COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels,
SEC(2008) 273

COMMISSION STAFF WORKING DOCUMENT

Annex to the

proposal for a Directive of the European Parliament and of the Council amending Directive 2001/82/EC and Directive 2001/83/EC as regards variations to the terms of marketing authorisations for medicinal products

IMPACT ASSESSMENT

COM(2008)123

Lead DG: ENTR; other involved services: DG SANCO, RTD, INFSO, MARKT, SG.
Agenda Planning reference: 2008/ENTR/016.

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1. PROCEDURAL ISSUES AND CONSULTATION OF INTERESTED PARTIES

1.1. Organisation and timing

This project is referenced in the Commission Agenda Planning as 2008/ENTR/016. It is also part of the Commission Simplification Rolling Programme for 2006-2009[1] and of the Commission Legislative and Work Programme 2008[2].

The impact assessment work started in 2006, through bilateral 'brainstorming' discussions with stakeholders and a targeted consultation on the basis of an Issue paper in October-December 2006 (see section 1.2.1). This was followed by a public consultation in July-September 2007 (see section 1.2.2).

A Commission inter-service steering group was established early in 2007 and met on 29 March and 27 June 2007. Commission services invited were DG SANCO, RTD, INFSO, MARKT and SG.

1.2. Consultation and expertise

There has been extensive consultation with all stakeholders on this proposal. Consultation included:

– A targeted consultation on key items for improvement of the system;

– An internet-based public consultation;

– A questionnaire for Member States competent authorities, to gather quantitative and qualitative data;

– Dedicated workshops and roundtable meetings;

– Bilateral meetings with stakeholders.

A dedicated website has also been set-up for this initiative:

http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

1.2.1. Targeted consultation

On 20 October 2006, the Commission released an Issue paper outlining key items for possible improvements of the regulatory framework on changes to the terms of marketing authorisations of medicinal products. This document was sent to all Member States permanent representations and national competent authorities, the European Medicines Agency, the Council of Europe's Directorate for the Quality of Medicines, as well as all major European industry associations.

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[1] See "Commission Working Document: First progress report on the strategy for the simplification of the regulatory environment", COM(2006) 690 final, 14.11.2006.

[2] http://ec.europa.eu/atwork/programmes/docs/clwp2008_en.pdf (see page 32)

The Issue paper was open for comments until the end of 2006. 28 contributions were received. A summary of the comments received is provided in Annex I to this Impact Assessment (section 8.1).

1.2.2. Public consultation[3]

A public consultation was conducted from 10 July to 21 September 2007. This public consultation complied with the Commission's general principles and minimum standards for consultation[4]. 19 responses were received. A summary of the comments received is provided in Annex II to this Impact Assessment (section 8.2).

1.2.3. Questionnaire

In order to gather qualitative and quantitative data, a questionnaire for Member States competent authorities (both human and veterinary side) was released, namely on the number of variations processed annually and on the type of national legislation regulating those variations. The questionnaire was released on 20 February 2007; responses were collected in March-April 2007; 25 Member States authorities (22 on the human side, 23 on the veterinary side) responded.

1.2.4. Dedicated workshops and roundtable meetings

The Commission has held a series of workshops and roundtable meetings with the various interested parties. Member States competent authorities were specifically consulted on several occasions:

– At the meeting of the Heads of Medicines Agencies on 22 February 2006 and of the Pharmaceutical Committee on 27 March 2006 (veterinary side) and 2 May 2006 (human side), the Commission announced its intention to review the regulatory framework on variations.

– The first key items for improvement of this framework were discussed at the meeting of the Heads of Medicines Agencies on 30 November 2006, as well as at the meeting of the Pharmaceutical Committee on 5 December 2006 (human side) and 20 March 2007 (veterinary side), on the basis of the Issue paper referred to in section 1.2.1.

A dedicated workshop with all the major European industry associations concerned was also held on 12 December 2006, on the basis of the Issue paper referred to in section 1.2.1.

1.2.5. Bilateral meetings with stakeholders

In addition to the means of consultation outlined above, various bilateral meetings with a number of interested parties (*e.g.* individual Member States authorities, individual pharmaceutical companies, industry associations etc.) were conducted in 2006-2007 on this project, to discuss the available policy options and their likely impact.

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[3] All results of the public consultation are available at: http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

[4] See http://ec.europa.eu/civil_society/consultation_standards/index_en.htm

1.3. Impact Assessment Board

This impact assessment was submitted to the Impact Assessment Board (IAB) on 29 October 2007 and discussed on 28 November 2007. The comments made by the IAB have been taken into account in the following way:

(1) The policy context and the precise elements of the envisaged legislative framework have been further explained. The relation between this 'co-decision' proposal and the ongoing review of the Variations Regulations at 'comitology' level[5] has been outlined in more details. The fact that the 'co-decision' proposal alone does not bring any impact as long as the Commission has not exercised its implementing powers has been clearly stated.

(2) The magnitude of the problem has been further illustrated by providing essential quantitative information. More quantitative elements in the problem description (number of variations, disparities in approval time across member states, workload and financial costs incurred by variations etc.) have been provided, together with illustrative examples. Cases of variations (improvements) to medicines which were not implemented because of a too stringent regulatory framework have also been listed.

(3) The results of the stakeholder consultation have been presented in a more integrated manner throughout the report. Quotes from all involved stakeholders, including Member States authorities and industry associations which so far have used a 'purely national' variations system, have been outlined.

[5] http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

2. PROBLEM DEFINITION

2.1. What is the issue?

Within the European Community, medicines are regulated throughout their entire lifetime. Their placing on the market cannot be made without a marketing authorisation. The requirements for granting a marketing authorisation are fully harmonised at Community level, through EU legislation[6] (timeline for evaluation, format of the application, etc.). The authorisation can be given through three main ways: the 'centralised' procedure (a single authorisation process, a single authorisation valid in the whole EU); the 'mutual recognition' procedure (one Member State acting as a reference competent authority and carrying the evaluation for the other concerned Member States); and the 'purely national' procedure (one evaluation/authorisation per Member State)[7].

Changes to medicines that are subsequent to their placing on the market, such as change in the production process, change in the packaging or change in the address of the manufacturer, are called **'variations'**. They are handled according to a specific Community legislative framework: the 'Variations Regulations'[8].

The Variations Regulations are implementing measures adopted by the 'comitology' regulatory procedure. The legal basis for these implementing measures is laid down in the EU pharmaceutical legislation[9]. However, this legal basis is currently established in such a way that it limits the scope of the Variations Regulations only to certain types of medicinal products, namely those which have been authorised under the so-called 'centralised' or 'mutual recognition' procedure. On the other hand, the current Variations Regulations do not apply to changes to marketing authorisations granted at purely national level by Member State competent authorities (hereby referred to as 'purely national' marketing authorisations, see Figure 1).

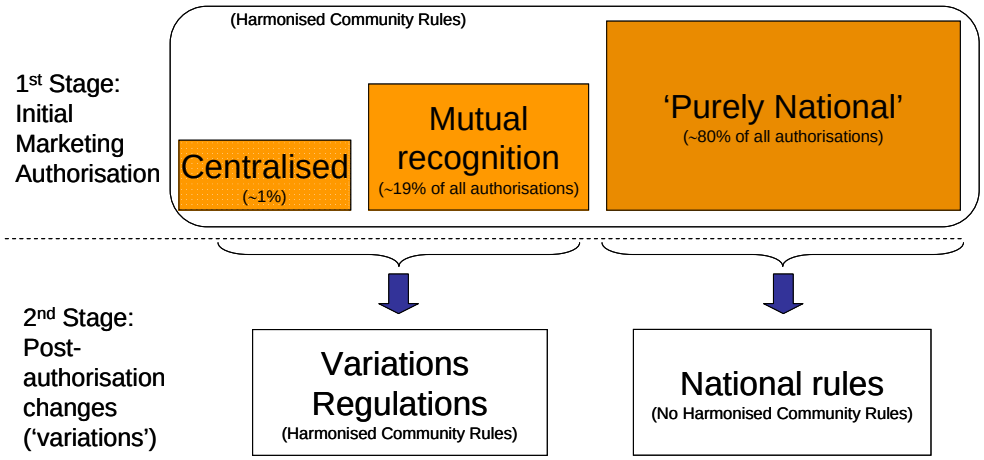

Figure 1: Current regulatory picture in the field of pharmaceuticals.

