Revision of the Variation Regulations

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

Industry-Proposals and Consultation Paper from the European Commission,

Impact on Industry and Health Authorities

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1. List of Abbreviations

AESGP	Association of European Self-Medication Industry
ANDA	Abbreviated new drug application
APIC	Active Pharmaceutical Ingredients Committee
BACPAC	Bulk Actives Post Approval Changes
BAH	Bundesverband der Arzneimittel-Hersteller, Germany
BLA	Biologics License Application
CAMP	Consortium for the Advancement of Manufacturing of Pharmaceuticals (Board members: Abbott, Bristol Myers Squibb, Glaxo Smith Kline, Johnson & Johnson, Wyeth)
CAPA	Corrective And Preventing Action
CBE	Change being effected
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	Chemistry Manufacturing and Control
CMD (h) or (v)	Coordination Group for Mutual Recognition and Decentralised Procedures (human) or (veterinary)
CP	Centralised Procedure
cGMP	Current Good Manufacturing Practice
GMP	Good Manufacturing Practice
CMS	Concerned Member State
Commission NTA WP	European Union Commission Notice to Applicants Working Party
CTD	Common Technical Document
DCP	Decentralised Procedure
EDQM	European Directorate of Medicines
EBE	European Biopharmaceutical Enterprises
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generics Medicines Association
EMEA	European Medicines Agency
EVM	European Vaccine Manufacturers
EU	European Union
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
ISPE	International society for technical professionals in the health care manufacturing industry
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder

MR	Mutual Recognition
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual recognition procedure
NTA WP	Notice to Applicants Working Party
NDA	New drug application
ONDC	Office of New Drug Chemistry
ONDQA	Office of New Drug Quality Assessment
PACPAC	Packaging and Post-approval Changes
PAT	Process Analytical Technology
PDUFA	Prescription Drug User Fee Act
PhRMA	Pharmaceutical Research and Manufacturers of America
PL	Package leaflet
RMS	Reference Member State
SPC	Summary of product characteristics
SUPAC	Scale up and Post-approval Change

2. Introduction

During the life cycle of medicinal products for human use the documentation, which has been submitted to the health authority and which is the basis of the marketing authorisation, will be changed by the submission of variations. These variations can be adjustments to the state of the art in science, in technology and in knowledge or they might become necessary because of up-scaling of the production or furthermore due to economical decisions such as additions of production facilities or the change of the supplier of the active ingredient. (1)

In the last 20 years the pharmaceutical industry has evolved through mergers and acquisitions from many smaller and local companies to larger global companies and from facilities supplying local or regional markets to fewer strategic facilities supplying the global market. (2)

International operating companies serving many markets and regions are confronted with the following situation: The number and diversity of Variation Regulations to be followed is high. For a change the regulations of each specific country have to be followed. The requirements to the regulatory filing and the procedures differ throughout the world. Until a certain change is approved and can be implemented varies considerably from country to country. (2) Thus the planning when a change can be realised is highly challenging even for the European Union especially when the product is purely nationally authorised in each country. The time management of changes requires resources without adding any value. The uncertain timescales of approvals in the different countries and regions and the complexity of implementing post-approval changes lead to a situation, which is so rigid as to almost block improvements. (3)

In the European Community more than 80% of the marketing authorisations are purely national. At present changes to these marketing authorisations are not subject to harmonised Community rules. (4)

The consequences in terms of public health, administrative burden and overall functioning of the internal market in pharmaceuticals are (4):

- From a public health perspective, there is no justification why the scientific criteria for evaluating changes to medicinal products should be different from one Member State to the other.

- From a legal perspective it is questionable if it makes sense that the requirements for granting the initial marketing authorisation are fully harmonised at Community level, and the changes to these marketing authorisations are not.

