A comparison of the EU and US regulatory frameworks for the active substance registration of microbial biological control agents.

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ABSTRACT

BACKGROUND

Microbial bio control agents (MBCA) are biopesticides based on living microbes. They provide a huge potential for the control of pests and diseases, but have trouble reaching the EU market. According to several authors, this is caused by the regulatory regime, which is less supportive compared to that of the US. The main objective of this paper is to present regulatory differences between the US and the EU and the resulting effects and developments of registration in both regions.

RESULTS

Results show that EU registration is more complex due to differences between EU and member state (MS) level processes, large actor heterogeneity and low flexibility. As a result, EU registration on average takes about 1.6 years more than US registration. Regulatory amendments improved EU level processes and led to a significant contraction of procedural timespans, but processes at MS level did not improve and have become a larger procedural obstacle.

CONCLUSION

Results correspond with the idea that EU registration is complex and lengthy compared to that of the US. In order to improve regulation, national level processes should be targeted for amendments. To that end, the authors suggest various ways of expanding registration capacity of MS.

KEYWORDS

Biopesticides, (microbial) bio control agents, (M)BCA, EU, US, registration, regulation.

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1. INTRODUCTION

Microbial biological control agents (MBCA) contain living microorganisms such as bacteria, fungi or viruses for the control of weeds or pests and diseases of crop plants and are regulated in the European Union (EU) at both EU and Member State (MS) level.[1,2,3] MBCAs need to undergo a comprehensive risk assessment to ensure food safety. However, assessments are based on rules that were originally developed for synthetic pesticides and opportunities for improving risk assessment efficiency exist.[1,4]

The EU assessment procedure was first laid down in Directive 91/414/EEC, in an attempt to harmonize the – until 1993 – national registration schemes within the EU.[5,6] This directive was repealed by Regulation No. 1107/2009 in 2011.[3] The amendment was designed to create regulatory circumstances that better fit the specific requirements of MBCAs[1]. With the implementation of Regulation No. 1107/2009, only 26 % of registered active substances and Plant Protection Products (PPP) passed the review against Directive 91/414/EEC.[7]

The market change, driven by the new regulation, created opportunities for novel pesticide products. Ever since, the market share for MBCAs has grown accordingly.[4,8] However, regulatory complexities cause for demanding regulatory standards. Following the challenge of meeting these standards, a lack of experience, knowledge and resources from several EU or MS authorities cause for lengthy registration procedures.[1,9] As a result, relatively few MBCAs are available on the market in the EU compared to the Unites States (US).[1,10] As the largest market for MBCAs next to the EU, the US takes a different approach in MBCA registration and regulation.[7,11] Although both regions follow the Organisation for Economic Cooperation and Development (OECD) standards for risk assessment, the US registration procedures have proved to be less lengthy. This has led to a greater and more constant registration of MBCAs in the US.[1,11,12]

The regulatory differences between the US and the EU may pose a problem for the latter. Similar to a non-tariff trade barrier, regulatory differences pose a significant burden to international trade.[13] Next to hampering trade, the EU regulatory system restricts the development of the MBCA sector[1,9,10] and the EU's capacity for innovation.[1,14] Finally, the EU community is barred from the environmental and agronomical benefits of MBCA usage.[15,16] Altogether, the EU regulatory framework for registration of MBCAs seems to be restrictive, and opportunities for improvement without reducing product safety exist.[17] The objective of this paper is to (1) provide an overview of the EU and US regulatory frameworks for MBCA registration, (2) to determine the differences between the two regulatory frameworks including the length in approval time, (3) to present the resulting differences in terms of registration numbers and trends and (4) to suggest possibilities for improvement.

2. MATERIALS AND METHODS

We determined the organisation and structure of the EU framework by analysing the designated policies and relevant secondary literature. The same was done for the US framework. The resulting framework overviews allowed for a regulatory comparison.

In order to determine the regional registration statistics and their developments, we derived information from the EU and the US online pesticide databases and related documents.[18] The retrieved data allowed us to determine and analyse procedural timespans for all active substances that underwent registration.

For EU registration, the procedural timespan is considered to run from the date on which an applicant submits an application (start of the calculation of procedural timespan) to the date on which the end products is registered on national or member state (MS) level (stop of the calculation of procedural timespan). All specific registration phases are considered followed by a one-day margin, unless specifically mentioned otherwise in EU reports. At this stage we do not have final PPP registration dates at MS level available. Hence, it is not possible to determine procedural timespans of PPP registration at the MS level. It should therefore be noted that, based on the maximum legal EU timeframe, 27% of the entire registration timeline (i.e. active substance + PPP registration) is not included.

For US registration, the timespan is considered to run from the date on which an applicant submits an application (start of the calculation of procedural timespan) to the date on which the active substance and its end product are included in the US federal register (stop of the calculation of procedural timespan). Data are provided by the Environmental Protection Agency's (EPA) list of biopesticide active ingredients[19], the US Federal Register and the linked Federal notices and rules and Biopesticide Registration Action Documents for each active substance.[20] We considered a reference period running from January 2000 to September 2017, as this is the most up-to-date available data

3. RESULTS

3.1 EU regulatory framework

In the EU, registration of MBCAs is performed in two steps. During the first step, the active substance is evaluated. Data requirements for the evaluation are given in Regulation No 283/2013 and inclusion in the list of approved active substances follows procedures according to Regulation No. 1107/2009.[3,5,21] During the second step, the PPP itself is evaluated at MS level.[3,4,21] The two steps do not necessarily need to be separate and subsequent: under specific circumstances, a MS can give provisional authorisation of products prior to inclusion of the list for approved active substances. However, one should note that the possibility for such an authorisation is limited as it depends on several criteria.[3,21]

3.1.1 First step - evaluation of active substances at EU level

We consider three subsequent phases within active substance registration: the rapporteur member state (RMS) phase, the risk assessment phase and the risk management phase.

In the RMS phase, the applicant composes a dossier which contains all information on the active substance and (at least) one representative PPP. The applicant then requests for registration of the active substance by delivering the dossier to a MS of its own choosing. Within 45 days, the chosen MS starts an evaluation procedure and this is hence called the designated Rapporteur Member State (RMS). The authorities of the RMS

first check the completeness of the dossier, after which they evaluate it and subsequently distribute their Draft Assessment Report (DAR) to the other MSs, the applicant and the EFSA.[22] The RMS has a maximum period of twelve months, with a possible extension of six months if the RMS decides that it needs additional information from the applicant (Fig. 1).[3]

Subsequently, the EFSA provides assessments of risk and risk communication on all aspects related to food safety, during the risk assessment phase. After the EFSA assessed the risks, their assessment undergoes a peer review process during a period of three months, involving all MSs and the EFSA itself. As the result of the peer review process, the EFSA releases a scientific report with conclusions of its peers within four to eight months.[3] Then, the European Commission (EC) – currently represented by the Directorate General for Health and Food Safety (DG SANTE) – prepares a dossier which aims at inclusion of the active ingredient into the "list of approved active substances". An inclusion into the list of approved active substances implies that an active substance is eligible for use in a PPP in the EU (Fig. 1).[3]

MSs subsequently vote in the Standing Committee (SC), currently called the Standing Committee on Plant, Animals, Food and Feed (PAFF Committee)[3,21], for approving the dossier prepared by the EC. This part is known as the risk management phase.[24] The approval will only be reached by qualified majority vote, indicating that 55% of the MS, holding at least 65% of the population, agree.[25] After a positive risk assessment and vote session within the SC, the active substance is included in the list of approved active substances and a notice of inclusion is published in an EU official journal. The inclusion takes between about six to twelve months from the date on which the dossier of the EC is presented. A "regular" active substance keeps its status for ten years. Generally qualified as "low risk" active substances, biopesticides can be granted a 15 year period of registration (Fig. 1).[3,21]

[Insert Fig. 1]

3.1.2 Second step - PPP evaluation at national level

The second step is to have the PPP itself registered at the national level. For use of the PPP in field crops, EU MS are divided in three evaluation zones, coarsely linked to climatic conditions:

- Zone A - North: Denmark, Estonia, Finland, Latvia, Lithuania, and Sweden;
- Zone B - Central: Austria, Belgium, Czech Republic, Germany, Ireland, Luxembourg, Hungary, the Netherlands, , Poland, Romania, Slovenia, Slovakia and the UK;
- Zone C - South: Bulgaria, Croatia, Cyprus, France, Greece, Spain, Italy, Malta and Portugal

For use in greenhouse areas, post-harvest treatments, treatment of empty storage rooms or seed treatments, the EU is considered a single zone.[3]

National registration requires a dossier with efficacy data to be submitted to a Zonal Rapporteur member state (zRMS) which evaluates the product on behalf of all the MSs in its zone. All MSs in the respective zone may grant authorizations, unless their specific national conditions justify alternative conditions of use (mitigation measures) or refusal of authorization. For use in field crops, it is possible to apply for more than one zone as

the zRMS should do the evaluation of data not related to environmental and agricultural conditions. PPP applications should be evaluated within twelve months by the zRMS. If the initially submitted data does not fulfil requirements, a maximum of six months additional time may be given in order to submit additional data requested by the zRMS. If these data are not submitted on time, the application is refused. For PPPs containing a not (yet) approved active substance, the MS should start the evaluation after the DAR is received. The evaluation of applications for PPPs by MSs should be done within six months after approval of the active substance.[3]

In addition to the zonal registration procedure, mutual recognition can be applied for after authorisation of the product in a first MS. If the MS where authorisation was granted belongs to the same zone, mutual recognition shall be granted within 120 days. In case authorisation was granted by a MS or zRMS which belongs to a different zone, the authorisation can be recognized by a single MS, but not for the whole zone. To ensure consistency in MS evaluations, Annex VIB of Directive 91/414/EC provides uniform principles specific for evaluation and authorization of microbial PPPs. The same principles are also followed when active substances require re-registration.[3,5]