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6 Directives 2001/82/EC, 2001/83/EC, and Regulation (EC) No 726/2004.

7 Today, if a new product is to be authorised in several Member States, the mutual recognition or centralised procedure is compulsory; but the vast majority of products have been authorised at purely national level before that legal obligation was established.

8 Commission Regulation (EC) No 1084/2003 and Commission Regulation (EC) No 1085/2003.

9 Legal basis: Article 39 of Directive 2001/82/EC, Article 35 of Directive 2001/83/EC, and Articles 16 and 41 of Regulation (EC) No 726/2004.

As shown in 2, purely national marketing authorisations represent the vast majority of authorisations (more than 80%) in the European Community, both in the human sector and in the veterinary sector. Variations to purely national marketing authorisations also represent the majority of variations (more than 60% in the human sector, more than 70% in the veterinary sector).

Marketing Authorisations…	**Human sector**	**Veterinary sector**
Purely national	127936 (80.5%)	23292 (84.1%)
Mutual-recognition	30695 (19.3%)	4328 (15.6%)
Centralised	368 (0.2%)	72 (0.3%)
Total	158999	27692
Variations…	**Human sector**	**Veterinary sector**
To purely national authorisations	126167 (63.4%)	6518 (71.8%)
To mutual-recognition authorisations	72548 (36.4%)	2492 (27.5%)
To centralised authorisations	412 (0.2%)	67 (0.7%)
Total	199127	9077

Figure 2: Number of marketing authorisations and variations at the purely national, mutual recognition and centralised levels.

Data gathered with the Questionnaire referred to in section 1.2.3. Data from Norway and Iceland are also included. Data relate to the year 2006.

Although purely national authorisations are granted, like any other marketing authorisation for medicinal products within the EU, in accordance with harmonised Community requirements[10], changes to purely national authorisations are at present not subject to harmonised Community rules.

In the absence of Community harmonisation, changes affecting purely national authorisations are therefore handled according to national rules. In some Member States, national requirements on changes to purely national authorisations nevertheless follow the Variations Regulations, by analogy. But in the majority of Member States, the national rules vary from one country to the other, leading to disharmonised requirements (Figure 3): either the variations conditions are different (one change is considered as 'low risk' in one Member State but not in others), or the timelines for review of the changes vary (it takes *x* days to evaluate one change in one given Member State, *y* days in another etc.).

[10] These requirements are laid down in Directive 2001/82/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

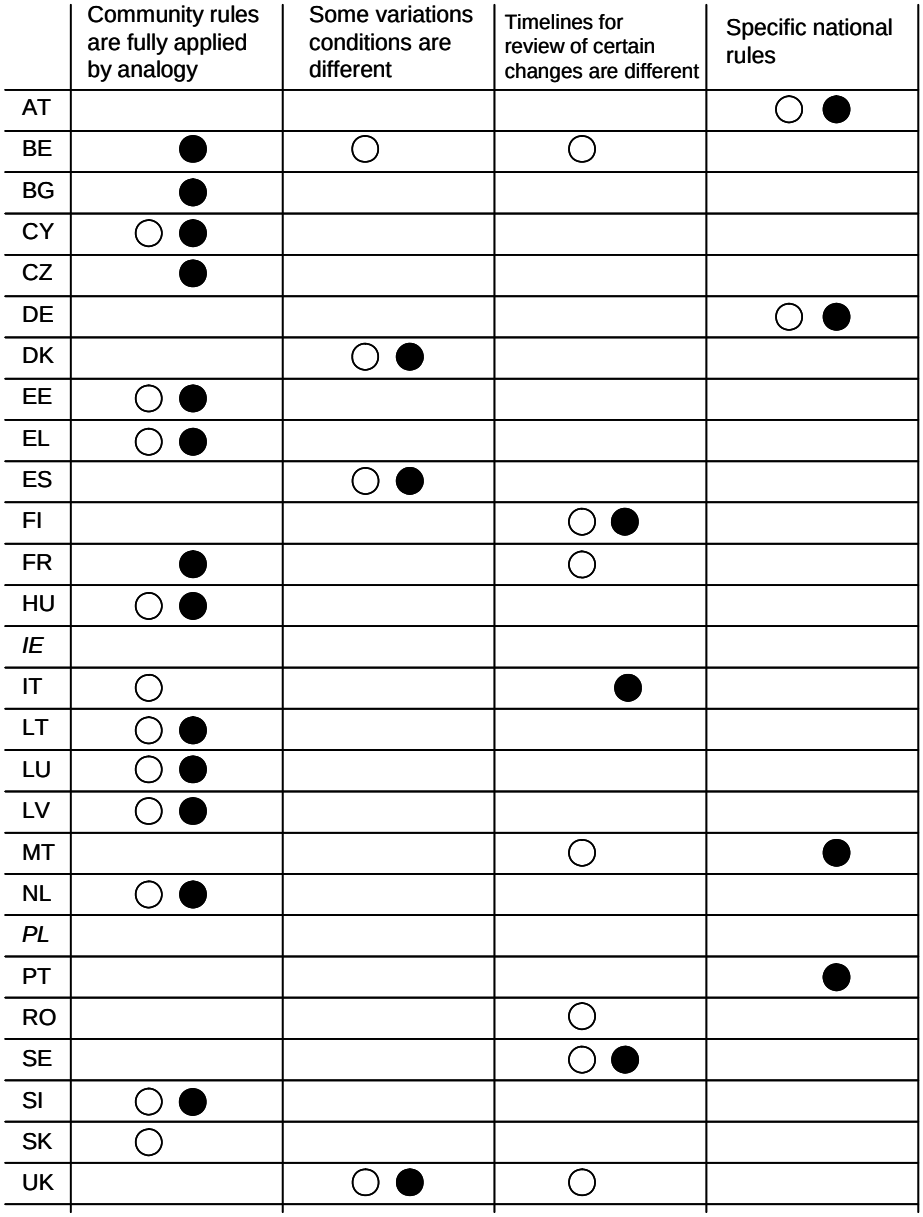

Figure 3: Rules governing variations to purely national authorisations.

● Veterinary sector ○ Human sector

Data gathered with the Questionnaire referred to in section 1.2.3; data for Ireland (IE) and Poland (PL) could not be provided.

By extracting the data for those Member States which do not fully follow the Community variations rules (Figure 3 second, third and fourth columns; human sector: AT, BE, DE, DK, ES, FI, FR, MT, RO, SE, UK; veterinary sector: AT, DE, DK, ES, FI, IT, MT, PT, SE, UK), and taking account of the distribution of variations in the various Member States (Figure 5), one can estimate that (Figure 4):

– **46% of variations affecting 55% of marketing authorisations** are not fully regulated by the harmonised Community variations requirements;

– **45% of variations affecting 44% of marketing authorisations** are not fully regulated by the harmonised Community variations requirements.

	Human sector	Veterinary sector
Purely national marketing authorisations (MAs) (AT, DE, DK, ES, FI, IT, MT, PT, SE, UK)	87095 (55%)	12064 (44%)
Total number of marketing authorisations (whole EEA)	*158999*	*27692*
Variations to purely national MAs (AT, BE, DE, DK, ES, FI, FR, MT, RO, SE, UK)	91590 (46%)	4082 (45%)
Total number of variations (whole EEA)	*199127*	*9077*

Figure 4: Number of variations and marketing authorisations which are not fully regulated by the harmonised Community variations requirements.

Data gathered with the Questionnaire referred to in section 1.2.3. Data from Norway and Iceland are also included. Data relate to the year 2006.