- From a practical perspective the current situation increases the administrative burden for pharmaceutical companies and for the Competent Authorities of the Member States since the authorities have to follow different legal requirements, depending whether they are dealing with changes to a purely national marketing authorisation or not. The implementation of certain changes, including changes, which may benefit patients by improving the safety/efficacy profile of the concerned product, may be delayed, impaired or even prevented by the legal uncertainty caused by the different rules in the different countries.

- The discrepancies amongst Member States may 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.

- The amount of variations, which is rising from year to year, and the growing workload on industry and authorities leads to missing of timelines on the authority side and important improvement of the medicinal product being implemented with long delays on the industries side.

The new concepts of International Conference of Harmonisation (ICH) on Pharmaceutical Development, Quality Risk Management and Quality Systems lead to shift of paradigm from testing to document the quality of a product to continuous quality assurance. These are not considered in the current Variation Regulations. (5)

The following essay presents the current discussion of the revision of the Variation Regulations Commission Regulation (EC) No. 1084/2003 and No. 1085/2003 in the European Union and its impact on industry and health authorities focusing on medicinal products for human use.

The trigger was the EU initiative “Better regulation” commission policy, which is aiming to reduce bureaucracy in order to strengthen the European industry.

The chronology is: In March 2006 the European Federation of Pharmaceutical Industries and Associations with the European Vaccine Manufacturers and European Biopharmaceutical Enterprises (EFPIA/EVM/EBE) and other European pharmaceutical Industry associations were informed by the EU Commission, that the process on reworking of the Variation Regulation would be started. In September 2006 EFPIA/EVM/EBE sent the proposal for the revision of the regulations to the European Commission, which is based on the current system, the experiences with national regulations and on the implication of the new ICH guidelines Q8 Pharmaceutical Development, Q9 Quality Risk Management and Q10

Pharmaceutical Quality System. On 20 October 2006 the Consultation Paper ´Better Regulation of Pharmaceuticals: Towards a Simpler. Clearer and More Flexible Framework on Variations´ was published by the European Commission. On 12 December 2006 an industry workshop with observers from the EMEA and stakeholders of the industry took place. Among others EFPIA/EVM/EBE, the Association of the European Self-Medication Industry (AESGP), the Active Pharmaceutical Ingredients Committee (APIC) and the European Generics Medicines Association (EGA) participated.

The following essay starts with a short overview of the history of the EU variation guidelines, of the current Variation Regulation, and the developments of the ICH guidelines. The variation systems in Germany and Austria as well as in the United States of America have influenced the discussions considerably. The industry proposals including the discussion papers from EFPIA/EVM/EBE, Bundesverband der Arzneimittelhersteller, Germany (BAH), AESGP, APIC and the Consultation Paper from the EU Commission are discussed in respect to their impact on industry and health authorities.

2.1 History of the EU Variation Guidelines

In February 1995 the European Agency of Medicinal Products (EMEA) was established as an important prerequisite for a consistent European regulatory system under Commission Regulation (EC) No 2309/93 (6). The ´concertation procedure´ for certain high-technologically products was introduced by Council Directive 87/22/EEC in 1986 but was never widely used since there was no clear advantage compared with the established national marketing authorisation procedure was substituted in 1995 by the new Centralised Procedure (CP) under the auspices of Council Regulation 2309/93. Also in 1995 the Mutual Recognition Procedure (MRP) replaced the ´multi-state procedure´, which was established by Council Directive 75/319/EEC in 1976. The MRP had to be used for products, which were not from biotechnological origin, and for which a marketing authorisation was applied for in more than one Member State.

Before 1995 there was no consistent variation system in place neither for the ´concertation procedure´ nor the ´multi-state procedure´.