3.2 US regulatory framework

In the US, both the PPP and its active substance are evaluated by two central authorities: the Environmental Protection Agency (EPA), which governs the active substance registration and the Food and Drug Administration (FDA), governing the maximum residue levels (MRL).[1,12]

The EPA has authority based on statutes within (1) the Federal Food, Drug and Cosmetic Act (FFDCA 1938) and the (2) Federal Insecticide, Fungicide and Rodenticide Act (FIFRA 1947).[11,12] Third, the Food Quality Protection Act (FQPA 1996) sets additional standards for new and old pesticides, making requirements regarding processed and unprocessed foods more uniform.[12] Finally, the Pesticide Registration Improvement Act (PRIA) established specific fees and specific timelines for different types of pesticide registration actions that may vary between four to eighteen months. There have been three versions of the PRIA: the PRIA 1, the PRIA 2 (renewal) and the PRIA 3 (extension), which were implemented in 2004, 2007 and 2012 respectively.[22] BCA data requirements are listed in Title 40 of the Code of Federal Regulations (40 CFR) Part 158 and more specifically, data requirements for MBCA are listed in Subpart V: Microbial Pesticides 40 CFR 158.2100 through 40 CFR 158.2174.[27] The EPA also published guidelines and data requirements that need to be fulfilled to support registration. These may include the Office of Chemical Safety and Pollution Prevention (OSCPP) series 830, 850, 870 and 885.[28,29,30,31] Prior to the formal start of the procedure, an applicant may approach the EPA in a pre-submission meeting. Though not required, these meetings are recommended by the EPA. In these meetings the applicants are advised what studies are necessary for the product up for submission. These studies depend on the preliminary identification of the product and the amount of data that is available form literature or other sources. The applicant then submits a summary of the meeting(s) to the agency as to receive comments and confirmation of completeness.[21,26]

Following the optional pre-submission meetings, the applicant must undergo three steps in processing an application to determine whether the application is complete and contains sufficient information for the Agency to make a regulatory decision. First, the EPA checks whether the application is complete enough to be assigned to a division for review in the initial screen for completeness, which takes 21 days. Second, a preliminary technical screen is done to determine if the data is (1) accurate and complete, (2) consistent with proposed labelling and any tolerance and tolerance exemption and (3) such that subject to full review could result in the granting of the application. If information is not sufficient in the second step, the applicant has 10 business days to respond by providing the required information. Failure to comply with the response period will result in the rejection of the application.[27] From receiving the meeting summaries onwards, the Biopesticides and Pollution Prevention Division (BPPD) has a maximum of 19 months from receipt of a complete application until the registration decision according to the PRIA 3 timelines.[12,26,27] A registration decision may result in either a registration, a renegotiation due to inadequacies, or in a full rejection (Fig. 2).[27]

[*Insert Fig. 2*]

If data are missing or classified as "supplementary", if risk is low enough to market the product, or if there is any other reason to be flexible, the US framework may allow for conditional registration in the form of (1) emergency exemptions or (2) state-specific registrations. A registration is valid for 15 years throughout the US.[21,27]

In terms of finance, the US has some special regulations. First of all, the US Department of Agriculture (USDA) may offer grants needed for registration related research. The USDA does this through the Inter-Regional Research Project Number 4, an initiative constructed to support of the registration of minor use pesticides.[32] Secondly, Small and Medium sized Enterprises (SMEs) may be funded through the "Small Business Innovative Research program"[11] Next to these financial advantages, the US may provide financial exemptions to SME or government bodies, which are often exempted from EPA reviewing fees.[21]

The US framework also allows for an exemption of registration altogether in case of minimum risk pesticides. All MBCAs placed on the EPA's 25b list which is found under 40 CFR 158.25(f), these pesticides and their active substances are exempted from federal registration under certain conditionss.[29,30] It should however be noted that states may not agree with the EPA's 25b list, which may still lead to mandatory registration at US Federal State level.[33]

3.3 Exemptions and waivers EU and US

In the US, certain data requirements may be met with a "waiver" which, if accepted, allows the applicant to not provide certain studies as are normally required by the OCSPP guidelines. The applicant has to apply for a waiver based on published literature or by providing their own data.[11,26,27] Formally, the waiver system does not exist in the EU. However, EU applicants may provide a scientifically reasoned justification for not providing certain parts of the registration dossiers.[3] Formal data waivers in the US are accepted more easily than a reasoned case is in the EU.[21]

3.4 Overall comparison EU and US regulatory frameworks

The US regulatory framework is less complex than the one used by the EU in multiple ways. In the EU, more authorities are involved: EU level processes are run by four major authorities, whereas there are only two in the US. In addition to EU level processes, national registration requires MS authorisation. This creates a heterogeneous procedure in the EU, leading to several hurdles for registration (Table 1).

[*Insert Table 1*]

3.5 Developments EU and US registration

In total 47 and 73 MCBAs have been registered since January 2000 in the EU and the US, respectively (Appendix 1 and 2). Of those, 13 MCBAs have been registered both in the EU and the US. 34 of the MCBAs registered in the EU have been registered prior to the reform in 2009 and 14 after the reform. The approval length on average took 1678 days in the EU. The average procedural timespan for active substance registration dropped with 476 days with the implementation of Regulation No. 11007/2009. Average PPP registration takes 629 days.[39] In the US, the average procedural timespan is 588 days less than EU registration under Regulation No. 11007/2009 (Fig. 3).

[*Insert Fig. 3*]

Starting with the first harmonised EU registration in 2001, the EU shows modest and irregular registration of just under two active substances during the first eight years. In 2009, the EU's list of approved active substances was expanded by 17 re-registered active substances (which were already on the EU market under the former national market registration).[40] The 2009 peak thus does not show an actual net expansion of the EU's list of approved active substances or potential market for MBCAs. From 2013 onwards, the implementation of Regulation No. 1107/2009 seems to bear fruit as the cumulative number of registrations increased steadily at a rate of more than four active substances per year. In the US, annual registration of new active substances is more constant: the registration rate has been an approximate four active substances per year throughout the reference period (Fig. 4).

[Insert Fig. 4]

3.5.1 Development first step - active substance registration on EU level

For analysing the procedural timespan for registration, 31 observations (applications) were available. Data for observations is pulled from specific DG Sante review documents. The observations include new and successful registrations only (i.e. excluding registration reviews and non-approved active substances). The oldest observation dates January 2001 and the newest dates March 2017. With a minimum of 1103 days and a maximum of 4,159 days, the observed procedural timespans show a maximum difference in range of 3,056 days. Although the mean timespan is 2,109 days, the median with 2,116 days exceeds that.

Annex I presents the timespan overview of EU registration cases, running from the date of application to the date of approval within the reference period 2000 to 2017. Timespans vary substantially: documentation shows cases of more than eleven years all the way down to recent cases with a procedural time of approximately three years. Procedural time spans such as the one for *Spodoptera exigua nuclear polyhedrosis virus* (11.4 years) or *Pseudomonas chlororaphis strain MA342* (9.8 years) were mainly caused by inexperience with the – at that time – novel integrated EU approach for active substance registration.[21] The inexperience caused for uncertainty about what data to collect or submit and led to a particular lengthy RMS phase.[40] Procedural timespans seem to contract over time.

A correlation analysis confirms a negative correlation between the procedural timespan and date of application. A linear regression analysis for this relation, including the regulatory amendment as extra variable, shows that there is a significant negative influence of both variables on the procedural timespan. The outcomes of the analysis allow for an estimation of the trends in procedural timespans through a linear function (1) (Table 2).

$$Y_i = \alpha + \beta X_t + D_{Reg.\ 1107/2009} + \varepsilon_i \quad (1)$$

The linear model represents the procedural timespan for active substance registration in days. Denoted by Y_i, the procedural timespan is the dependent. The independent variable is the moment in time the registration procedure started, given by the number of days since the first application and denoted by βX_t. The regulatory change caused by the shift from Directive 414/91 EC to Regulation No. 1107/2009 is denoted by a dummy variable $D_{Reg.\ 1107/2009}$. The dummy variable takes into account the effect of the regulatory reform. The intercept value α represents the initial time length in days. The values for the regression model imply that the estimated procedural timespan on the starting day of the reference period (t_0) is 3195 days. From that moment on, each subsequent day on the timeline results in a 0.181-day decline in procedural timespan. The qualitative coefficient "Regulation No. 1107/2009" implies that – on average – the procedural timespan has dropped 632 days under Regulation No. 1107/2009 compared with the average timespan under Directive 91/414/EC (Table 2).

The procedural timespan in the EU thus declined steadily under Directive 91/414/EEC. After the implementation of Regulation No. 1107/2009, the timespan made a further but sudden drop (Fig. 5).

[*Insert Fig. 5*]

Separate regression analyses for Regulation No. 1107/2009 and Directive 91/414/EC show that an active substance registered under Regulation No. 1107/2009 and on time value t_0 (1 October 2013), would be registered 933 days faster than an active substance under registered under Directive 91/414/EC and on time value t_0 (7 January 2001) would have been. The significant daily decline under Directive 91/414/EC is caused by

a contraction of the risk management phase: the RMS phase remains roughly the same and the risk assessment phase increases under Directive 91/414/EC (Fig. 6). The lesser daily decline under Regulation No. 1107/2009 seems to be caused by the contraction of both the risk assessment and risk management phase (Fig. 7). However, given the limited number of observations for Regulation No. 1107/2009 this cannot yet be considered significant (Table 2).

[*Insert Fig. 6 and Fig. 7*]

3.5.2 Development of EU active substance registration broken down in phases

After the implementation of Regulation No. 1107/2009, the RMS timespan decreased by 33.5%. The risk assessment phase decreased by 51.6 %. The risk management phase decreased by 62.5% (Fig. 8). Overall, the average procedural timespan decreased by 48.2%.