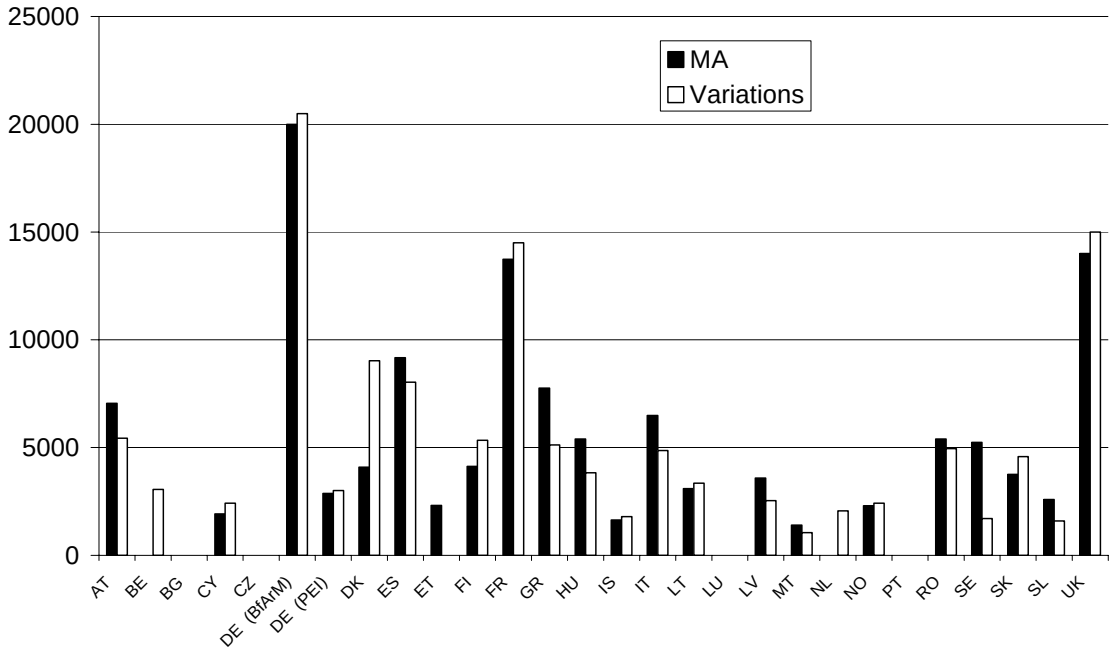

Figure 5: Distribution of purely national marketing authorisations (MA) and variations.

Data gathered with the Questionnaire referred to in section 1.2.3; the data shown here relate only to the human sector; the pattern in the veterinary sector is similar. Data for DE are separated between BfArM (Federal Institute for Drugs and Medical Devices) and the Paul Ehrlich Institute.

2.2. What are the underlying drivers of the problem?

The issue of disharmonised regulation of variations at purely national level is directly related to the legal basis of the Variations Regulations, and the way this legal basis is laid down in the EU pharmaceutical legislation. Currently, this legal basis is established in such a way that all variations to purely national marketing authorisations are excluded from the scope of the harmonised Community Variations Regulations.

The issue is all the more striking as all the other steps in the lifecycle of a medicinal product, such as evaluation of the initial marketing authorisation application, granting of the authorisation or post-marketing vigilance, do follow harmonised Community legal requirements.

As long as this legal basis is not amended and the Member States do not engage in voluntary harmonisation of their national specific rules, the issue described in section 2.1 will remain.

2.3. Who is affected, in what ways, and to what extent?

The situation of having different requirements in different Member States has negative consequences in terms of public or animal health, administrative burden and overall functioning of the internal market in pharmaceuticals.

From a health perspective, there is no justification why the scientific criteria for evaluating changes to medicines should differ from one Member State to the other. Indeed, why should a change affecting a given medicinal product be scientifically assessed in a different way, depending whether the concerned product is authorised at purely national level or not?

From a legal perspective, it also appears inconsistent that the requirements for the granting of the initial marketing authorisation are fully harmonised at Community level, while the post-authorisation requirements are not.

From a practical perspective, the current situation increases the administrative burden both for pharmaceutical companies and for Member States competent authorities. Ultimately, this is detrimental to patients.

Finally, discrepancies amongst Member States as regards purely national variations may also affect the functioning of the internal market, by hindering the free movement of medicinal products initially authorised at a purely national level but subsequently undergoing mutual recognition.

2.3.1. Effect on pharmaceutical companies

The quantity of variations submitted by companies to Member States competent authorities at purely national level is usually very high. As typical examples, the data outlined in Figure 6 show that the number of variations submitted at purely national level varies between 100 and 270 per year per company in the case of medium-sized pharmaceutical enterprises, and between 1500 and 2000 per year in the case of larger companies who have more products in their portfolio. It is also important to note that undertakings very often operate globally but on the basis of purely national

authorisations: from the information gathered during the consultation process, it appears that the vast majority of purely national marketing authorisations relate to products which are authorised in more than one Member State. Conversely, only a minority of medicines are authorised at purely national level in one single Member State.

Year	**2001**	**2002**	**2003**	**2004**
Medium-size non-generics company	172	263	146	113
Year	**2003**	**2004**	**2005**	**2006**
Medium-size (generics) company	-	161	214	200
Larger-size (generics) company	-	-	1500	2000

Figure 6: Typical number of variations processed at purely national level.

Data source: industry, human sector.

In terms of regulatory burden and fees, the typical estimate is that variations take around 50% of the workload and 60% of the fees paid by pharmaceutical companies in regulatory matters (Figure 7).

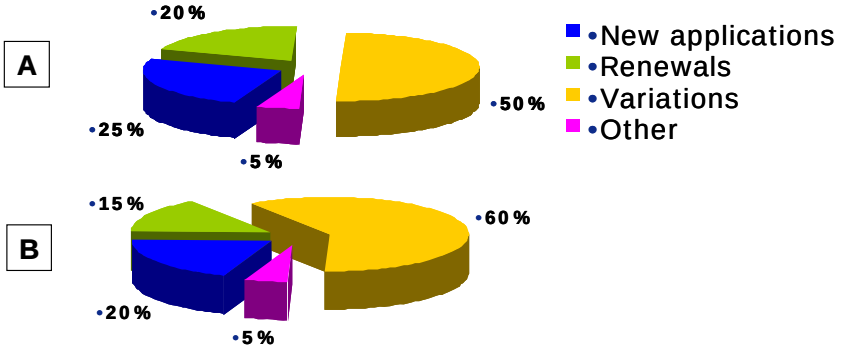

Figure 7: Typical distribution of workload and regulatory fees for pharmaceutical companies.

Data source: veterinary industry. From the data available, the pattern in the human sector appears similar. Diagram A relates to workload, diagram B relates to regulatory fees.

Different rules in different Member States also lead to different approval times in the various national markets, thereby raising complex logistical issues for the actual implementation of changes. As shown in Figure 8, the maximum approval time vary between 1 and 6 months for minor variations, 1 and 12 months for moderate variations, and 3 and 15 months for major variations. This means that companies have either to wait for the 'slowest' approval before marketing the concerned changed product, or to manage different versions of the product (changed vs. unchanged) in the various national markets.

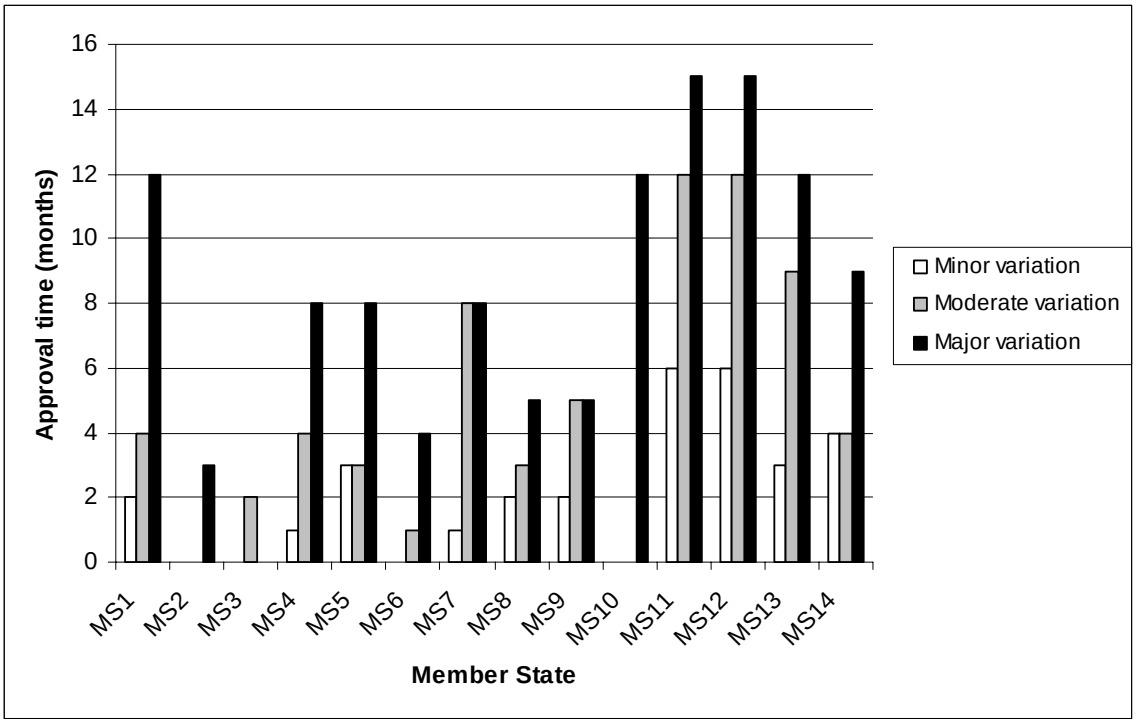

Figure 8: Variability in approval times for minor, moderate and major 'purely national' variations in a representative sample of 14 anonymised Member States.