In 1995 the Commission Regulation (EC) No 541/95 came into force defining a variation system for medicinal products, which had been authorised via MRPs, ´ex-concertation procedures´ as well as products for which has been referrals according to the articles 13 and 14 of Directive 75/319/EEC or articles 21 and 22 of Directive 81/851/EEC. For variations for products being authorised via the CP Commission Regulation (EC) No 542/95 was implemented. (1)

Variations were categorised in type I ´minor variations´ as notification procedure and type II ´major variations´ as approval procedure. (7, 8)

In annex II of the Commission Regulation (EC) No 541/95 and No 542/95 the conditions leading to a new application were listed. Each variation application should concern not more than one change with the exception of consequential changes. (1, 8)

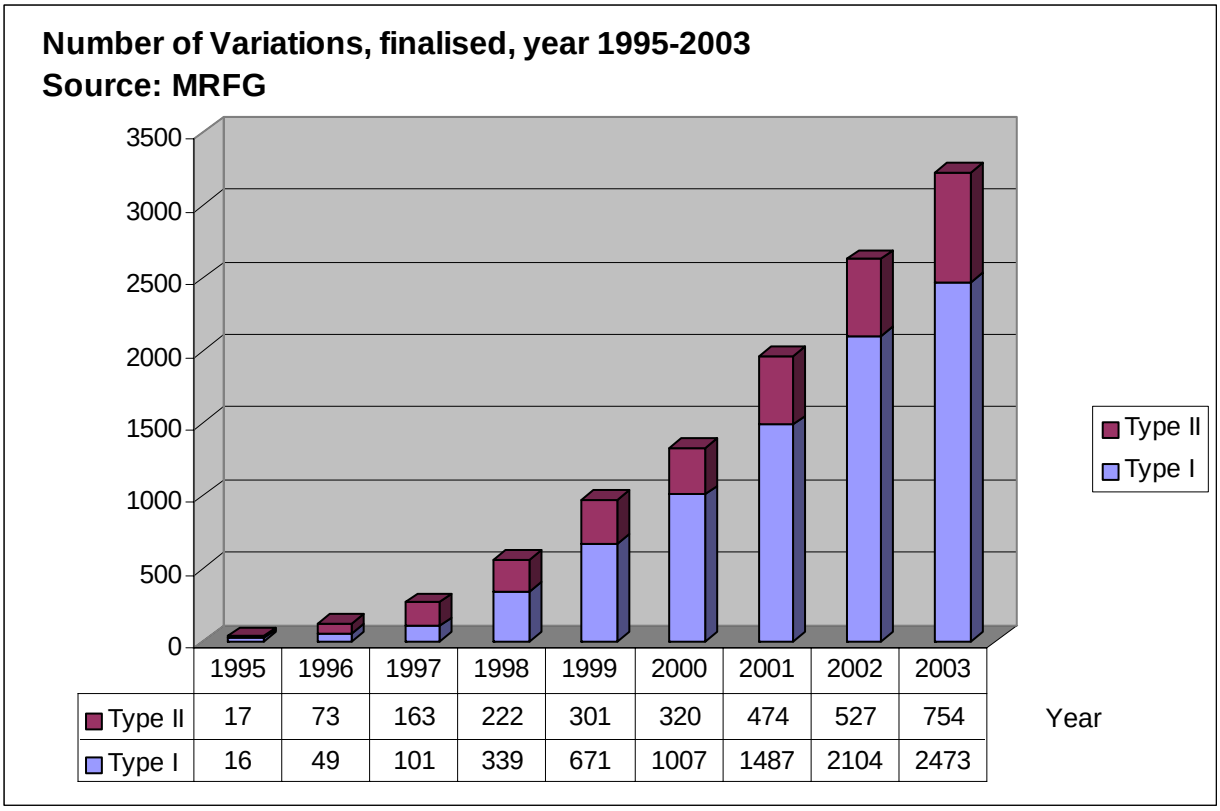
All changes falling under type I variations (notification) were defined and listed in annex I of the regulations specifying 33 changes for MR variations and for Centralised Procedure. If 30 days after the start of the procedure the Reference Member State (RMS) had not sent any objections to the marketing authorisation holder, the variation was considered accepted by all Member States. (1, 8)

Changes, which were not defined as type I variations and for which a new marketing authorisation was not necessary were automatically type II variations not taking into consideration if the change concerned the quality of the product or if it was only minor but not listed in annex I of the regulations. For MR variations the approval procedure included the assessment by the RMS and by the Concerned Member States (CMSs).

