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From synthesis of the active substance to the registration of plant protection product

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Abstract: Plant protection products which are environment friendly, more selective and with a new mode of action are welcomed to be placed on the market and used. The reasons for the growing demand for new active substances are among others the withdrawals of the old ones due to new, more strict requirements and problems with resistance of harmful organisms against the existing active substances.
The paper mentions selected methods used at present by chemical researchers to make their efforts in the process of inventing new molecules to be used in plant protection more efficient and less cost consuming. The requirements which should be fulfilled after the development of a new active substance to obtain the permission for use in the European Union (so called Annex 1 listing) are presented and discussed as well as the data and formalities demanded to place new plant protection products on the market in one of the member states. The legal requirements are analyzed as well as the time and costs necessary to register the new plant protection product.

Keywords: plant protection products in EU, placing plant protection products on the market, registration of plant protection products, registration of active substance

Plant protection products which are environmentally friendly, more selective and with a new mode of action are welcomed to be placed on the market and used. The reasons for the growing demand for new active substances are among others, the withdrawals of the old ones due to new, more strict requirements [1] and problems with resistance of harmful organisms against the existing active substances [2, 3].

DEVELOPMENT OF ACTIVE SUBSTANCES

Chemists in numerous laboratories are working on new molecules which could be efficiently used in plant protection. Their task is, however, not simple. It is estimated that at present only one in every 150.000 compounds tested reaches the market while in the 80's it was one in every 15.000 [4], so that the task of scientists has become even more time-consuming and costly. The complexity of the task encourages researchers to look at new ways of conducting their studies.

New technologies can inundate researchers with too much information and too many potential targets and candidate compounds. Another problem is that studies involving these new technologies tend to be very expensive. This situation is encouraging crop protection companies to look at new ways of conducting their research. They are beginning to turn away from large scale studies.

One of the new "small scale" technologies is the field of microfluids which involves transporting and controlling small quantities of liquids on a microscopic scale. Microfluids open up the possibility of performing a range of standard laboratory activities, such as separating compounds and synthesizing chemicals – these activities happen faster on smaller scales and on smaller scale require smaller quantities of samples and chemical reagents. This facilitates are saving of both: time and costs [4].

Another way to save time and money is to conduct preliminary studies on computer. This idea is not new, but over the years these techniques have became increasingly sophisticated. For example, software has been developed, which instead of modeling the atoms in molecule and the bonds between them, models the molecule's molecular field (comprising its electronic and steric properties) [4].

However, the working out of the new active substance is only the beginning. The period from inventing a new molecule – no matter how efficient – to placing a plant protection product on the market is usually several years. To be placed on the market, the molecule, as well as the formulated plant protection products, have to undergo numerous studies to ensure their safety for humans and the environment, as well as their efficacy.

REGISTRATION REQUIREMENTS

The main act setting principles regarding placing plant protection products on the market of the EU member states is the Directive 91/414 [5]. The Directive states that the provisions governing authorization must ensure a high standard

of protection, which, in particular, must prevent the authorization of plant protection products which risks to health, groundwater and the environment and human and animal health should take priority over the objective of improving plant production.

The Directive states also that it is necessary, at the time when plant protection products are authorized, to make sure that, when properly applied for the purpose intended, they are sufficiently effective and have no unacceptable effect on plants or plant products, no unacceptable influence on the environment in general and, in particular, no harmful effect on human or animal health or on groundwater. Authorization should be limited to plant protection products containing certain active substances specified at Community level on the basis of their toxicological and ecotoxicological properties. The active substances meeting the broad safety criteria are listed in Annex 1 of the Directive 91/414.

In other words: to register a plant protection product with a new active substance, the active substance should first be assessed, approved and listed in Annex 1. To this purpose, the producer must perform all required studies and prepare documentation. Subsequently, the producer chooses a reporting member state – one from among the EU member states, which (for a fee) assesses the data regarding the active substance. The assessment of the reporting member state is then peer-reviewed by competent authorities from other member states. The active substance has also to receive the positive opinion of EFSA (European Food Safety Authority) and SCFCAH (Standing Committee on the Food Chain and Animal Health). Finally, the active substance must be approved for use in the EU by the European Commission and by the legal act included in Annex 1 of the Directive 91/414.

On the basis of the description above, we can assume that the procedure of assessing the submitted data is time consuming. Obviously, additional time is needed to prepare the data to assess.

The scope of data to be submitted is listed in Annex 2 of the Directive 91/414 and it is worth emphasizing that the list of required data (titles only) consists of several pages. Among others, the following information and study results are necessary: physical and chemical properties, information regarding the influence of the active substance on harmful organisms (including resistance), possibly dangerous properties, analytical methods for the determination of the active substance and breakdown products, toxicological, ecotoxicological and metabolism studies, studies regarding residues after treatment, fate and behavior in the environment and data regarding representative plant protection products containing the active substance.