Data source: industry.

2.3.2. Effect on Member States authorities

Because national rules can be different from Community rules as regards variations, Member States authorities may have to follow different legal requirements, depending whether they are dealing with changes to purely national authorisations or not. This is important as national competent authorities do not only have to deal with purely national marketing authorisations. In accordance with the EU pharmaceutical legislation, they also have to review marketing authorisations processed under the mutual recognition procedure. Besides, a number of Member States experts are also involved at the centralised level, evaluating medicinal products submitted to the EMEA.

From the feedback gathered during the consultation process, the vast majority of Member States authorities -including those who have a national specific system- considered in principle that there is *"no practical need for different legislation for pharmaceuticals which have been approved on a purely national basis and for those pharmaceuticals which have undergone a mutual recognition procedure or have been approved in a decentralised procedure"*[11]. The importance of amending the content of the current Variations Regulations to simplify the system was, however, also stressed:

> *"In principle, the harmonisation of the regulations for the amendment of national marketing authorisations with the EU procedures is welcomed.*

[11] Contribution to the targeted consultation; see section 8.1. This quote comes from a Member State competent authority where national specific rules are in place.

However, from our point of view, there is the need to more profoundly discuss the actual design of the intended administrative procedures laid down in the Variations Regulations. In particular, the simplification of administrative procedures should be highlighted. Proposals for an amendment of the above directives and of the Regulations No. 1085/2003 and 1084/2003 should thus be treated simultaneously – which is, as we understand it, the intention of the Commission anyway"[12].

"As it was not a legal requirement Austria has not implemented into national law the classification and time lines for variation procedures as stated in the Variations Regulation for pure national authorised products. (…) Nevertheless we agree with the concept of having a harmonised approach for maintaining a marketing authorisation independent of the licensing procedure, as long as the outcome of the reviewed Variation Regulation are simple and flexible procedures – adequate to the change"[13].

2.3.3. Effect on patients

Although patients are not directly affected by the regulatory framework on variations, data gathered through the various consultations demonstrate that different rules in different Member States generate legal uncertainty and a higher regulatory burden which can delay, impair or even prevent the introduction of certain changes, including changes which may benefit patients by improving the safety/efficacy characteristics of the concerned products.

As examples, Annex III to this Impact Assessment (section 8.3) lists changes which the industry chose not to implement due to the regulatory environment. Annex IV (section 8.4) also lists examples of changes which were implemented by the industry, but with difficulties due to the regulatory environment. Most of these changes lead to actual improvements for the patients (fewer impurities.

It should also be noted that patients and consumers' associations who responded to the public consultation were strongly in favour of further harmonisation of the rules concerning variations:

"We welcome the European Commission's initiative aimed at clarifying the legislative framework for marketing authorisation variations within the European Union. (…) Marketing authorisation procedures in the European Union are so heterogeneous that it is difficult, and sometimes impossible, for European citizens (particularly healthcare professionals and patient organizations) to understand what is going on"[14]

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12 Contribution to the public consultation; see section 8.2. This quote comes from a Member State competent authority where national specific rules are in place.

13 Contribution to the public consultation from Austria; see section 8.2.

14 Joint contribution of The Medicines in Europe Forum and The International Society of Drug Bulletins to the public consultation; see section 8.2

2.4. How would the problem evolve, all things being equal?

If nothing is done to address the harmonisation issue outlined above, the situation is likely to worsen for all stakeholders, namely Member States competent authorities and the industry. With time, national provisions will evolve and are more likely to diverge more and more than to converge. As a result, pharmaceutical companies as well as national competent authorities may be confronted with increasingly divergent, or even contradictory, regulatory requirements. On the other hand, the likelihood that different national provisions would converge with time is very low, as there is no particular mechanism or incentive in place at Community level to bring such convergence.

2.5. Does the EU have the right to act? Treaty legal basis and subsidiarity

The main legal basis of the whole Community pharmaceutical legislation is Article 95 of the Treaty establishing the European Community. The EU has the right to act in this context by adopting measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States, which have as their object the establishment and functioning of the internal market.

The subsidiarity principle applies insofar as the proposal does not fall under the exclusive competence of the Community. The proposal seeks to harmonise an area where, by definition, action of Member States alone is not sufficient to bring full harmonisation and currently leads to divergent approaches.

EU action appears as the most efficient way to achieve a genuine harmonisation and to ensure that all authorised medicinal products are subject to the same criteria for the approval, administrative handling and supervision of changes, regardless of the legal procedure under which those medicinal products have been authorised.

It is important to note that most of the purely national authorisations are related to relatively ‘old’ products which have often been authorised before the ‘centralised’ authorisation procedure was established (1995), but which are actually authorised in a large number of Community Member States (one product=one authorisation in Germany, one authorisation in Poland, one in Italy etc.). As a result, changes to these products simultaneously affect a large number of marketing authorisations in several Member States. The burden and complications caused by the current lack of harmonisation of the rules governing these changes are hence very high for industry operators.

It should also be borne in mind that the current situation increases the administrative burden for Member States competent authorities, who have to apply different rules depending whether they deal with a purely national authorisation, a mutual recognition procedure or a centralised authorisation. As a result, regulators’ resources (and industry’s, see above) are being diverted away from public or animal health protection.

Finally, the feedback gathered during the consultation phase demonstrates that the vast majority of stakeholders, including Member States authorities which have national systems in place, support harmonisation in this field.

3. OBJECTIVES

3.1. General policy objectives and operational objectives

The main policy objectives of this initiative are to achieve simplification and an equal level of patients safety through harmonisation (the operational objective), thereby ensuring that all authorised medicinal products, irrespective of their legal status, are subject to the same criteria for the evaluation, approval and administrative handling of variations (compare Figure 1 with Figure 9). In theory, this can be achieved through convergence of national legislations (*i.e.* without Community regulatory action), or through a legal proposal of the European Commission amending the legal basis of the Variations Regulations, followed by an amendment to the scope of these Regulations at comitology level.

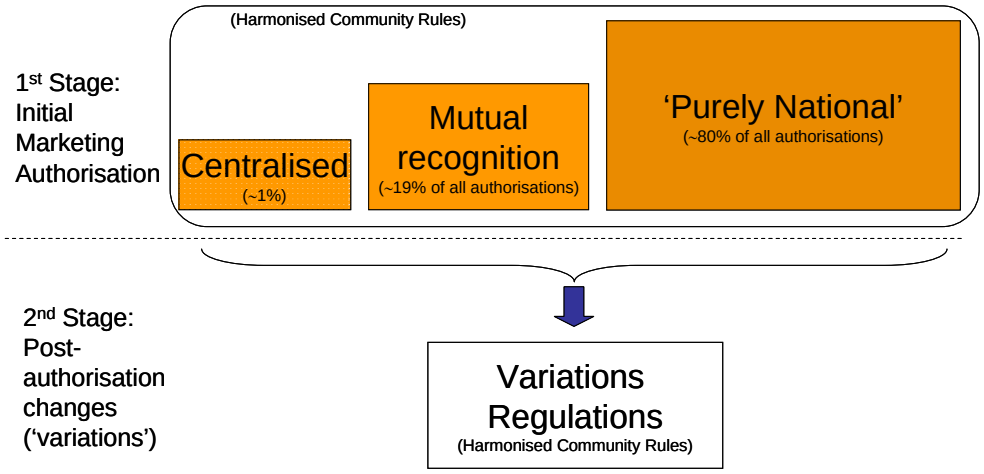

Figure 9: Goal of the initiative (regulatory harmonisation).

This initiative is part of a broader **'Better Regulation of pharmaceuticals'** project to make the system governing variations simpler, clearer and more flexible. This project requires action at two levels:

1. Harmonisation by application of the Variations Regulations to all marketing authorisations for medicinal products within the Community; and

2. Simplification of the actual *content* of the Variations Regulations, so as to reduce the administrative burden and make the system more flexible.