The following years showed that the workloads on authority and industry side were tremendous. Due to an increasing number of Mutual Recognition applications the number of minor variations was rising.

The table below shows the number of variations per year and type from 1995 to 2003. The number of type I variations increased from 1995 to 2003 by 155 times and the number of type II variations by 44 times.

Figure 1: MRP Variations from 1995 to 2003



	1995	1996	1997	1998	1999	2000	2001	2002	2003
Type II	17	73	163	222	301	320	474	527	754
Type I	16	49	101	339	671	1007	1487	2104	2473

Inconsistencies and repetitions in annex I of the regulation led to irritations between industry and authorities.

The variation system had to be amended in order to simplify the procedure, to reduce the workload on authorities and industry and to be prepared for the EU enlargement.

Limitations for the revision were set by the adoption of Directive 2001/83/EC as amended. According to article 35 of Directive 2001/83/EC the fundamental system for variations was manifested:

“Any application by the marketing authorisation holder to vary a marketing authorisation which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorised the medicinal product concerned.
The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorisation.
These arrangements shall include a notification system or administration procedures concerning minor variations and define precisely the concept of a minor variation.
These arrangements shall be adopted by the Commission in the form of an implementing Regulation in accordance with the procedure referred to in Article 121(2).” (9)

The last sentence has been deleted with Directive 2004/27/EG coming into force on 30 April 2004.

Besides others one proposal from industry was to achieve the same regulatory framework for variations in the Mutual Recognition and the Centralised Procedure. Furthermore the industry suggested bulk or group variations, where the same change affects many marketing authorisations in order to reduce the amount of submissions. (10)

Although the intensive discussions between the Commission Notice to Applicants Working Party NTA WP and the different industry associations these industry proposals were not implemented into the new regulations, in spite of their potential to reduce the administrative burden on industry and authorities considerably.

2.2 Overview of the Current Variation Regulations and Its Impact on Industry and Authorities

2.2.1 General Aspects

Currently the main drivers for pharmaceutical variations are (10):

- Retrospective applications of ICH/CHMP quality guidelines
- Implementation of new or revised CHMP guidelines
- Implementation of new harmonised pharmaceutical monographs
- Company mergers e.g. legal entity
- Economical reasons such as up-scaling, site transfers, change of the supplier of the active ingredient

Depending on the type of the marketing authorisation of a medicinal product the variation procedure has to follow the Commission Regulation (EC) No 1085/2003 for centrally authorised products and to Commission Regulation (EC) No 1084/2003 for products which were authorised via Mutual Recognition Procedure, ex-concertation procedure or products which went through a referral according to Articles 32, 33 and 34 of Directive 2001/23/83/EC. For all nationally approved products the Variation Regulations of the specific country applies.

2.2.2 Mutual Recognition Variations

2.2.2.1 Regulations and Guidelines

The new Variation Regulation - Commission Regulation (EC) No 1084/2003 replacing Regulation (EC) No 541/95 is in force since 01. October 2003. It is binding for all EU-Member States, Iceland, Norway and Liechtenstein. The Commission Regulation (EC) No 1084/2003 applies to medicinal products authorised via the MRP, Decentralised Procedure, ´ex-concertation´ procedure as well as products which went through referrals according to the articles 32, 33 and 34 of Directive 2001/83/EC (1).