After listing the active substance in Annex 1, it is possible to start the registration procedure of the plant protection products containing the active substance. In contrast to the active substance, plant protection products are registered on the member states level. Placing plant protection products on the market in each member state takes place on the basis of an independent decision of the registration authority.

It is worth emphasizing that in spite of the common market there is no legal possibility of sale or use plant protection products registered in other EU countries. In effect, this means that at present a given product registered and used for example in Germany, cannot be legally used in Poland unless it is registered in Poland. Even if an identical plant protection product is registered in two member states, the import of this product (for example because of price difference) must be permitted by the registration authority – even if the product is imported for the private use of a given farmer.

The general requirements regarding the data necessary to register the plant protection product are given in Annex 3 of the Directive 91/414. However, each member state can add its own rules; for example, concerning the language of application or the registration procedure.

The procedure of registration of plant protection products is, however, similar in most member states: to register a plant protection product, the producer should apply to the responsible authority (usually the Ministry of Agriculture, the Ministry of Health, a governmental agricultural institute or other governmental body). The responsible authority performs the check of completeness and sends the data to other authorities or appointed scientists for opinions regarding efficacy and phytotoxicity, residues, influence on human health and influence on the environment. After due consideration and discussion of these opinions by the registration commission, the plant protection product can be placed on the market.

TIME TO REGISTER A PLANT PROTECTION PRODUCT

According to the author's own assessment, upon working out a new molecule, the producer needs at least 3-4 years to perform all the studies required to place the active substance in Annex 1. The minimum period to assess the dossier in the EU, and make the decision about listing the active substance in Annex 1 is a further 2 years (sometimes more).

The absolutely minimum period to perform the studies for the registration of a plant protection product is 2 years (the law requires efficacy data from more

than one vegetation season). But in practice, 2 years are very seldom sufficient and the realistically shortest period is in fact 3 years.

The time period provided for the registration of plant protection products after submitting the application with a complete data set is, according to the governing laws of most member states, above one year (in Poland it is 16 months). However, the actual period is often much longer than provided by law, and in fact seldom shorter than 2 years.

Taking into consideration that a producer can perform some studies for the registration of a plant protection product during the time when the active substance is being assessed, we can estimate that the shortest possible period from synthesis of the active substance to the registration of the plant protection product in one of the EU member states is 9 years*).

COSTS NECESSARY TO REGISTER A PLANT PROTECTION PRODUCT

Costs of performing registration studies are of course not fixed: depending on the active substance as well as intended use of the substance. Costs also depend on the strategy of the producer (how many studies they intend to perform – a broad scope for the producer's own knowledge or rather a more narrow approach of performing the minimum studies required). Costs differ depending on the country in which the studies were carried out, and on the contracts between the producer and laboratories. The cost of assessing the documentation also varies depending on the member state as well as the cost of plant protection product registration.

According to ECPA [6] (European Crop Protection Association) – an organization of plant protection products' producers – the cost of research, development and registration of a new plant protection product is now approaching 200 million Euros, depending on the number of countries in which it is used, and the number of crops on which it is used. Costs of discovery, development and registration of a new plant protection product in the European Union according to ECPA shows the Figure 1 [7].

*) To shorten this period, the EU has allowed so-called "provisional approvals", which means registration of plant protection products before Annex 1 listing of the active substance on the basis of positive preliminary assessment of submitted data. This avenue, however, is to be closed soon.

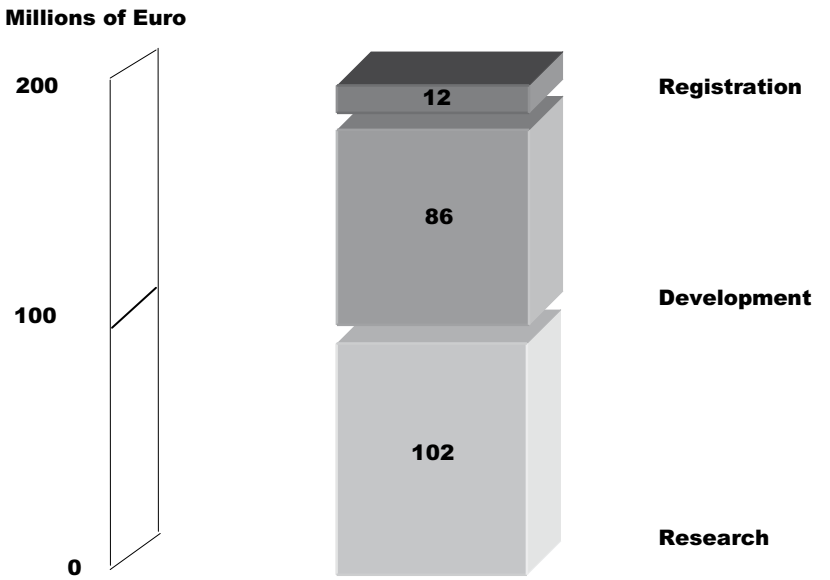

Figure 1. Discovery and development costs of a new plant protection product in the year 2000.