The proposal to which this Impact Assessment refers is of purely legal nature. It only consists of an amendment to the existing legal basis of the Variations Regulations. Alone, it therefore does not achieve the abovementioned objectives of simplification and harmonisation. It only empowers the European Commission with the legal competence to subsequently modify the scope and content of the Variations Regulations, in order to make the rules concerning variations clearer, simpler, more flexible and truly harmonised.

It is therefore important to note that this proposal alone does not affect the scope and content of the Variations Regulations, as long as the Commission has not exercised its

implementing powers by 'comitology'. Genuine harmonisation by extending the scope (point (1) above) and simplification by amending the content (point (2) above) of the Variations Regulations will therefore be achieved through a review by 'comitology' procedure, which is currently ongoing[15].

3.2. Consistency with other EU policies and horizontal objectives

The objectives outlined in section 3.1 are consistent with the overall objective of the Community pharmaceutical legislation, which is to remove disparities between national provisions in order to ensure the proper functioning of the internal market for medicinal products, while at the same time safeguarding a high level of protection of public, human and animal health. The proposal also respects Article 152(1) of the Treaty establishing the European Community, which lays down that a high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities.

4. POLICY OPTIONS

4.1. Options considered

Several policy options have been considered by the Commission when preparing its proposal.

4.1.1. Status quo

The 'status quo' option means that the scope of application of the Community Variations Regulations would remain unchanged. As a result, variations to purely national marketing authorisations (see section 2.1) would remain subject to national rules, which can differ or diverge.

The only clear benefit of the ‘status quo’ option is legal certainty. Operators (Member States authorities, regulators and pharmaceutical companies) which are used to various national rules would not have to adapt to changes to these rules.

The main drawback of the ‘status quo’ option is that it would leave the situation as it is today and hence would not address the harmonisation issue faced both by the industry and Member States. The issue is all the more important as purely national authorisations are the vast majority of authorisations, both in the human and veterinary sector.

Almost all stakeholders who contributed to the consultation process explicitly requested to avoid 'status quo' and to initiate Community action to address the issue described in section 2.1.

4.1.2. Convergence of national legislations

This option means that no regulatory action is taken at Community level. Rather, the Commission would coordinate and facilitate convergence of national legislations by

[15] http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

putting in place a Community platform to share best practices and discuss differences between these legislations.

This option would avoid ‘imposing’ harmonisation through Community regulatory action, but would require significant resources at Community level. It is likely that full harmonisation would take a long time to be established through this option, as each Member State has its own reasons to believe its national requirements and specificities are well founded. Interestingly, no stakeholder (including Member States authorities) suggested this option during the consultation phase.

4.1.3. Partial harmonisation

A 'partial harmonisation' option means that only the technical requirements would be harmonised, while procedural aspects such as the timelines for evaluation of changes would remain subject to specific national rules. For example, the risk-based classification of changes to the manufacturing process (low-risk changes *vs.* high-risk changes) and their regulatory categorisation would be harmonised at Community level, but the timing for the examination of those changes could be different from across Member States.

The main benefit of this option is that it partially addresses the harmonisation issue, establishing Community criteria for the scientific assessment of changes, while preserving flexibility for Member States authorities in the administrative handling of variations (for administrative reasons, some Member States authorities might argue they need more time than others to process one given variation). The main problem with this option is that it would not address the logistical complications that disharmonised procedures across various Member States -*e.g.* different timelines for evaluation of changes- do entail (see Figure 11).

4.1.4. Full harmonisation, no transitional period

A 'full harmonisation, no transitional period' option means that both the technical requirements and the procedural aspects would be harmonised through:

(1) a legal proposal amending the current legal basis of the Variations Regulations. This proposal would have no direct practical effect, but would be necessary to empower the Commission with the legal competence to modify the Variations Regulations by 'comitology' procedure in order to bring harmonisation;

(2) A modification of the scope and content of the Variations Regulations by 'comitology'.

This option would readily address the harmonisation issue. However, the consultation process, in particular feedback from the Member States authorities, demonstrated that a number of stakeholders have been working under national, sometimes diverging frameworks for many years already, and are actually used to these frameworks. Any proposal to modify the scope of the Variations Regulations and to bring changes to purely national authorisations within this scope should therefore take into account the workload that such a regulatory 'shift' would entail.

4.1.5. Full harmonisation, with transitional period

A 'full harmonisation, with transitional period' option is similar to the previous option above (see section 4.1.4), with the addition of a delay before the modification of the scope of the Variations Regulation by 'comitology' (indent (2) in section 4.1.4 above) is actually applied. This delay is intended to facilitate adaptation of all stakeholders to the new regulatory framework.

It should be noted that the transitional period does not come from the 'co-decision' legal proposal itself, but from the delay of application of the subsequent 'comitology' modification of the Variations Regulations.

4.2. Options discarded at an early stage

The 'status quo' and 'convergence' options (see sections 4.1.1 and 4.1.2, respectively) were discarded at an early stage, for the following reasons:

– No stakeholder supported one of these options during the consultation phase. On the contrary, a large majority of stakeholders strongly supported Community regulatory action to avoid a status quo (see quotes below);

> *"[Industry association] strongly supports the proposal to ensure harmonisation at National level of variations procedures and requirements by including national marketing authorisations into the competence of the variations regulation. This change would make the system simpler and the outcomes more predictable."*[16]

– The likelihood that coordination alone, without Community action, would ensure not only convergence but ultimately harmonisation of national legislations, is very low;

– The 'convergence' option would require significant resources at Community, as well as the political commitment of all Member States to cooperate.

5. ANALYSIS OF IMPACTS

As mentioned in section 3.1, this initiative is part of a broader 'Better Regulation' project requiring action at two levels: co-decision (this proposal) and comitology. It is important to note that an amendment to the existing legal basis of the Variations Regulations, such as what is suggested in the 'Full harmonisation' scenarios (sections 4.1.4 and 4.1.5), would alone not have any impact as long as the Commission has not exercised its implementing powers at 'comitology'. Genuine harmonisation and simplification by amending the Variations Regulations will therefore be achieved through the review by 'comitology' which is currently ongoing[17].

Because this impact assessment only relates to the first, 'co-decision' level and not to the 'comitology' level, and because the outcome of the ongoing 'comitology' review is not

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16 Contribution to the targeted consultation; see section 8.1. This quote comes from a major EU industry association.

17 http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

known yet, a detailed assessment -in particular as regards the administrative burden- cannot be done at present.

Nevertheless, a proportionate qualitative analysis of the overall project has been carried out (see below). A separate impact assessment on the 'comitology' part should enable to complete the picture and get a detailed view of the economic, competitiveness and health impact of the initiative.

5.1. Economic and competitiveness impacts

In order to compare the economic and competitiveness impact of the three options which were not discarded at an early stage (see section 4.1), three main criteria affecting the economic performance and competitiveness were listed:

– Harmonisation, *i.e.* whether the option addresses the harmonisation issue;

– Feasibility/flexibility, *i.e.* whether the option is doable for stakeholders, namely Member States authorities and companies, and leads to a system that is not too rigid;

– Simplification and impact on the regulatory burden, on the short term and long term, *i.e.* whether the option will overall lead to a reduction or to an increase of this burden, and whether the option actually leads to a simplification of the overall (Community and national) regulatory framework on variations.

The positive and negative impacts for each option have then been ranked on the basis of these criteria, using a qualitative weighing (Figure 10):

	Partial harmonisation	Full harmonisation, no transitional period	Full harmonisation, with transitional period
Harmonisation	+	+++	+++
Feasibility	+++	+	++
Regulatory burden *(short term)*	--	---	-
Regulatory burden *(long term)* and Simplification	+	+++	+++

Figure 10: Comparing the economic and competitiveness impact of the three options

5.1.1. 'Partial harmonisation'

This option would, by definition, not lead to a genuine harmonisation and therefore would not fully address the issue at stake. Lack of harmonisation regarding the timelines for evaluation of post-authorisation changes can have a very negative impact on the economic performance and competitiveness of pharmaceutical companies, especially small and medium-sized enterprises (SMEs), since if forces undertakings to manage stocks of different versions of the same product for various national markets (Figure 11; see also Figure 8 and section 2.3.1).