[Insert Fig. 8]

With the implementation of Regulation No. 1107/2009, the time-wise proportions of the three phases within the total procedure changed. The RMS phase increased, whilst the share of the risk management phase decreased. This caused the RMS phase to become the relative bottleneck after the regulatory reform (Fig. 9).

[Insert Fig. 9]

Only eleven MS have performed an RMS between 2000 and 2017. Under Directive 91/414/EEC, Sweden, Italy and Estonia have been the most encouraging as RMS: they kept a low average timespan. The United Kingdom comes out as least encouraging RMS, explained by one exceptional lengthy registration case. As second slowest performer, longer RMS timespans in the Netherlands were more common. This might have been caused by a lack of resources and experience, especially since the Netherlands was RMS for four out of the five “first-ever” active substances.

After the reform, RMS timespans decreased in general. Belgium, Germany, France and the Netherlands are the only ones to have yet performed an RMS under Regulation No. 1107/2009. Germany being an exception, the reform caused France, Belgium and the Netherlands to respectively become the three most encouraging RMS candidates in terms of the average timespan (Fig. 10).

[Insert Fig. 10]

3.5.3 Development second step - PPP registration on national level

On average, PPP registration took 629 days from 2013 to 2015. In 2013 and 2014, four out of five zRMS procedures exceeded the procedural deadlines, leading to legal compliance of only 21%. For the subsequent approval of the efficacy report by the other MSs in the designated zone, all decisions exceeded procedural deadlines and only 15% of all decisions were legally compliant. Finally, mutual recognition exceeded deadlines

in five out of seven cases, leading to a legal compliance of 29%. Due to such delays in PPP registration, the EU is witnessing an increasing number of emergency registrations, but mainly for inorganic active substances.[23]

3.5.4 Development of overall US registration

For analysing the procedural timespan for US registration, 62 observations were available. Data for observations is pulled from rules, notices and supporting material from the Federal Register. The observations include initial successful registrations only. This also concerns two cases which are subsequent to an EUP. The oldest observation dates December 2001, the newest dates June 2017. With a minimum of 51 days and a maximum of 2060 days, the observed procedural timespans have a maximum range in difference of 2,009 days. Although the mean is 778 days, the median is 683 days.

Annex II presents timespans in the US. Lengthy cases may be caused by joint registrations for both the US EPA and the Canadian Pest Management Regulatory Authority (PMRA) (e.g. *Chondrostereum purpureum strain HQ1*), others are caused by submitting insufficient dossiers (e.g. *Vertillicum Isolate WCS 850*). However, due to missing documentation in the Federal Register (i.e. registration actions documents or Federal notices), not all outliers can be explained. Procedural timespans seem to decrease slightly over time.

A correlation analysis confirms an overall negative correlation between the procedural timespan and date of application in the US. Since the PRIA 1 came in to force in 2004[22], the maximum duration of the US registration procedure became more consistent. The implementation of the PRIA 2 and PRIA 3 seem to have further contributed to this trend (Fig. 11).[39] Regression analysis does not show a significant effect for the PRIA amendments as variable. The regression analysis for the procedural timespan in days (dependent) and the days since the first US registration (independent) within the reference period (2000 – 2017), does show a significant negative relation between procedural timespan and date of application (Table 2).

[Insert Fig. 11]

The model developed through linear regression again represents the procedural timespan for active substance registration in days (1). The variables indicate the same as they do for the EU, but for the US the dummy variable for Regulation No. 1107/2009 is omitted. The values show that the estimated procedural timespan on the starting day of the reference period (t_0) is 974 days. From that moment on, each subsequent day on the timeline results in a 0.065-day decline in procedural timespan (Table 2).

[*Insert Table 2*]

3.6 EU versus US developments

Based on the analyses of the registration procedure in both regions, estimations show a significant trend of a decreasing procedural timespan for active substance registration. Although the procedural timespan still is substantially shorter in the US, the gap between the EU and the US became substantially shorter due to a daily

contraction under Directive 91/414 EEC and the sudden contraction driven by the implementation of Regulation No. 1107/2009 (Fig. 12).

[Insert Fig. 12]

3.7 Same active substances, different fates

Thirteen active substances have been registered in both the EU and the US, of which eleven can be compared based on their documentation. The difference in procedural timespans with the US varies substantially. With a difference of 196 and 249 days, registration of *Verticillium albo-atrum strain WCS850* and *Bacillus Pumilus QST 2808*, respectively, were the only shared cases with the shortest timespan in the EU. With an additional 2475 days in the EU, the case for zucchini yellow mosaic virus shows the largest difference (Fig. 13). In spite of these already substantial differences, it should be noted that the US timespan includes PPP registration, whereas the EU timespan includes active substance registration only. Two active substances were registered in the EU first and on average, US registrations were completed 1269 days earlier.

[*Insert Fig. 13*]

A major share of the EU's protracted procedural timespan is caused by protracted RMS phases. In the case of *Zucchini Yellow mosaic Virus*, the applicant failed to supply supplemental information to the EFSA.[34] For the registration of *Candida oleophila* strain O, *Coniothyrium minintans and Bacillus amyloliquefaciens,* requests for supplementary studies caused the RMS phase to be lengthy.[35,36,37] In the case of *Paecilomyces lilanicus* protraction was due to both the RMS phase and the need for expert consultation in the peer review phase.[38]

4. DISCUSSION

The MBCA registration procedure in the EU seems substantially slower compared to the procedures in the US, taking an additional 1.62 years (43%) on average. The EPA's up-front screening process tends to deny some applications at the outset. This has a positive effect on the measurement of the time length, but that it is not captured in the data. Nevertheless the calculated average delay in registration leads to foregone benefits of using the MBCA and thus to costs of delay. Indicatively, Benjamin et. al. show that the (foregone) socioeconomic benefits of biological control of European corn rootworm in potato and maize might attribute to € 48.7 million annually for France, Italy, Spain, Germany and Romania combined.[41] Although costs of delay will depend on many factors and will vary per MBCA, this gives an indication of the economic importance of the EU's delay in registration compared to the US.

When looking at an almost similar EU process such as the approval process for GMO techniques, we see a delay of 1.93 years (39.9%) in the EU compared to the US.[24] The GMO approval process is delayed mostly due to a MS voting gridlock.[42] Given the absence of such a problem in the MBCA registration process, one can reason that there is potential for the timespan of the MCBA registration process in the EU to further decrease.

Both the sudden contraction in 2009 and the subsequent continuous contraction of the procedural timespan for all EU-level processes (risk management phase and risk assessment phase) show that the implementation of Regulation No. 1107/2009 is paying off in this regard. The contraction is likely to be further supported by a growing demand for organic products[8,43] and a societal pressure to move towards a more sustainable mode of food production altogether.[44] By gaining more experience, it is also likely that increased efficiency in risk assessment and management will contribute to the continuous contraction of the procedural timespan.[45]

But although the timespan for EU-level processes did improve, MS level processes are still lagging, suggesting that this is where the EU can gain in terms of efficiency. Adding to that, Zilberman and Wesseler show that the economic importance of the first two years of the procedure is larger than that of subsequent years.[46] This is interesting in the context of EU registration, as the RMS phase (first phase, ±1.5 years) became a larger bottleneck after implementing Regulation No. 1107/2009: EFSA review documents in the EU pesticide database show that five out of nine RMS cases exceeded their deadline between 2009 and 2016. Streamlining the RMS phase should therefore be one of the focus points for improvement of EU procedures. As RMS with a designated evaluation authority (England, France, Sweden, Netherlands) tend to perform more efficient through swifter accumulation of relevant experience[6], a strategy for improvement could be to restrict RMS participation to these MS. Another strategy could be to appoint certain cases to RMS with experience within a specific category (e.g. related to target pest/disease, or crop).

In addition to the RMS phase, PPP registration poses another obstacle at MS level. So far, stricter guidelines related to deadlines at MS level have not been successful.[47] The remaining low levels of regulatory compliance suggest that the EU should therefore within its mandate rather expand MS registration capacity by addressing the lack of resources, infrastructure or experience. This can be done through exchange with the EFSA or successful RMS such as Belgium, France and the Netherlands. As one of these strong performers, the Netherlands have provided an example of how to expand capacity for registration of biopesticides through the so-called “Green Deal Project”, a three year project in which the Dutch government worked on improved national BCA registration together with key public and private stakeholders. Outcomes and follow-ups focussed not only on capacity improvement but also on new legislative forms which enable higher success ratios for low-risk active substances and PPP (through e.g. waivers and financial support measures).[48]

5. CONCLUSION

The EU regulatory framework for pesticide active substance registration governs all types of pesticides (i.e. both chemical and organic). The procedure takes two steps, the first concerning active substance registration on EU level and the second concerning PPP registration on a MS level. On average, both steps combined take 65.7 months under Regulation No. 1107/2009. Opposite to the EU framework, the US framework is accustomed to biopesticides. Furthermore, the PPP and the active substance are evaluated simultaneously. On average, US registration takes 25.7 months. The US procedure is more flexible: as it is less heterogeneous, involves a smaller range of actors and consumes less time, trumps the EU system through data “waivers”, financial exemptions and conditional registrations.

The result of the initial regulatory discrepancies between the two regions is that, between 2000 and 2005, the number of registered active substances that were registered under harmonized EU regulation lagged compared to the US. But US numbers only slightly increased after 2005 and since the regulatory reform in 2009, EU registrations have been rising. Though both regions show a steady and significant decrease of the procedural timespan between 2000 and 2016, the decrease is the strongest in the EU, causing the gap between both regions to decrease. Under Directive 91/414/EEC, the EU procedural timespan decreased significantly over time. After Regulation No. 1107/2009 was implemented, the procedural timespan shows another significant but sudden (i.e. immediate) decrease. The amendment caused all three phases for active substance registration to contract, but the RMS phase has become the larger obstacle. Having an experienced and well-performing RMS has therefore become more important. With the majority of MS failing to comply with regulatory standards and delaying registration, PPP registration has become another important obstacle. Processes on MS level thus seem to be the biggest bottleneck and should be prioritized by the EU.