In addition the following guidances were published:

- Notice to Applicants Volume 2A Chapter 5 - Variations (updated version - February 2004)
- Notice to Applicants Volume 2C :
    - Guidelines on Dossier Requirements for Type IA and Type IB Notifications (Updated version –July 2006)
    - Variation Application Form (Updated version – February 2007)
    - Guideline on the Categorisation of New Applications (NA) versus Variations Applications (V) (October 2003)
    - MRFG/CMD(h) Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedure (Updated version –June 2006)
    - MRFG press releases
    - CMD(h) Urgent Safety Restriction, Member States Standard Operating Procedure (updated version – December 2005)

With the new regulation a simplified and rapid notification procedure is introduced for certain minor changes, which do not affect the approved quality, safety or efficacy of the product. Such a change does not need the prior evaluation by the Reference Member State. For other types of minor variations the assessment by the Reference Member State is still required before the change can be implemented. (11)

The changes are classified in (1):

a) Type IA/IB notifications according to annex I of Commission Regulation (EC) No 1084/2003

b) Non MR variations because the change has to be proceeded according to national law of the Member State

c) Non MR variations because the change is classified as line extension according to annex II of Commission Regulation (EC) No 1084/2003, for example change or addition of a new strength or pharmaceutical form

d) Non MR variations because the change is a new marketing application

e) All changes, which are not covered by the above-mentioned definitions, are type II variations.

Examples for non MR variations but changes according to national law of the Member State are transfers of marketing authorisations (Commission Regulation (EC) No 2141/96) and labelling changes concerning the ´blue box´, which have no impact on the harmonised SPC, PL and labelling, or other special national issues such as co-promotion or sample pack size in Germany.

Line extensions are changes where the trade mark is kept. Examples are applications for additional indications, strengths. (52) If the trade mark shall not be kept it will be a new application.

The former type I variations (notifications) with 33 changes listed are now differentiated in type IA and IB variations with 46 changes listed in annex I of Commission Regulation (EC) No 1084/2003. Some changes are more specified and others have been added such as change in ATC-code, which was not listed before and therefore fell under a type II variation.

The table below gives an overview of the types of variations.

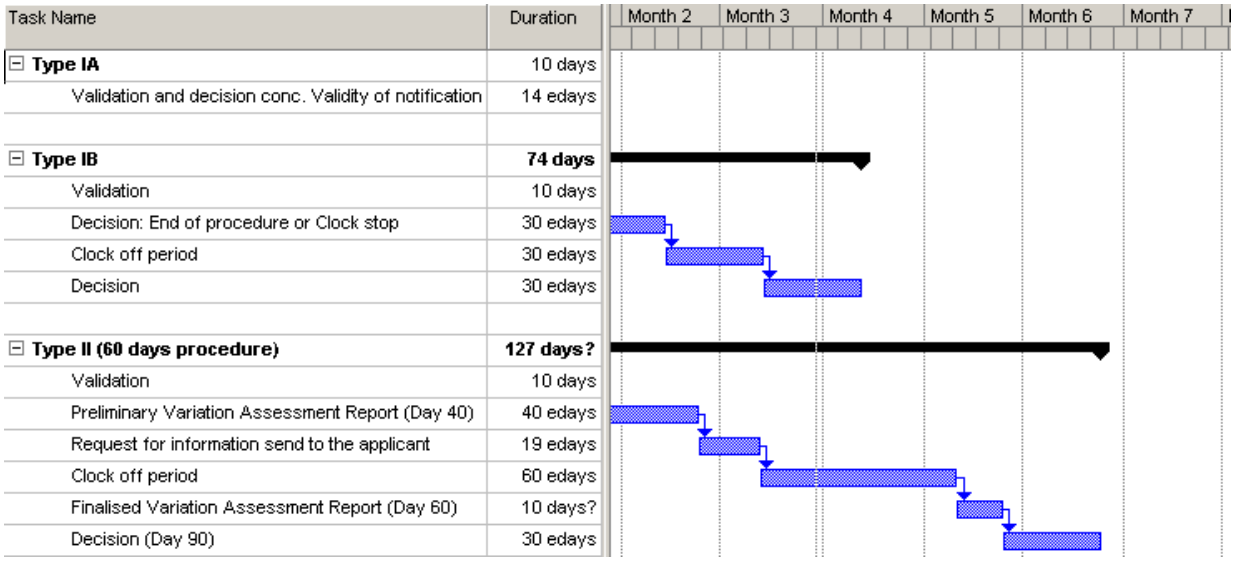
Table 1: Overview: The Types of Variations (12, 13)