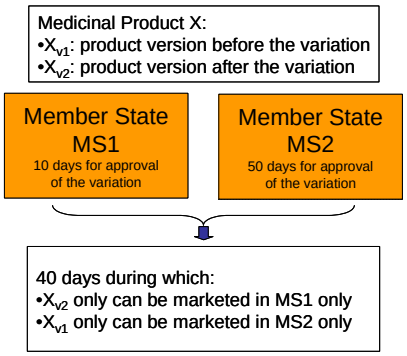

Figure 11: Impact of the 'partial harmonisation' scenario on the logistics of products.

This logistical issue of having two manage different versions of the same product for different national markets within the EU was emphasised by a number of stakeholders in the consultation process (see section 8 and the example below).

Example - Implementation of a Continuous Improvement Programme – need to maintain different processes

Data source: industry (contribution to the first round of consultation, see section 8.1)

A sterile modified release product manufactured in 2 strengths aseptically in 2 separate plants at the same manufacturing site, has been subjected to continuous improvement over a number of years as sales have consistently exceeded expectations. The product is 'mature' having been marketed for >12 years.

70 changes were logged at the manufacturing site for the year 2004, 25 of these required regulatory evaluations before implementation. submissions are required in about 40 markets (including national EU ones). Due to the regulatory process and the responses to questions asked during evaluation there are subtle differences between the data-sets registered in many markets, thus there are variants of the documentation needed to be submitted.

All submissions need to be monitored for date of submission and approval; the improvements are not implemented until approval. The approval times vary from 0 days to not yet approved after 360 days. The consequences for manufacturing are that different production 'streams' are implemented for different market groups (i.e. a pre-change and a post-change stream as a minimum), this increases stock and costs and results in slowing of the supply chain throughput.

The feasibility of the 'partial harmonisation' option is relatively high: because the degree of harmonisation is lower, Member States authorities and pharmaceutical companies would have less effort to make to adapt. Avoiding to harmonise the timelines for approval of variations also brings more flexibility for Member States regulatory authorities.

No transitional period is foreseen in the 'partial harmonisation' option. Therefore, the regulatory burden would probably increase on the short term, as all stakeholders would have to comply with the new rules readily. On the long term, however, the partial harmonisation is expected to decrease the overall burden entailed both by regulators and by the industry and lead to a relative simplification of the overall framework, since it

would remove current disparities between national requirements as regards technical aspects.

5.1.2. 'Full harmonisation, no transitional period'

The 'full harmonisation, no transitional period' scenario would fully address the harmonisation issue as it would encompass all aspects (technical and procedural) of the Variations Regulations. This is expected to have a very positive impact on the economic performance and competitiveness of pharmaceutical companies, especially those who operate in several EU national markets.

The feasibility of this option, however, is moderate since no transitional period is foreseen. In the absence of a transitional period, economic operators would have to adapt readily to the new rules. This is expected to lead to a short-term increase of the regulatory burden, especially for those Member States authorities which currently apply specific national rules. On the long term, however, the regulatory burden is expected to decrease significantly, thanks to the full harmonisation. The scenario would also lead to substantial simplification.

The importance of a limited transitional period was highlighted by a number of stakeholders in the consultation process, not only from Member States authorities but also from part of the industry (see quotes below).

> *"EFPIA/EVM/EBE consider that the transition period is an essential factor for the success of the revision of legislation on Variations as the introduction of new processes will be a major undertaking for both competent authorities, especially national competent authorities, and industry. We recommend that the duration and modalities for the implementation of the future post-authorisation changes system be discussed with both competent authorities and industry. The timeframe for this transition period should accommodate the time needed for the development of necessary documents or guidelines to support a smooth implementation while not delaying the implementation of provisions aimed at making the post-authorisation changes system simpler, clearer and more flexible."*
>
> *"[Industry association, veterinary sector] fully supports the inclusion of national Marketing Authorisations (MAs) in the scope of the new Variations Regulations. IFAH-Europe recommends that the change in co-decision is initiated in parallel to the Comitology procedure to ensure that the system is, within the shortest timeline, simultaneously implemented by all competent authorities and applied to variations procedures to all products, following a 1-year maximum transition period."*[18]

5.1.3. 'Full harmonisation, with transitional period'

The 'full harmonisation, with transitional period' scenario is equivalent to the previous one in terms of harmonisation, long-term impact on the regulatory burden and

[18] Contributions to the targeted consultation; see section 8.1. These quotes come from major EU industry associations.

simplification. However, this option appears more feasible because it provides for a transitional period that would facilitate stakeholders' adaptation. The short term increase on the regulatory burden is also expected to be less significant, albeit not negligible.

5.2. Social and environmental impacts

5.2.1. Impact on public or animal health

The three short-listed options are all expected to have a significant and positive health impact, in four ways:

– By harmonising the criteria for classification and regulatory approval of variations, all three options should avoid that different health standards are applied in different Member States. This would avoid, for example, that one change is classified and evaluated as 'low risk' in one Member State, and as 'high risk' in another. Harmonisation through extension of the scope of the Variations Regulations should ensure that equally high standards of health protection would apply in the Community;

– By harmonising the timelines for approval and administrative handling of variations, the two 'full harmonisation' options should reduce the risk that patients in some Member States have a slower access to new versions of existing products than in others. The 'partial harmonisation' option, on the other hand, is not expected to bring such benefits;

– By providing -at least partial, if not full- harmonisation, the three short-listed options bring further simplification to the overall regulatory system. This should enable pharmaceutical companies and Member States regulatory authorities to allocate less human resources to purely administrative tasks and focus more on health-related matters. It would also make the system more understandable to all stakeholders, in particular patients (see quote below);

> *"The heterogeneity of the current marketing authorization procedures preclude European citizens, namely health professionals and patient and consumer organisations, from understanding the process through which medicines' authorizations are appraised, granted and reviewed. If citizens are expected to make informed decisions in what concerns their health and their treatments, simplified and transparent procedures are key"*[19].

– Finally, harmonisation and simplification should also facilitate the introduction by pharmaceutical companies of certain variations (*e.g.* improvements in the manufacturing process) which enhance the public or animal health benefits of the affected product(s).

5.2.2. Other impacts

The three short-listed options are not expected to have major impacts other than those discussed in the above sections.

[19] Contribution from Health Action International Europe to the public consultation; see section 8.2.

5.3. Uncertainty and sensitivity analysis

In each of the three short-listed options, the proposal consists of an amendment to the legal basis of the Variations Regulations, in order to include within the scope of these Regulations all marketing authorisations for medicinal products circulating within the Community. As mentioned in section 3.1, this proposal does not affect the content of the Variations Regulations itself. For this, a review at comitology level is currently ongoing.

Therefore, the impact on simplification of the present co-decision proposal will be determined by the outcome of the review at comitology level. The effect of this proposal will be all the more positive as the 'comitology' review genuinely makes the system clearer, simpler and more flexible.

5.4. Impacts outside the European Union

With the change of legal basis of the Variations Regulations and the establishment of an EU-harmonised framework, manufacturers from third countries may find it easier and more attractive to access the European market, thus increasing competition in Europe. In addition, a harmonised EU-framework could positively influence EU companies' access to third country markets, if international convergence and mutual recognition of regulatory frameworks are actively strived for. However, the main effect of the proposal relates to EU internal harmonisation and the functioning of the internal market; the impact outside the European Union is therefore expected to be limited.

5.5. Impacts over time

In the short term, manufacturers as well as Member States competent authorities will need to adapt to the harmonised requirements. This adaptation should be very easy in countries which already apply the Community Variations Regulations by analogy (see Figure 3), but may be more difficult in the others. This may bind resources and increase the regulatory burden for a limited period of transition.

Nevertheless, in the mid to long term an increased attractiveness of the sector due to legal clarity, certainty and harmonisation should compensate and reverse all these short-term effects. In particular, a harmonised framework will increase companies' ability to expand their activities from one EU national market to the others. A harmonised framework should also facilitate the introduction of changes that improve the safety/efficacy profile of the concerned medicinal products.

5.6. Potential obstacles to compliance

In general, none of the three short-listed options is expected to cause substantial compliance issues. However, the 'full harmonisation, no transitional period' and the 'partial harmonisation' options may be more difficult to implement, in the short term, in those Member States which have a very specific national system in place (AT and DE in particular; see Figure 3). This emphasises:

– The need for an appropriate transitional period; and

– The importance of the outcome of the review conducted at comitology level (see section 5.3).

These two points were explicitly stressed by certain Member States during the consultation process, and to a lesser extent by some industry associations (see section 8).