Given the limited number of observations, we analysed registration by applying linear models. However, as the MBCA market is diverse and complex, registration trends will likely depend on more than just time and regulatory amendments as factors. Factors might for example include the regulator's preference or bias in prioritizing certain cases (based on e.g. complexity or familiarity), the origin of an applicant or other regulatory amendments. In order to account for such non-linearities, future research should consider multivariate regressions to control for compositional effects. For a comprehensive approach, such an analysis should also be performed for data on PPP registration.

Apart from analysing registration itself, it would be interesting to determine what the current regulatory framework entails for the EU economically. A suggestion for future research would therefore be to use the results in this study for an attempt to determine the cost of the EU's procedure compared to e.g. the US system. As has been done for the introduction of vitamin-A enriched rice in India, Wesseler's and Zilberman's calculation of a government's or regulator's "perceived costs" could serve as a method to financially express a regulatory regime.[46] These quantified results could then be used in order to target or prioritize parts of a regulatory framework and its possible regulatory amendments.

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TABLES

Table 1: Overview of the framework comparison between the EU and the US. Source: author's elaboration.

Aspect	EU regulatory framework		US regulatory framework
Regulation	Regulation No. 1107/2009		40 CFR Part 158
	Regulation No. 283/2013		
Regulation type	Based on chemical pesticides		Accustomed to biopesticides
Guidelines	None		OSCPP Series 830, 850, 870 or 885
Procedural time span	EU (AS only)	EU + MS (Incl. PPP)	Max. 7 months (Experimental use permit)
	Max. 26.5 - 47.5 months	Max. 59.5 – 65.5 months	Max. 18 months (Regular)
Registration period	10 years		15 years
	15 years (low-risk AS)		
Authorities involved	RMS		EPA - BPPD
	EC - DG SANCO		FDA
	EFSA		
	SCFCAH		
	zRMS (national PPP registration)		
Barriers	Long-lasting procedural time span		
	Multiple RMSs: differ in expertise		
	National registration still a hurdle		

Table 2: Multiple regression output for the procedural timespan of active substance registration in days over time and under regulatory amendments in the EU and the US.

	Coefficient	SE[‡]	P-value
EU overall			
Intercept	3194.676	193.960	0.000
Days since first application[†]	-0.181	0.054	0.002
Regulation No. 1107/2009	-632.302	247.401	0.016
EU Directive 91/414/EEC			
Intercept	3200.600	247.619	0.000
Days since first application[†]	-0.183	0.070	0.018
EU Regulation No. 1107/2009			
Intercept	2267.353	870.808	0.025
Days since first application[†]	-0.136	0.132	0.323
US overall			
Intercept	974.604	95.514	0.000
Days since first application[†]	-0.65	0.026	0.016

[†]Slope of the function, change in procedural timespan over time (days since first application)

[‡]Standard error

GRAPHICAL ABSTRACT

A comparison of the EU and US regulatory frameworks for the active substance registration of microbial biological control agents.

Coen Frederiks* and Justus H.H. Wesseler

This article compares regulation of microbial biopesticide registration in the EU and the US, discussing regulatory differences and resulting obstacles. EU registration takes substantially longer, lagging mostly on national level.

[Insert image]

APPENDIX

Appendix 1: Overview of the considered active substances in the EU within the reference period (2000-2017).

Active substance	Year first registered	RMS phase		Risk assessment phase		Risk management phase		Timespan in days	Regulatory framework
Paecilomyces fumosoroseus "PFR 97"	2001	18-05-94	9-12-97	10-12-97	31-03-99	1-04-99	27-04-01	2426	Directive 91/414/EEC
Pseudomonas chlororaphis strain MA342	2004	15-12-94	7-04-98	8-04-98	31-05-98	1-06-98	30-03-04	3578	Directive 91/414/EEC
Ampelomyces quisqualis strain AQ10	2005	12-04-96	28-10-97	29-10-97	31-03-99	1-04-99	8-10-04	3276	Directive 91/414/EEC
Spodoptera exigua nuclear polyhedrosis virus	2007	12-07-96	1-11-99	2-11-99	31-05-02	1-06-02	15-05-07	4159	Directive 91/414/EEC
Coniothyrium minitans Strain CON/M/91-08 (DSM 9660)	2004	10-09-97	13-03-00	14-03-00	1-02-02	2-02-02	4-07-03	2304	Directive 91/414/EEC
Gliocladium catenulatum strain J1446	2005	19-05-98	15-06-00	16-06-00	28-02-03	1-03-03	8-10-04	2509	Directive 91/414/EEC
Bacillus subtilis str. QST 713	2007	19-04-00	15-05-01	16-05-01	28-02-03	1-03-03	14-07-06	2479	Directive 91/414/EEC
Paecilomyces lilacinus strain 251	2008	15-09-02	3-11-04	4-11-04	3-12-07	4-12-07	22-01-08	2147	Directive 91/414/EEC
Adoxophyes orana GV strain BV-0001	2013	29-11-04	13-08-08	14-08-08	12-07-12	12-07-12	13-07-12	2986	Directive 91/414/EEC
Paecilomyces fumosoroseus strain Fe9901	2013	4-02-05	29-03-07	30-03-07	31-01-13	1-02-13	15-03-13	3161	Directive 91/414/EEC
Zucchini Yellow Mosaik Virus, weak strain	2013	16-03-05	30-06-06	1-07-06	27-09-12	28-09-12	20-11-12	2999	Directive 91/414/EEC
Bacillus thuringiensis subsp. Aizawai strains ABTS-1857 and GC-91	2009	30-11-05	1-11-07	2-11-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Bacillus thuringiensis subsp. Israeliensis (serotype H-14) strain AM65-52	2009	30-11-05	1-11-07	2-11-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Bacillus thuringiensis subsp. Kurstaki strains ABTS 351, PB 54, SA 11, SA12 and EG 2348	2009	30-11-05	1-11-07	2-11-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Bacillus thuringiensis subsp. Tenebrionis strain NB 176 (TM 14 1)	2009	30-11-05	1-11-07	2-11-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Beauveria bassiana strains ATCC 74040 and GHA	2009	30-11-05	1-11-07	2-11-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Cydia pomonella Granulovirus (CpGV)	2009	30-11-05	1-11-07	2-11-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Lecanicillium muscarium (formerly Verticillium lecanii) strain Ve6	2009	30-11-05	1-07-07	2-07-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC

Metarhizium anisopliae var. anisopliae strain BIPESCO 5/F52	2009	30-11-05	1-07-07	2-07-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Phlebiopsis gigantea (several strains)	2009	30-11-05	1-04-07	2-04-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Pythium oligandrum M1	2009	30-11-05	1-06-07	2-06-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Streptomyces K61 (formerly S. griseoviridis)	2009	30-11-05	1-04-07	2-04-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Trichoderma asperellum (formerly T. harzianum) strains ICC012, T25 and TV1	2009	30-11-05	1-06-07	2-06-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Trichoderma atroviride (formerly T. harzianum) strains IMI 206040 and T11	2009	30-11-05	1-07-07	2-07-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Trichoderma gamsii (formerly T. viride) strain ICC080	2009	30-11-05	1-06-07	2-06-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Trichoderma harzianum strains T-22 and ITEM 908	2009	30-11-05	1-07-07	2-07-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Trichoderma polysporum strain IMI 206039	2009	30-11-05	1-10-07	2-10-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Verticillium albo-atrum (formerly Verticillium dahliae) strain WCS850	2009	30-11-05	1-07-07	2-07-07	10-07-08	11-07-08	11-07-08	1248	Directive 91/414/EEC
Candida oleophila strain O	2013	12-07-06	15-11-11	16-11-11	14-03-13	14-03-13	15-03-13	2638	Directive 91/414/EEC
Helicoverpa armigera nucleopolyhedrovirus (HearNPV)	2013	7-08-06	26-09-08	27-09-08	10-08-12	11-08-12	15-05-13	2490	Directive 91/414/EEC
Spodoptera littoralis nucleopolyhedrovirus	2013	2-01-07	26-04-09	27-04-09	10-08-12	11-08-12	15-05-13	2342	Directive 91/414/EEC
Trichoderma atroviride strain I-1237	2013	28-08-07	19-04-11	20-04-11	14-05-12	15-05-12	20-11-12	2104	Directive 91/414/EEC
Pseudomonas sp. Strain DSMZ 13134	2014	28-08-07	3-11-09	4-11-09	12-11-12	13-11-12	16-06-13	2349	Directive 91/414/EEC
Aureobasidium pullulans (strains DSM 14940 and DSM 14941)	2014	17-04-08	19-12-09	20-12-09	2-04-13	3-04-13	16-07-13	2116	Directive 91/414/EEC
Trichoderma asperellum (strain T34)	2013	22-04-09	16-05-11	17-05-11	20-04-12	21-04-12	20-11-12	1501	Directive 91/414/EEC
Bacillus firmus I-1582	2013	4-08-10	12-07-11	13-07-11	16-08-12	17-08-12	15-03-13	1154	Regulation No. 1107/2009
Streptomyces lydicus WYEC 108	2015	6-08-10	4-05-12	5-05-12	14-10-13	15-10-13	14-07-14	1609	Regulation No. 1107/2009
Bacillus amyloliquefaciens subsp. plantarum D747	2015	21-10-10	14-01-13	15-01-13	27-03-14	28-03-14	10-10-14	1623	Regulation No. 1107/2009
Bacillus pumilus QST 2808	2014	3-12-10	8-05-12	9-05-12	25-07-13	26-07-13	20-03-14	1368	Regulation No. 1107/2009
Pepino mosaic virus strain CH2 isolate 1906	2015	30-07-12	8-01-14	9-01-14	18-12-14	19-12-14	29-04-15	1103	Regulation No. 1107/2009

