmark	Cereal	790.39	14.1%	7.15	14.8%	4	<u>262.8</u>
Romania	Corn	29.27	3.24%	0.98	68.4%	1	<u>243.8</u>

➤ Major Trends in the Market:

1. In Brazil, Argentine and Uruguay, the prices have no significant differences, and are much lower than Europe/
2. The cereal application price in Brazil is much higher. The reason lies in the joint promotion of seed treatment between Monsanto and BASF. (So we can estimate the potential margin)
3. In Argentine, due to the competition of Azoxystrobin (ranked No.1 in fungicides), BASF can not raise the price. So, the price in Argentine can be regarded as reference price to Chinese generic manufacturers.



4. Case Study: Pyraclostrobin—Market Analysis

North America

➤ BASF formulations in USA

Active Ingredients	Content %	Formulation Type
Pyraclostrobin+boscalid+lambda-Cyhalothrin	3.06+5.622+0.5	Seed Treatment
Pyraclostrobin+boscalid	1.75+3.5	Seed Treatment
Pyraclostrobin	20	WDG
Pyraclostrobin	98	TC
Pyraclostrobin	23.6	EC
Pyraclostrobin	20	EC
Pyraclostrobin+boscalid	12.8+25.2	WDG
Pyraclostrobin+Dimethomorph	6.7+12	WDG
Pyraclostrobin+Metconazole	12+7.4	EC
Pyraclostrobin+boscalid	12.8+25.2	Soluble concentrate/solid
Pyraclostrobin+boscalid	16.8+11.2	WDG
Pyraclostrobin	90.2	TC
Pyraclostrobin+Metconazole	12+7.4	EC
Pyraclostrobin	18.4	EC
Pyraclostrobin+Thiophanate-methyl	4.22+37.92	EC
Pyraclostrobin+boscalid	9+18	EC
Pyraclostrobin	23.3	EC
Pyraclostrobin+Metconazole	13.64+5.14	EC
Pyraclostrobin+Metalaxyl+Triticonazole	7.57+4.54+7.57	Suspension
Pyraclostrobin+Triticonazole	0.38+0.43	Granule
Pyraclostrobin+Fluxapyroxad	21.26+21.26	Suspension
Pyraclostrobin+Fluxapyroxad	28.58+14.33	Suspension
Pyraclostrobin	23.06	EC
Pyraclostrobin+Metiram	5+55	WDG
Pyraclostrobin+Metalaxyl+Triticonazole	1.59+0.93+1.59	Suspension http://en.ncbdata.com
Pyraclostrobin+Fluxapyroxad	28.58+14.33	Suspension



4. Case Study: Pyraclostrobin—Market Analysis

North America

Country	Crop	Treated Area (1000 ha.)	% Crop Area	Revenue (Mio. USD)	% in Products	Rank	Ave. Price (TC USD/kg)
USA	Cereal	1520.02	9.54%	19.63	24.4%	2	148.4
USA	Corn	2055	2.72%	34.80	10.08%	4	147.25
USA	Soybean	2147.86	21.23%	51.99	34.76%	1	147.20
USA	Vine	236.56	8.54%	4.99	7.1%	6	163.33
Canada	Cereal	674.47	3.01%	13.25	6.3%	5	280.36
Brazil	Cereal	1299.57	9.22%	13.01	13.91%	3	250.3
Brazil	Corn	2455.76	5.28%	27.19	17.4%	2	140.18
Brazil	Soybean	19385.52	9.9%	199	15.93%	2	156.96

➤ Main Trends in the Market:

- 1. BASF promote Pyraclostrobin in a “non-differentiate” mode on major crops. (Headline is the main formulation in all sections, with no difference in pricing.)**
- 2. Due to the competition of Azoxystrobin, PRISTINE (Boscalid / Pyraclostrobin) price in TC has no difference with Headline (single formulation on cereal and soybean)**
- 3. Due to the high end product, Twinline (Pyraclostrobin+Metconazole 130 g/l+80 g/l SC) in Canada, the price is much higher than that of USA**

5. Case Study: Pyraclostrobin—Competition Analysis

➤ Competitive products situation:

Azoxystrobin is the only competitive product to Pyraclostrobin globally. As Syngenta launches Azoxystrobin 5 years ahead of BASF's pyraclostrobin, and Azoxystrobin has good performance and layout in all market, the competition to pyraclostrobin is strong. (In target crop, formulation development, and pricing)

➤ Regional Competition:

1. In Argentina, Azoxystrobin holds the 1st rank in fungicides. So BASF has to take the low price promotion mode, so as to grasp the market and extend the coverage. Now the growth rate of Pyraclostrobin is higher than Azoxystrobin
2. In EU, pyraclostrobin gains competency by diversified formulations, and targeting on specified diseases. The profit is gained by formulation differentiation in niche markets.
3. In seed treatment, BASF tends to achieve cooperation with Monsanto for more market share (50%+ in 2012/2013). And due to that, Brazilian price is higher than Argentine price.