6. COMPARING THE OPTIONS

6.1. Weighing of the impacts and results

All aspects analysed in section 5 were weighed in a qualitative way. Figure 12 summarises the results discussed in section 5.

		Partial harmonisation	Full harmonisation, no transitional period	Full harmonisation, with transitional period
Economic and competitiveness Impact	Harmonisation	+	+++	+++
	Feasibility	+++	+	++
	Regulatory burden *(short term)*	--	---	-
	Regulatory burden *(long term)* and Simplification	+	+++	+++
Public Health Impact	Avoid double public health standards	+++	+++	+++
	Ensure equal patients access to products	+	+++	+++
	Focus resources on public health issues	+++	+++	+++
	Facilitate introduction of changes	++	+++	+++
	Uncertainty/sensitivity Influence of the 'comitology' review	moderate	important	important
	Obstacles to compliance	May be significant in some Member States (AT/DE)	May be significant in some Member States (AT/DE)	ok
	Preferred option	✘	✘	✓

Figure 12: Weighing of the three short-listed options.

From an economic and competitiveness perspective, the 'partial harmonisation' option would not bring the intended benefits of genuine harmonisation. It could even worsen the situation by maintaining or raising additional logistical complications (see section 5.1.1). No industry stakeholder advocated this option during the consultation phase (see section 8). The 'full harmonisation, no transitional period' option would be positive on the long term, but the short-term difficulties caused by the absence of a transitional period could have a very negative impact, especially on SMEs due to lack of resources in regulatory affairs. Interestingly, both Member State authorities and industry associations requested, during the consultation phase, to introduce a transitional period (see section 8).

From a health perspective, the three short-listed options would be expected to have a positive impact. The only drawback relates to the 'partial harmonisation' scenario, which

may lead to inequalities in terms of patients' access to treatments amongst Member States.

Finally, the importance of the review of the content of the Variations Regulations, which is currently ongoing, is particularly high in the case of the two 'full harmonisation' options. This importance was particularly stressed during the public consultation phase, both by Member States authorities and by certain industry associations. The review at 'comitology' level should therefore be conducted with caution, in consultation with all interested parties, in order to fully realise the benefits of a 'full harmonisation' scenario.

On the basis of the above analysis, the ‘full harmonisation, with transitional period’ option was preferred as the most balanced approach to achieve the intended objective (genuine harmonisation), while facilitating stakeholders’ adaptation to the system. It is also the option preferred by the majority of stakeholders who contributed to the consultation process.

6.2. Highlight trade-offs and synergies

There is a trade-off between the objective to be achieved, *i.e.* genuine regulatory harmonisation, and the need to provide sufficient time to operators to adapt to the new rules. This is one of the reasons why the option ‘full harmonisation, with transitional period’ was considered more appropriate. The suggested duration of the transitional period in the Commission proposal is one year. A few interested parties proposed, during the public consultation, to extend this period to *e.g.* two years. On the other hand, this proposal was not advocated by the majority of stakeholders, which put more emphasis on the need to bring harmonisation as soon as possible. The suggestion to wait until the review at 'comitology' level has been successfully completed before launching this proposal (this suggestion was made by one industry stakeholder, see section 8.2) was also rejected for similar reasons, as it would delay harmonisation by several years.

There is also a trade-off between the benefits of full harmonisation and the disadvantage for companies of losing a purely national system which might offer some positive aspects that an EU system does not have. For instance, certain industry associations outlined in the public consultation their acceptance of the EU-wide harmonisation through this legal proposal *"if, and only if, the revised variation system does not jeopardise the current well-functioning variation system in place in some Member States"* (see section 8.2). On the other hand, a number of operators (industry associations but also other stakeholders) claimed that overall, the benefits of an EU-wide harmonisation would be more important.

Finally, there is potential synergy between this proposal and the ongoing review, at comitology level, of the content of the Variations Regulations (see also sections 5.3 and 6.1). This review is expected to further simplify the procedures for evaluating post-authorisation changes to medicinal products.

7. MONITORING AND EVALUATION

7.1. Monitoring indicators

As the proposal only consists in an amendment to the legal basis of the Variations Regulations, the first parameter to monitor will be the actual implementation in the

Member States which do not already apply the Variations Regulations by analogy. This can be checked through the regular and frequent meetings of Member States authorities with the Commission (*e.g.* meetings of the Pharmaceutical Committees, of the Heads of Agencies, of the Coordination Groups for Mutual Recognition and Decentralised Procedures (CMD(v), etc.).

Other monitoring parameters may be considered, such as:

– the number of written requests/complaints from pharmaceutical companies on the application of the Variations Regulations at purely national level;

– the number of variations applications submitted and authorised at purely national level (although this parameter does not only depend on the regulatory framework and its harmonisation).

All the above data should provide a robust *ex-post* picture of the impact of the proposal.

7.2. Arrangements for ex-post evaluation

As mentioned in section 7.1, the Commission and Member States competent authorities meet regularly. They will thus have ample and regular opportunities to monitor the impact of the harmonisation of the Variations regulatory framework. No additional arrangements beyond those already in place in the pharmaceutical area are therefore proposed.

7.3. Other points raised during the consultation process

Two technical points, which are not addressed in the above sections, were raised during the consultation process (see section 8):

– Certain medicinal products, namely traditional herbal medicinal products and homeopathic medicinal products, are not covered by the standard marketing authorisation procedure but can be approved, under certain conditions, through a simplified registration procedure[20]. The question was raised during the consultation whether changes to such registrations should be included within the scope of this harmonising proposal. Since the initial, simplified registration system is by definition a lighter system than the standard marketing authorisation procedure, it would appear disproportionate to subject post-approval changes to registrations to the same stringent rules as variations to marketing authorisations. Besides, no stakeholder but one raised this issue. For these reasons, the suggestion to include changes to simplified registrations within the scope of this proposal was not followed.

– One stakeholder requested to use the opportunity of modifying Directive 2001/83/EC in order to amend the general definition of a medicinal product. This proposal was rejected, as such an amendment is not necessary to achieve the intended objectives outlined in section 3.1. and would require a separate legislative proposal on its own.

[20] See Articles 13 and 16a of Directive 2001/83/EC and Article 16 of Directive 2001/82/EC.

8. ANNEXES

8.1. Annex I: summary of the targeted consultation

This section summarises the contributions made by stakeholders to DG Enterprise and Industry's targeted consultation on variations conducted in October-December 2006. It also refers to comments provided in the framework of several stakeholders meetings held in the meantime:

– 30 November 2006: meeting of the Heads of Medicines Agencies;

– 5 December 2006: meeting of the Pharmaceutical Committee (human side);

– 12 December 2006: workshop with all major European industry associations.

Stakeholders were invited to express their position on the basis of an Issue paper outlining key items for improvements[21].

Contributors

The Commission received **28 contributions**. Many of them, in particular the ones from the industry, are the results of wider consultation. The participants can be divided into 2 categories:

Industry:

- AESGP - Association of the European Self-Medication Industry
- APIC - Active Pharmaceutical Ingredients Committee
- EFPIA - European Federation of Pharmaceutical Industries and Associations, including:
    - EBE - European Biopharmaceutical Enterprises
    - EVM - European Vaccines Manufacturers Association
- EGA - European Generic Medicines Association
- EGGVP - European Group for Generic Veterinary Products
- Europabio - European Association for BioIndustries
- IFAH-Europe - International Federation for Animal Health - Europe
- Leem - "Les Entreprises du médicament", French association of the pharmaceutical industry
- IPFA - International Plasma Fractionation Association
- PPTA- Plasma Protein Therapeutics Association
- PhRMA - The Pharmaceutical Research and Manufacturers of America
- Pharmagal Bio Ltd, Slovak Republic

Regulatory authorities (national, Community or international):

- AFMPS - Belgian Federal Agency for Medicines and HealthCare products
- AGES - Austrian Agency for Health and Food Safety

[21] See http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

– Paul Ehrlich Institut (Germany)
– DKMA - Danish Medicines Agency
– France, including the AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé)
– IMB – Irish Medicines Board
– The Netherlands – Medicines Evaluation Board, human and veterinary, and Ministry of Public Health, Welfare and Sport, Ministry of Agricultural Affairs
– Poland - The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
– MPA - Sweden's Medical Products Agency
– INFARMED - Portugal's National Authority of Medicines and Health Products
– MHRA – UK Medicines and Healthcare Products Regulatory Agency
– European Pharmacopoeia Department, Council of Europe
– European Medicines Agency (EMEA)

All contributions received provided valuable information for the Commission's further action in this field.