Trichoderma atroviride strain SC1	2016	6-11-12	27-05-14	28-05-14	20-04-15	21-04-15	19-05-16	1338	Regulation No. 1107/2009
Beauveria bassiana strain 147	2017	6-11-12	2-10-14	3-10-14	3-12-16	4-12-16	23-03-17	1673	Regulation No. 1107/2009
Beauveria bassiana strain NPP111B005	2017	6-11-12	7-10-14	8-10-14	6-12-16	7-12-16	23-03-17	1674	Regulation No. 1107/2009
Saccharomyces cerevisiae strain LAS02	2016	9-03-13	4-12-14	5-12-14	18-12-15	19-12-15	19-04-16	1215	Regulation No. 1107/2009
Bacillus amyloliquefaciens MBI 600	2016	28-06-13	5-01-15	6-01-15	4-12-15	5-12-15	12-07-16	1176	Regulation No. 1107/2009
Bacillus amyloliquefaciens strain FZB24	2017	19-06-13	13-04-15	14-04-15	6-10-16	7-10-16	23-03-17	1442	Regulation No. 1107/2009
Mild Pepino Mosaic Virus isolate VC 1	2017	2-12-13	10-11-15	11-11-15	6-12-16	7-12-16	24-01-17	1213	Regulation No. 1107/2009
Mild Pepino Mosaic Virus isolate VX 1	2017	2-12-13	10-11-15	11-11-15	6-12-16	7-12-16	24-01-17	1213	Regulation No. 1107/2009

Appendix 2: Overview of the considered active substances in the US within the reference period (2000-2017).

Actie substance	Year first registered	Submission date	Notice of application	Closing of comments	Final decision	T	Regulatory framework
Pseudomonas chlororaphis strain 63-28	2001	20-11-1998			21-12-2001	1127	Pre-PRIA
Bacillus subtilis var. amyloliquefaciens Strain FZB24	2000	8-2-1999			20-1-2000	346	Pre-PRIA
Trichoderma harzianum Rifai strain T-22	2000	7-4-1999			14-6-2000	434	Pre-PRIA
Chondrostereum purptireum isolate PFC 2139	2004	15-4-1999			20-9-2004	1985	Pre-PRIA
Metarhizium anisopliae Strain 52	2003	28-5-1999			6-6-2003	1470	Pre-PRIA
QST 713 strain of Bacillus subtilis	2000	16-6-1999			30-8-2000	441	Pre-PRIA
Coniothyrium minitans strain CON/M/91-08	2001	1-7-1999	24-6-2000	24-7-2000	1-3-2001	609	Pre-PRIA
Indian Meal Moth Granulosis Virus	2001	7-3-2000	31-8-2001	30-9-2001	21-12-2001	654	Pre-PRIA
Bacteriophage active against Xanthomonas campestris pv. vesicatoria and Pseudomonas syringae pv. Tomato	2005	19-4-2000			9-12-2005	2060	Pre-PRIA
Streptomyces lydicus strain WYEC 108	2004	27-4-2000	1-8-2000	1-9-2000	24-5-2004	1488	Pre-PRIA
Bacillus pumilus strain QST 2808	2004	31-5-2000	8-5-2002	8-6-2002	3-11-2004	1617	Pre-PRIA
Alternaria destruens Strain 059	2005	7-7-2000			5-5-2005	1763	Pre-PRIA
Pseudozyma flocculosa strain PF-A22 UL	2002	4-10-2000			27-9-2002	723	Pre-PRIA
Bacillus licheniformis SB3086	2003	29-12-2000	26-6-2002	26-7-2002	4-2-2003	767	Pre-PRIA
Bacillus Pumilus strain GB34	2001	7-5-2001	31-12-2001	30-1-2002	13-3-2003	675	Pre-PRIA
Beauveria bassiana strain 447	2002	19-9-2001			1-9-2002	347	Pre-PRIA
Puccinia thlaspeos strain woad (dyer's woad rust)	2002	14-11-2001	8-3-2002	8-4-2002	6-6-2002	204	Pre-PRIA
Verticillium isolate WCS850	2005	1-3-2002			19-10-2005	1328	Pre-PRIA
Beauveria bassiana HF23	2006	1-3-2002	7-12-2005	6-1-2006	27-12-2006	1762	Pre-PRIA
Chondrostereum purpureum strain HQ1	2005	3-9-2002	24-12-2003	23-1-2004	3-6-2005	1004	Pre-PRIA
Aspergillus flavus strain AF36	2003	14-2-2003	12-3-2003	3-7-2003	23-7-2003	159	Pre-PRIA
Paecilomyces lilacinus strain 25 1	2005	14-11-2003	14-11-2003	14-12-2003	30-3-2005	502	Pre-PRIA
Asvereillus flavusem NRRL 21882	2004	20-1-2004	14-4-2004	14-5-2004	28-5-2004	129	PRIA 1
MUSCODOR ALBUS QST 20799	2005	4-7-2004			22-2-2006	598	PRIA 1
Chenopodium ambrosioides var. ambrosioides	2008	25-2-2005	18-5-2005	18-7-2005	16-4-2008	1146	PRIA 1
Pythium oligandrum DV 74	2007	25-5-2005	27-5-2005	27-7-2005	7-5-2007	712	PRIA 1
Pantoea agglomerans strain E325; NRRL B-21856	2006	22-6-2005			11-9-2006	446	PRIA 1
Zucchini Yellow Mosaic Virus - Weak Strain	2007	28-2-2006			6-8-2007	524	PRIA 1
Colletotrichum gloeosporioides f. sp aeschynomene and	2006	8-3-2006			28-4-2006	51	PRIA 1

fermentation medium							
Trichoderma hamatumisolate 382	2010	20-2-2007	22-7-2009	22-8-2009	13-7-2010	1239	PRIA 1
Candida oleophila Strain 0	2009	28-12-2007		28-3-2008	13-5-2009	502	PRIA 1
Trichoderma asperellum (ICC 012)	2010	8-2-2008	29-10-2008	29-12-2008	4-3-2010	755	PRIA 2
Trichoderma gamsii(ICC 080)	2010	8-2-2008	29-10-2008	29-12-2008	4-3-2010	755	PRIA 2
Pasteuria usgae - BL1	2009	5-5-2008	13-8-2008	13-10-2008	2-6-2009	393	PRIA 2
Pseudomonoa Fluorescens CL145	2011	3-12-2008	16-3-2009	16-4-2009	29-7-2011	968	PRIA 2
Isaria fumosorosea strain FE 9901	2011	1-5-2009	10-5-2010	10-6-2010	8-5-2011	737	PRIA 2
Bacillus subtilis strain CX-9060	2011	30-7-2009	10-3-2010	10-4-2010	15-12-2011	868	PRIA 2
Aureobasidium pullulans strain DSM 14941	2012	18-9-2009	10-3-2010	10-4-2010	31-1-2012	865	PRIA 2
Aureobasidium pullulans strain DSM 14940	2012	18-9-2009	10-3-2010	10-4-2010	31-1-2012	865	PRIA 2
Trichoderma virens strain G-41	2012	18-9-2009	10-3-2010	9-4-2010	6-2-2012	871	PRIA 2
Chromobacterium subtsugae strain PRAA4-1T	2011	22-12-2009	3-3-2010	3-4-2010	27-9-2011	644	PRIA 2
Bacillus thuringiensis subspecies galleriea, strain SDS-502, fermentation solids, spores and insecticidal toxins	2013	1-7-2011	10-3-2010	10-4-2010	6-6-2013	706	PRIA 2
Pasteuna spp (Rotylenchulusremformisnematode)-Pr3	2012	1-7-2010	24-11-2010	24-12-2010	26-7-2012	756	PRIA 2
Pasteuria nishizawae – Pn1	2012	1-7-2010	24-11-2010	27-12-2010	28-2-2012	607	PRIA 2
Bacillus amyloliquefaciens strain D747	2011	26-7-2010	2-2-2011	2-3-2011	8-12-2011	500	PRIA 2
eat-killed Burkholderia spp. strain A396 Cells and Spent Fermentation Media	2014	1-8-2010	2-2-2011	3-3-2011	28-2-2014	1307	PRIA 2
Bacillus thuringiensis subsp. kurstaki, strain VBTS-2546	2012	1-8-2011	12-10-2011	12-11-2011	4-9-2012	400	PRIA 2
pumilus strain BU F-33	2013	1-1-2012	27-6-2012	27-7-2012	12-6-2013	528	PRIA 2
Helicoverpa zea ABA Nucleopolyhedrovirus-U	2014	1-9-2012	12-3-2013	20-5-2013	5-3-2014	550	PRIA 2
Pseudomonas fluorescens, strain D7	2014	5-10-2012			28-8-2014	692	PRIA 3
Beauveria bassiana strain ANT-03	2014	25-3-2013	11-12-2013	10-1-2014	30-3-2015	735	PRIA 3
Bacillus subtilis strain IAB/BS03	2015	7-5-2013	21-4-2015	20-2-2015	5-2-2015	639	PRIA 3
Helicoverpa armigera nucleopolyhedrovirus strain BV-0003	2015	25-10-2013	18-4-2014	19-5-2014	3-11-2015	739	PRIA 3
Spodoptera exigua multinucleopolyhedrovirus (SeMNPV) strain BV-0004	2015	25-10-2013	18-4-2014	19-5-2014	2-12-2015	768	PRIA 3
Bacillus mycoides isolate J	2016	5-3-2014	4-2-2015	6-3-2015	3-10-2016	943	PRIA 3
Muscodor albus strain SA-13	2016	21-4-2014	21-1-2015	20-2-2015	15-11-2016	939	PRIA 3
Bacillus amyloliquefaciens strain PTA-4838	2016	24-9-2014	20-7-2015	19-8-2015	24-6-2016	639	PRIA 3
Bacillus thuringiensis ssp. kurstaki strain EVB-113-19	2016	14-10-2014	20-7-2015	19-5-2015	16-6-2016	611	PRIA 3
Spodoptera frugiperda MNPV-3AP2	2016	6-5-2015	18-5-2015	24-9-2015	24-10-2016	537	PRIA 3