Source: ECPA The ABCs of crop protection: Fast facts for European policy-makers http://www.ecpa.be/files/documentslive/23/13687_ABC-ENGLISH.pdf date of access the 09.07.2007

CONCLUSIONS

On the basis of the information given above, we can state that the path from synthesis of the active substance to the registration of a given plant protection product is long and complex. Agrochemical companies are still inventing new compounds, but in general opinion, these inventions are considered to be insufficient in number. Due to stricter requirements as to the safety of agrochemicals, numerous existing active substances have been withdrawn from the market and the developmental costs of the new ones are growing. Simultaneously, the number of the newly invented active substances is decreasing. The number of new active substances of plant protection products launched on the market has decreased from over 50 per year in the mid 90' to below 20 per year at present [8].

Decrease in the amount and number of active substances used in the member states of the European Union is noticeable especially in the case of insecticides.

This situation can contribute to the development of resistance against the available products in future.

However, there is not a simple recipe to change the present situation, not least because the decision to slacken the requirements and allow for the use of substances which have not been fully studied would be unthinkable. The only realistically possible solution is to simplify and speed up the procedures of review of the active substance, as well as the registration of plant protection products. This would facilitate companies in obtaining the demanded return from investment on new active substance development. The tendency to simplify the procedure of registration is visible in the proposed changes to the Directive 91/414 [9].

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Od syntezy substancji aktywnej do rejestracji środka ochrony roślin

Streszczenie

Środki ochrony roślin przyjazne dla środowiska, bardziej selektywne i posiadające nowe mechanizmy działania są oczekiwane na rynku. Przyczynami rosnącego zapotrzebowania na nowe substancje aktywne są między innymi wycofywanie substancji dotychczas stosowanych ze względu na nowe, bardziej rygorystyczne wymagania oraz zjawisko powstawania odporności wśród organizmów szkodliwych.

Chemicy w licznych laboratoriach opracowują nowe molekuły, które mogłyby być skutecznie stosowane w ochronie roślin. Nie jest to łatwe zadanie. Szacuje się, że obecnie tylko jeden na 150.000 badanych związków trafia na rynek, podczas gdy w latach osiemdziesiątych na rynek trafiał jeden na 15.000. Zatem badania mające na celu opracowanie nowych substancji aktywnych stają się coraz bardziej czasochłonne i kosztowne.

Jednak opracowanie nowej molekuły to tylko początek. Czas od jej syntezy do dopuszczenia nowego środka ochrony roślin do obrotu i stosowania to zwykle kilka lat. Przed dopuszczeniem do obrotu zarówno substancja aktywna jak i formulacja środka ochrony roślin muszą przejść wiele badań celem udowodnienia, że są skuteczne oraz nieszkodliwe dla ludzi i środowiska naturalnego.

Głównym aktem prawnym regulującym dopuszczanie środków ochrony roślin do stosowania w krajach Unii Europejskiej jest Dyrektywa 91/414. Zgodnie z wymaganiami przedstawionymi w Dyrektywie rejestracja środków ochrony roślin w państwach członkowskich odbywa się dwuetapowo: najpierw ocenie pod kątem bezpieczeństwa podlega substancja aktywna (ocena ta odbywa się na szczeblu unijnym i jej rezultaty są wiążące dla wszystkich państw członkowskich), a następnie rejestrowane są formulacje środków ochrony roślin na szczeblu państw członkowskich.

Świadectwem dopuszczenia substancji aktywnej do stosowania w ochronie roślin w krajach UE jest wpisanie jej do Załącznika 1 Dyrektywy 91/414

obowiązującego na poziomie unijnym. Państwa członkowskie rejestrując środki ochrony roślin umieszczają je w wykazie prowadzonym przez podmiot odpowiedzialny za rejestrację. Warto podkreślić, że mimo wspólnego rynku środki ochrony roślin dopuszczone do obrotu w jednym państwie członkowskim nie mogą być importowane przez rolników i stosowane w innym.

W artykule przedstawiono przebieg procedury rejestracyjnej środków ochrony roślin. Oszacowano także, iż okres od syntezy substancji aktywnej do rejestracji środka ochrony roślin w jednym z państw członkowskich wynosi co najmniej 9 lat. Zgodnie z szacunkami Stowarzyszenia Producentów Środków Ochrony Roślin, łączne koszty ponoszone na badania i rejestrację nowego środka ochrony roślin sięgają 200 mln Euro.