Summary of contributions

Note: The scope of the Issue paper on which this targeted consultation was based was broader than the sole issue of regulatory harmonisation and inclusion of changes to purely national variations (key item 1 in the Issue paper). This subsection only summarises stakeholders' comments on this 'key item 1'.

The vast majority of stakeholders welcomed the initiative and the overall goal to make rules governing post-authorisation changes to medicines simpler, clearer and more flexible, without compromising human and animal health. The proposal from the Commission to submit a legal proposal bringing further harmonisation was broadly supported. Conversely, no stakeholder considered that the issue could be addressed without such a proposal.

The principle of common harmonised rules for changes to all types of medicines, irrespective of their legal status and therefore including changes to 'purely national' marketing authorisations, was supported by the vast majority of industry stakeholders. Some highlighted the importance to ensure such harmonisation at the earliest opportunity, especially in the field of veterinary medicines. Other industry stakeholders stressed that harmonisation should not me misused to introduce additional and superfluous requirements at Community level. Two industry associations, while supportive of the principle, considered that harmonisation and inclusion of changes to purely national authorisations should be implemented only once the content of the Variations Regulations has been simplified.

Harmonisation was also favourably welcomed by regulatory authorities. The vast majority stressed the value of proceeding under the same rules, whatever the legal status of products. Certain Member States, however, highlighted the importance of timing and the need for a transitional period, in order to facilitate adaptation to the new rules and ensure a smooth transition. Finally, one authority raised the issue of inclusion, within the scope of the Variations Regulations, of traditional herbal medicinal products registered under the simplified registration procedure provided in Directive 2001/83/EC.

8.2. Annex II: summary of the public consultation

This section summarises the contributions made by stakeholders to DG Enterprise and Industry's public consultation on variations conducted in July-September 2007. This public consultation complied with the Commission's general principles and minimum standards for consultation[22].

Stakeholders were invited to express their position on the basis of a draft Directive, including draft articles, recitals and explanatory memorandum[23].

Contributors

The Commission received **19 contributions**. Many of them, in particular the ones from the industry, are the results of wider consultation. The participants can be divided into 3 categories: industry, national authorities, and other stakeholders.

Industry (associations or individual companies):

- AESGP - Association of the European Self-Medication Industry
- APIC - Active Pharmaceutical Ingredients Committee
- BPI – German Pharmaceutical Industry Association and VFA -Verband Forschender Arzneimittelhersteller
- EFPIA - European Federation of Pharmaceutical Industries and Associations, including:
    - EBE - European Biopharmaceutical Enterprises
    - EVM - European Vaccines Manufacturers Association
- EGA - European Generic Medicines Association
- IFAH-Europe - International Federation for Animal Health - Europe
- IPFA - International Plasma Fractionation Association
- MSD – Merck Sharp & Dohme (Europe) Inc., an affiliate of Merck & Co., Inc. (USA).
- PhRMA - The Pharmaceutical Research and Manufacturers of America
- Norgine – Individual European pharmaceutical company

National Regulatory authorities:

- AFMPS - Belgian Federal Agency for Medicines and HealthCare products
- AGES - Austrian Agency for Health and Food Safety
- France – French Ministry of Health
- France - AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé)
- Malta - Ministry Of Health, The Elderly And Community Care
- The Netherlands – Medicines Evaluation Board
- UK - MHRA Medicines and Healthcare Products Regulatory Agency

Other stakeholders:

- HAI – Health Action International Europe

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22 See http://ec.europa.eu/civil_society/consultation_standards/index_en.htm

23 http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

– The Medicines in Europe Forum and The International Society of Drug Bulletins (joint contribution)

All contributions received provided valuable information for the Commission's further action in this field.

Summary of contributions

Generally speaking, the comments received were highly similar to those gathered during the targeted consultation (see section 8.1).

First, the principle of harmonised rules for changes to all types of medicines, irrespective of their legal status and therefore including changes to 'purely national' marketing authorisations, was supported by the vast majority of stakeholders. The proposal was generally welcomed as *'a major step forward'*.

Several stakeholders, from the industry and from the national authorities, highlighted the importance of the transitional period as an essential factor for the success of the revision of the Variations Regulations. Certain contributions requested a longer period than only one year (*e.g.* two years); on the other hand, other stakeholders recommended that the timeframe for this transition period should accommodate the time needed for the development of necessary documents or guidelines to support a smooth implementation, while not delaying the achievement of harmonisation unnecessarily.

On substance, a number of stakeholders agreed to the proposal, but on the condition that the content of the Variations Regulations (which is to be amended by 'comitology') is first reviewed and simplified. Some contributions stressed that harmonisation in itself would be genuinely beneficial only insofar as the Variations Regulations would not add unnecessary requirements at national level. The process advocated by these stakeholders was therefore:

Reform of the substance of the Variations Regulations (comitology);

(3) Harmonisation to purely national authorisations (this proposal).

One contribution requested that step (2) (this proposal) is carried out only once the system has proven its superiority over existing national rules in a period of several years. One Member State national authority also highlighted that the benefits of national 'better regulation' initiatives which are currently being carried out should be preserved with harmonising Community legislation. Another authority recalled the quantity of variations processed at purely national level compared to centralised/mutual recognition, and stressed that this parameter should be taken into account.

Finally, other stakeholders took the opportunity of this public consultation to raise the broader issue of harmonisation and transparency of the whole European regulatory framework for approving new drugs and indications. One industry stakeholder also requested the Commission to use this proposal to amend further Directive 2001/83/EC as regards the definition of a medicinal product.

8.3. Annex III: Examples of changes (improvements) to medicinal products which industry chose not to implement due to the regulatory environment

Example No	Nature of the change	Reason for change .	Affect of Change on process and/or product	Effect the change was intended to have had	Reason for not implementing the change	Other information
1	Analytical Method Change - Modernization of impurity method to implement new improved technologies	New technology providing increased selectivity and detection	No effect on product or process. Improved assurance of impurity levels	Increased assurance of high quality of final product	Timing of receiving worldwide approvals would cause undue delay in implementing change	Improved assurance of high quality of product blocked by regulatory burden
2	Stopper Change	Supply Consistency; Manufacturability; Patient Convenience	Final product	Increased assurance of high quality of final product	Timing of receiving worldwide approvals would cause undue delay in implementing change	Improved assurance of high quality of product blocked by regulatory burden
3	manuf process drug product	efficiency / flexibility	no	none	costs	Not submitted. Efficiency improvement blocked due to high regulatory costs.
4	Process change	increase homogeneity	process and final product	increase homogeneity, tighten specs	different requirements and approval times would result in too many	Improved assurance of high quality of product blocked by regulatory burdens

Example No	Nature of the change	Reason for change .	Affect of Change on process and/or product	Effect the change was intended to have had	Reason for not implementing the change	Other information
					presentations	
5	change to tighter packaging material	improve stability, harmonize packaging	product stability	better or unchanged stability	new stability data required , despite already superior packaging material, too many submissions necessary	Improved assurance of high quality of product blocked by regulatory burdens
6	change in analytical methods	improve selectivity and shorten process	none		300 registrations are affected, regulatory effort too high	Efficiency improvements blocked due to regulatory burden

Data source: industry

8.4. Annex IV: Examples of changes (improvements) to medicinal products which were implemented with difficulties due to the regulatory environment

Example No	Nature of the change	Effect of the change	# submissions required globally	Time span for approval of all submissions	Other information (including estimated costs)
1	Manufacturing Site Change	Reduced risk to contamination from cytotoxic products	20	Up to 24 Months	Potential improved patient safety delayed until approvals were obtained.
2	packaging finished product	better closing	± 75	4 months in EU; > 6 -12 months for export countries	Euro 75000 Problem could not be solved completely for 6 months while waiting for approvals.
3	manufacturing site of the finished product	-	± 90	6-12 months in EU; 6-24 months in export countries	90,000 Euros
4	change of manufacturing site	-	237	30 days to 3 years	ongoing / 4 strengths
5	shelf-life extension	-	206	30 days to 3 years	ongoing / 3 strengths
6	test method FP	-	130	0-24 months in EU, 6-24 months in Export countries	about 130.000 Euro
7	manuf site finished product	-	99	5-24 months	90.000 Euro
8	Extend Expiry Dating	Increased flexibility with managing supply across the world	60	12 Months	Different expiry dates for different countries had to be managed.

Data source: industry