Phlebiopsis gigantea strain VRA 1992	2016	12-5-2015	5-8-2015	4-9-2015	18-7-2016	433	PRIA 3
Bacillus thuringiensissubsp. israelensis, Strain SUM-6218	2016	1-6-2015	4-4-2016	4-5-2016	9-11-2016	527	PRIA 3
Bacillus thuringiensis subspecies tenebrionis strain SA-10	2016	16-6-2015	17-12-2015	19-1-2016	28-10-2016	500	PRIA 3
Pseudomonas chlororaphis strain AFS009	2017	2-10-2015	18-5-2016	24-6-2016	23-6-2017	630	PRIA 3
Registration cases with missing data (not considered for timespan analysis)							
Bacillus sphaericus 2362, serotype H5a5b, strain ABTS 1743	2000						Pre-PRIA
Cydiapomonella granulovirus	2000						Pre-PRIA
Bacillus thuringiensis subsp. kurstaki strain EG7841 Lepidopteran active toxin	2002				4-9-2002		Pre-PRIA
Bacillus thuringiensis subsp. aizawai strain NB200	2005		19-9-2001		10-6-2005		PRIA 1
Bacteriophage active against zanthomonas campestris pv. Vesicatoria	2005				9-12-2005		PRIA 1
Pantoea agglomerans strain C-9-1	2006				8-9-2006		PRIA 2
Bacillus firmus strain I-1582	2008		7-3-2007	7-4-2007	28-4-2008		PRIA 2
Ulocladium oudemansii (U3 Strain)	2009		29-10-2008	29-11-2008	16-10-2009		PRIA 2
Brewer's yeast extract hydrolysate from Saccharomyces cerevisiae	2004		6-8-2003	6-9-2003	2-2-2004		PRIA 1
Bacillus thuringiensis subspecies kurstaki strain EG7841 Lepidopteran active toxin	2002				4-9-2004		Pre-PRIA
Dried fermentation solids & solubles of myrothecium verrucaria	2000				27-4-2000		Pre-PRIA

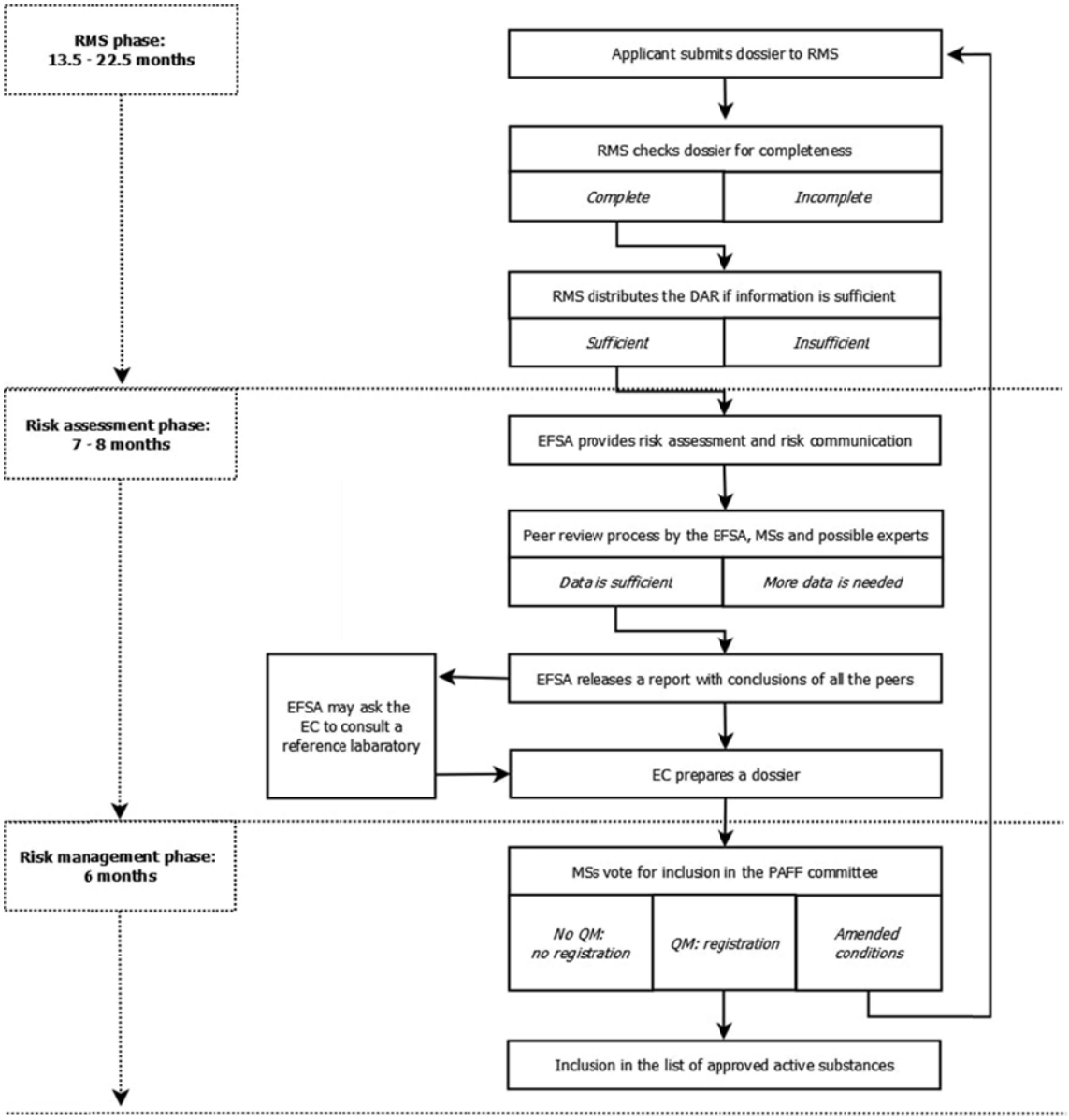

Figure 1: Regulatory framework for MBCA registration in the EU.

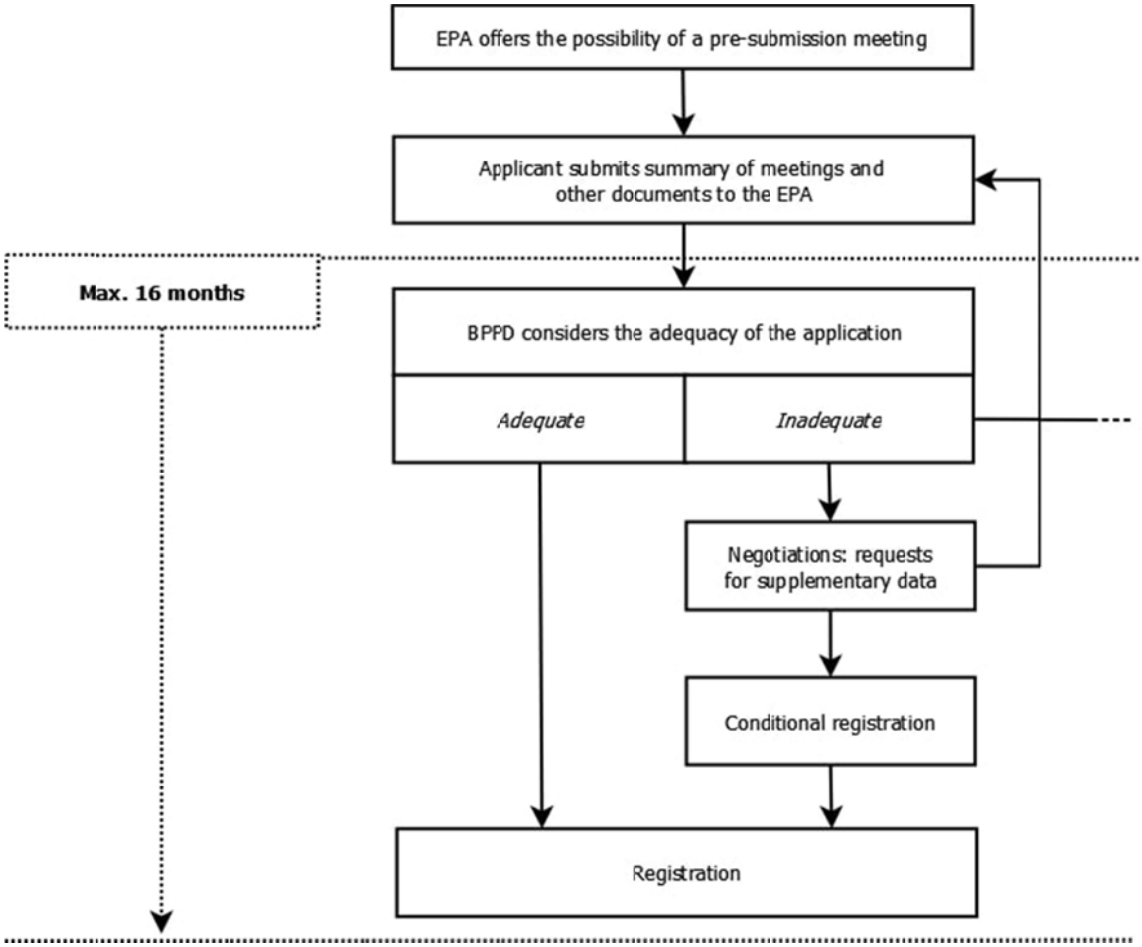

Figure 2: Regulatory framework for MBCA registration in the US.