➤ Conclusion:

Pyraclostrobin has competency against azoxystrobin in application fields and mixture diversity. However, as entering later in the market, Pyraclostrobin has pressure in pricing from Azoxystrobin (esp. generic Azoxy introduction to market).

Need to focus on the dynamic of generic introduction of azoxystrobin and its formulations, so as to balance the cost and price in end market. (Consider Picoxystrobin case...)

➤ Target countries of TC registrations:

1. Consider the priority of TC registration entry countries with the following factors:

A. Market size

B. Feasibility/Difficulty in TC registration

2. Possible TC source registrations (not independent): Korea, Taiwan, Thailand

3. TC/FP submission in the same time? Or in consequence?

➤ Technical consideration of TC registrations:

1. Content: EU: Min 97.5%, US EPA: Min 98%, Chinese generic manufacturers need to register TC with min. content 98%. (However, some of TC registrations under ICAMA shows 95% or 96%)

2. Equivalence in Impurities/Toxicology:

A. Make sure that the relevant impurities under FAO/EU/EPA are tested, e.g: DMS;

B. Try to acquire the BASF impurity information: like metabolites, side reaction by-products, EU/EFSA evaluation of the pathway impurities.

C. Focus on pro-screening in GLP labs. (Impurity justification and categorization*). In the synthesis of imp std samples, the “very difficult” std tend to be “non-equivalent”

D. If the impurity can not be justified for equivalence, and can't be purified, QSAR need to be considered for possible toxicological effects. (But pre-evaluation before entering formal QSAR is necessary! It is better, the impurity can be explained into: metabolites, degradants, etc.)

E. Toxicological equivalence (6-packs): Should comply with BASF's TC (Note China registered products, around 35% show “moderate toxic”)

➤ Timeframe of TC registration—Entry and Data Protection:

1. The EU re-evaluation of Pyraclostrobin has been initiated in 2014, and BASF's patent went of in 2015. As BASF will submit the dossier to EU commission as "sole submitter", generic manufacturers can only submit after 5 year's data protection (est. in 2019)
2. The data protection in Brazil is 5 years and has expired (BASF submitted in 2001). Generic manufacturers can directly register equivalent TC with no extra data compensation.
3. BASF is exclusive holder of all pyraclostrobin registrations in USA, and the data protection is 15 years (the earliest submitted data is from 2005). Generic manufacturers need to pay data compensation to BASF, and the amount is estimated to exceed 1 Mio. USD.

➤ Formulation Registration Considerations:

1. Choice in formulation types:

- Choose the mature formulations launched by MNC (EPA record can be the reference.);
- Consider the TC availability of the combination active(s), both in supply and GLP data;

2. Crop Selection:

- Select the crop, which pyraclostrobin has good performance and recognition
- Consider current portfolio of the company, try to seek the synergy with existing products (try to establish the "solution combination" with existing and new products)

➤ Key concern of TC GLP data generation:

1. Brazilian requirement (format) in TC/FP is the most sophisticated in all 4 target markets. Special concerns need to be addressed during data generation (Especially with GLP lab outside Brazil)
2. DMS analysis, and limit control
3. Potential QSAR evaluation requirement. EU/Brazilian labs are more familiar with the protocol, process and softwares
4. Validity of TC samples at least 3 years (for supplementary data generation). Brazilian authorities tend to ask for supplementary studies, during the process of evaluation.

➤ Budget of Registration Data:

Pyraclostrobin TC:

Contain: 5B, 6 pack, Ames, Micronucleus, Phy-chem properties

Total package price: 90,000 USD (Bioagri, Nutrichem+India labs)

Need to consider the universal acceptance of phy-chem data (Brazil, Argentine, USA, Taiwan)

Pyraclostrobin FP: (1 single/mixture formulation)

Contain: 6 pack, Ames, Micronucleus, Phy-chem properties, Eco-toxicities

Total package price: 67,000 USD (Bioagri)

****Need to firstly confirm the formulation type (market trends, recipe, etc)**

The above data can fulfill the TC requirement of EU, USA, Brazil, Argentine and Australia.

And the formulation requirement of USA, Brazil, ASEAN countries

The specified data would be generated locally. E.g: Efficacy data in EU. Suggest the local partner share the cost.



Q & A ?



Thank you!