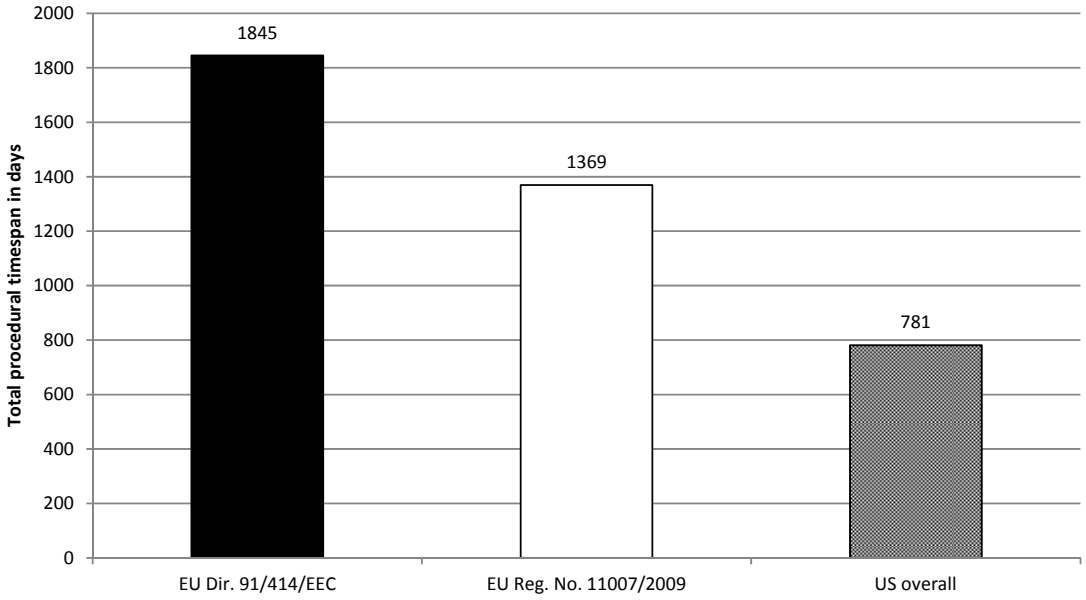

Figure 3 Average timespans in days for the US and under EU Regulation No. 1107/2009 and Directive 91/414/EEC.

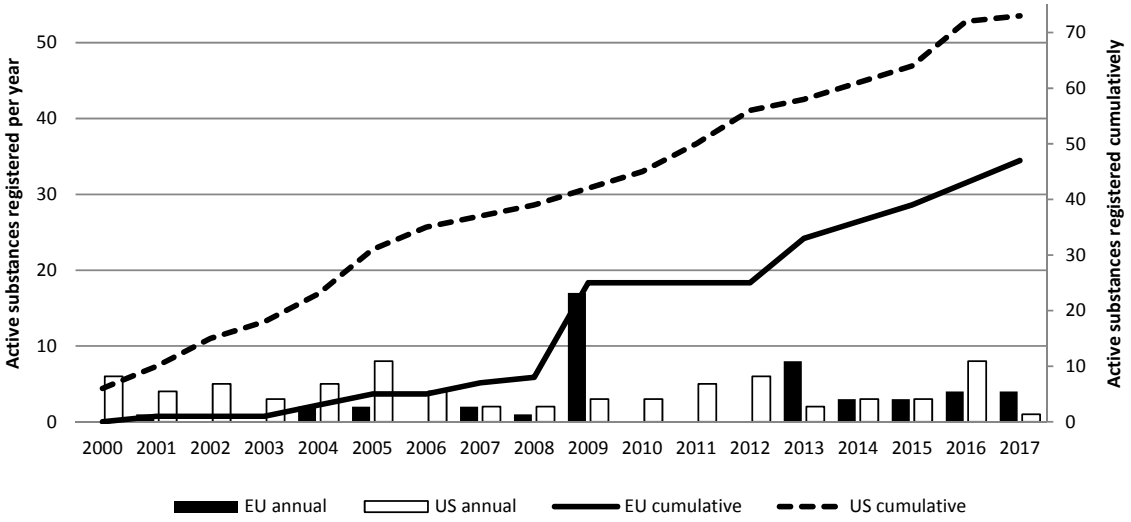

Figure 4: Annual and cumulative numbers of active substance registrations in the EU and in the US.

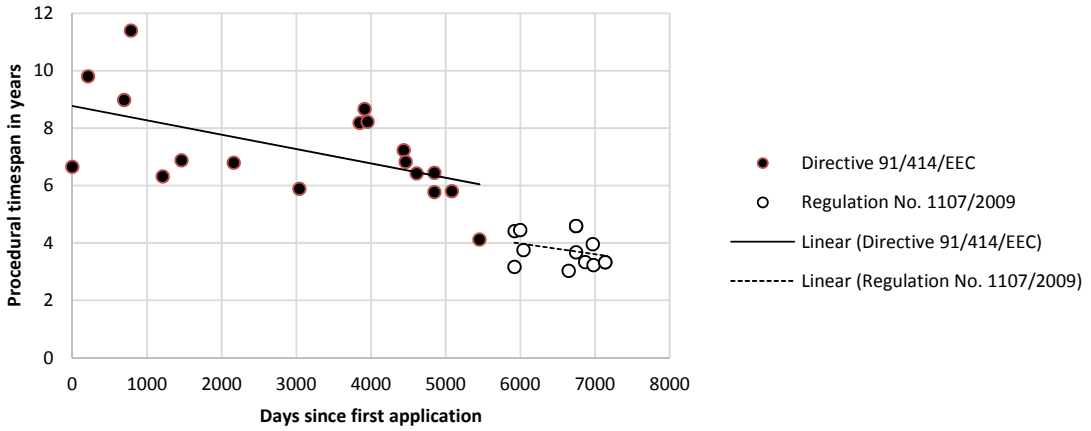

Figure 5: Procedural timespan of EU registration under Directive 91/414/EEC and Regulation No. 1107/2009 plotted against the number of days since the first application.

1107/2009 plotted against the number of days since the first application.

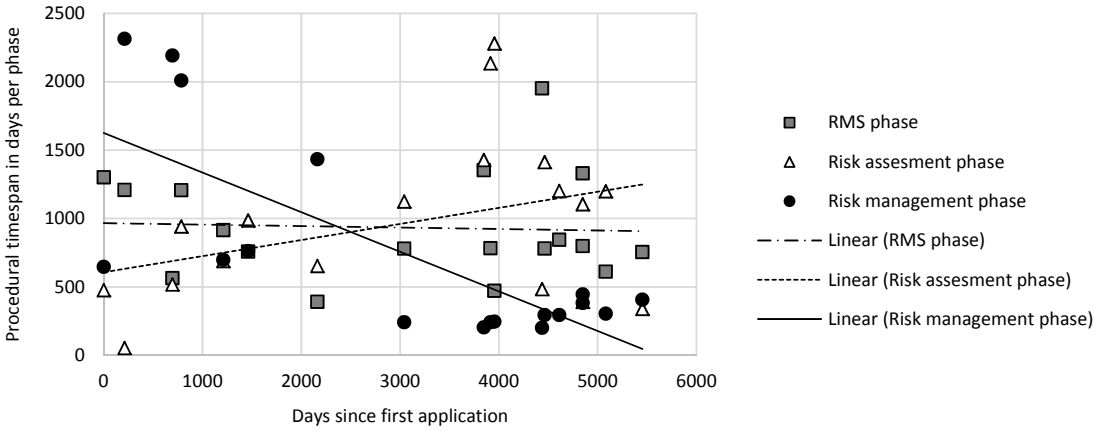

Figure 6: Procedural time span of the RMS, risk assessment and risk management phase phase in days plotted against the number of days since first the application under Directive 91/414/EC.

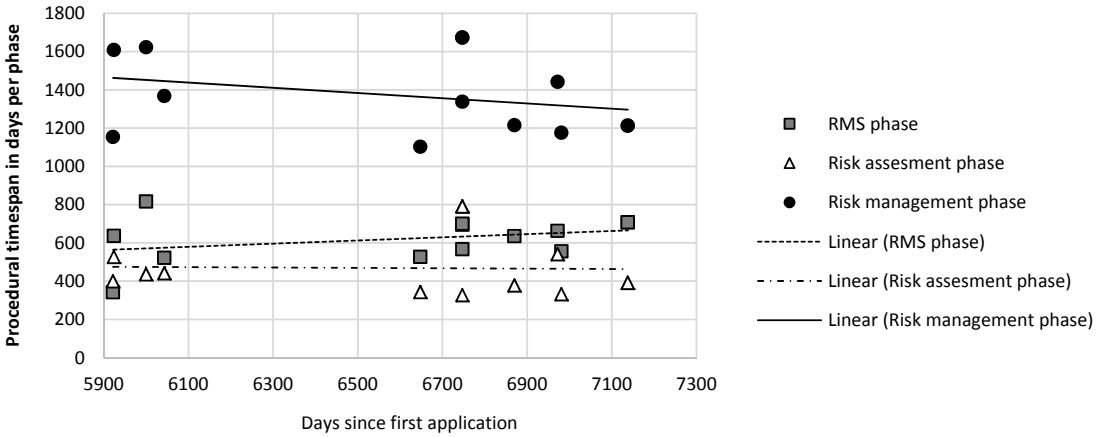

Figure 7: Procedural time span of the RMS, risk assessment and risk management phase phase in days plotted against the number of days since first the application under Regulation No. 1107/2009.

of days since the first application.

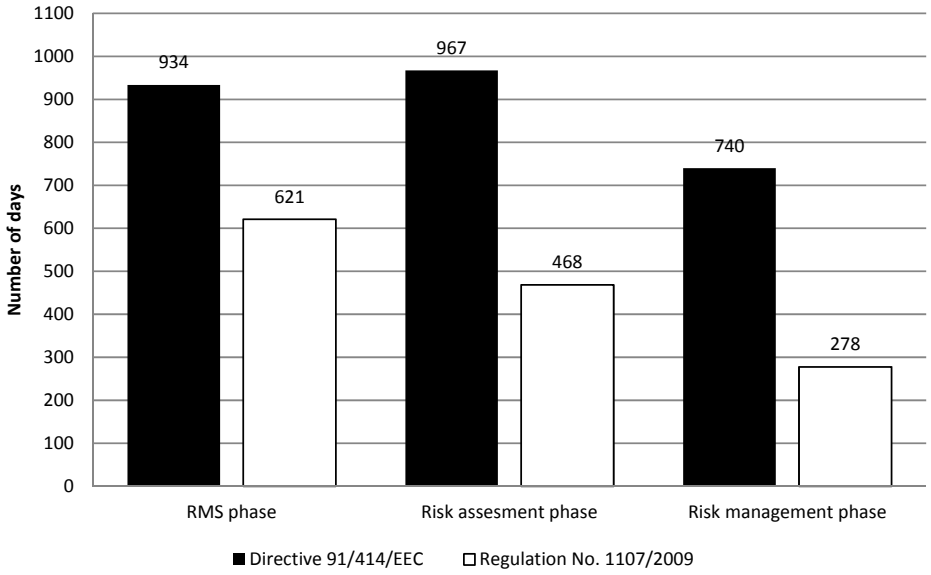

Figure 8 : Average number of days per phase of EU active substance registration under Directive 91/414/EEC and Regulation No. 1107/2009.

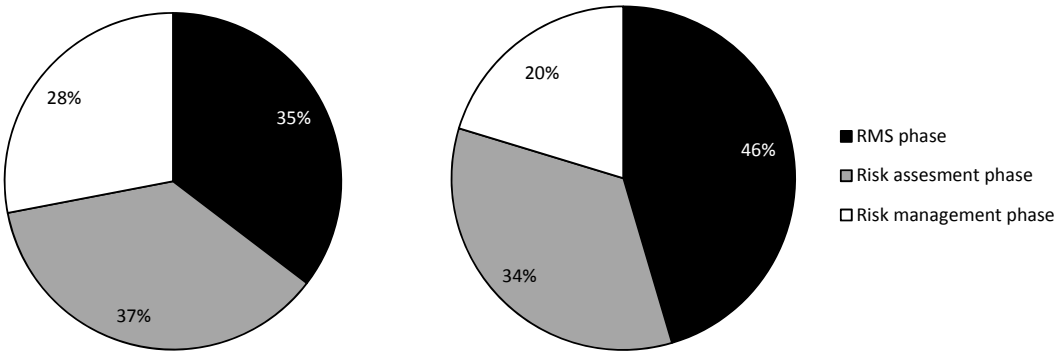

Figure 9: Relative build-up of procedural timespan for active substance registration in the EU before (left) and after (right) the implementation of Regulation No. 1107/2009.

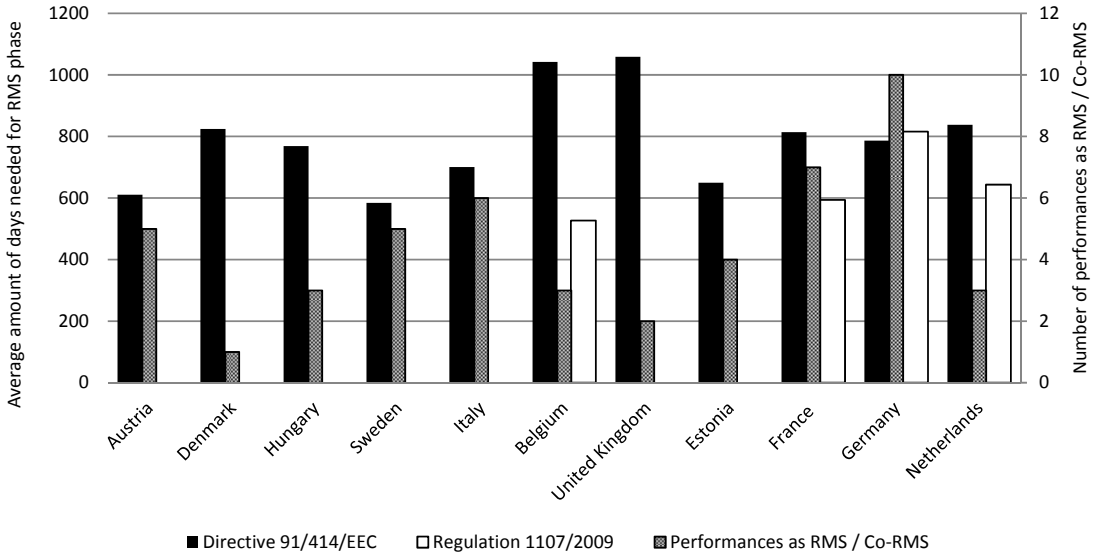

Figure 10: Number of performances as RMS per MS and the average number of days needed as RMS per MS under Directive 91/414/EEC and Regulation No. 1107/2009.

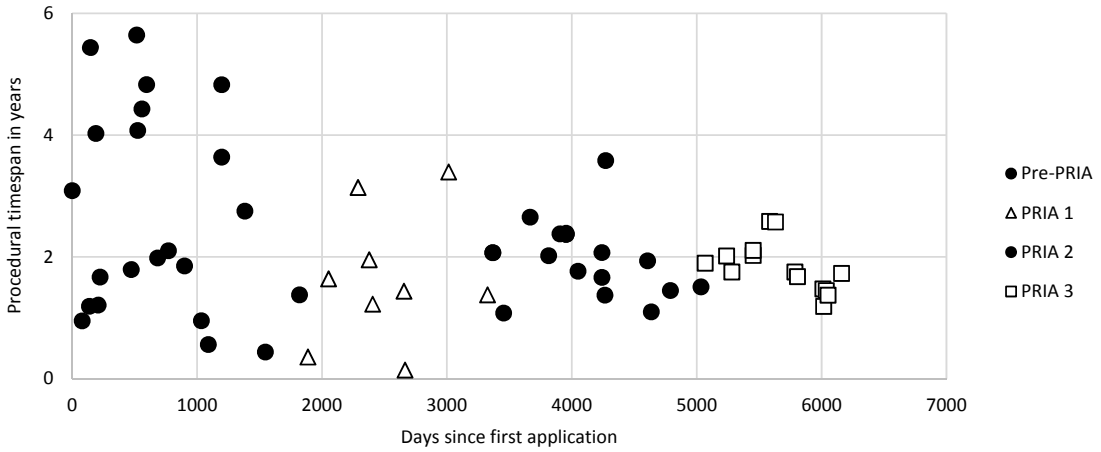

Figure 11: Procedural timespan of US registration under subsequent versions of the PRIA plotted against the number of days since the first application.

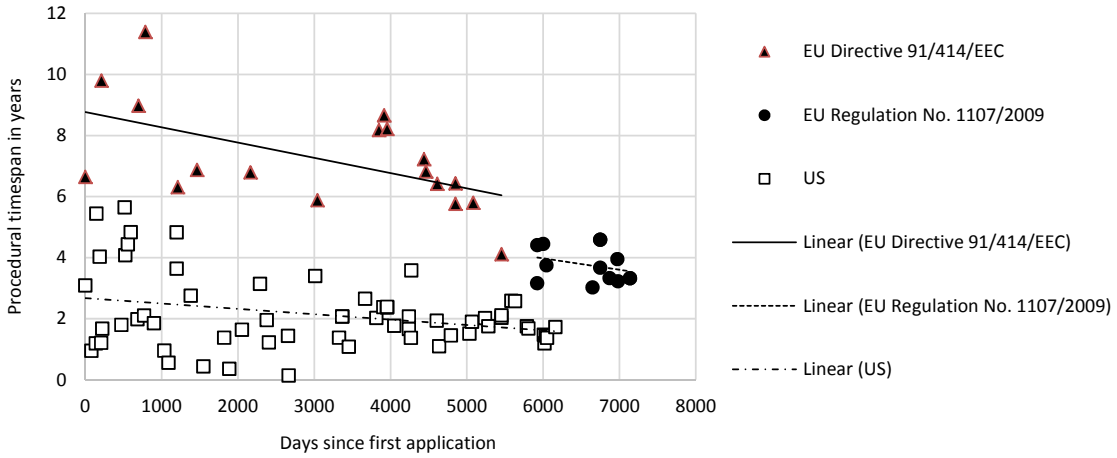

Figure 12: Procedural timespan of overall US registration and EU registration under Directive 91/41/EEC and Regulation No. 1107/2009 plotted against the number of days since the first application.

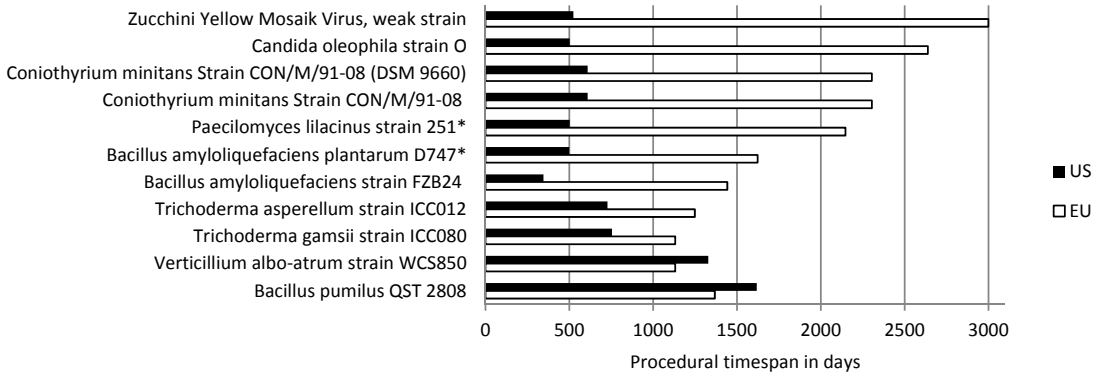

Figure 13: Comparison of timespan in days for active substances registered in both the EU and the US, cases marked with an asterisk started registration in the EU first.