Type	Assessment	Procedure	Conditions	Minimum time from submission to approval / notification letter (without clock stop)	Time from submission to approval with clock stop
Type IA	Minor variation No assessment	Tell and do Notification procedure	Categories and conditions defined	14 edays	14 edays
Type IB	Minor variation Assessment by RMS (CMS only by Notification No 2, No 41a2 or No 41b or by RMS on request)	Tell – wait – and do Notification procedure	Categories and conditions defined	10 days + 30 edays	10 days + 30 edays + 30 edays (clock stop) + 30 edays
Type II 30 days assessment	Major variation Assessment by RMS and CMS	Tell and wait Explicit approval	Reduced assessment; safety issues	10 days + 30 edays	10 days + 30 edays + 10 edays
Type II 60 days assessment	Major variation Assessment by RMS and CMS	Tell and wait Explicit approval	All changes which are not type IA or IB, safety or change/addition of the therapeutic indications	10 days + 90 edays	10 days + 90 edays + 60 edays (clock stop)
Type II 90 days assessment	Major variation Assessment by RMS and CMS	Tell and wait Explicit approval	Extended assessment, change to or addition of the therapeutic indications	10 days + 120 edays	10 days + 120 edays + 90 edays (clock stop)

edays – calendar days
days – working days

The time flows of the major variation types for CMC changes which are the majority are shown in the following diagram (Urgent Safety Restriction, Safety type II variation (30 day procedure) and type II as 90 day procedure for the change or addition of therapeutic indications are not considered).

Diagram 1: Time Flow of the Major Variation Types (12)



edays – calendar days days – working days

Following the guideline (12) the MAH should calculate half a month for a type IA variation and including clock stops for to 3 ½ months for a type IB variation as well as 5 months for a type II variation (60 days assessment).

But in reality the duration of the validation phase differs considerably from RMS to RMS and if the specified timelines of the procedure are followed. The timelines are not legally enforceable mandated for the Competent Authorities to amend a marketing authorisation or to issue an approval letter to the marketing authorisation holder (MAH) following the receipt of the translated SPC/PL/labelling where required (Regulation 1084/2003 Article 6 (10)). (13)

Industry experiences on timelines are shown in the table below (EFPIA Variations Survey 2005 on quality, safety and efficacy changes). The period covered was for members of the EU from 1st January 2004 and EU Accession members from 1st May 2004 to December 2004. (13)

Table 2: EFPIA Variations Survey 2005 on Quality, Safety and Efficacy Changes (24)

Description of Activity		Mutual Recognition Procedure				
		Type IA	Type IB	Type II, standard (approx. 60 days)	Type II, reduced (approx. 30 days)	Type II, extended (approx. 90 days)
Validation	Time taken from receipt of the application by the Agency to Day 0 (duration in days)	0 – 37	1 - 64	1 - 60	3 - 30	0 - 54
	Time according to guide-line (in working days)	10	10	10	10	10
Notification/ Decision	Time taken from Day 0 to Notification/Decision from Agency (duration in days)	0 – 223	9 - 611	3 - 450	0 - 307	140 – 249
	Time according to guideline (in days)	14 including validation	30 w/o clock stop 90 with clock stop	90 w/o clock stop 150 with clock stop	30 w/o clock stop 40 with clock stop	120 w/o clock stop 210 with clock stop
National Phase	Time taken from Notification/Decision from Reference Member State to updating of National Licence (duration in days)	0 – 229	0 - 270	3 - 450	0 - 307	30 – 300

The table shows that the durations of different phases vary considerably even for type IA variations. It can take up to the 6 fold of the time foreseen by the guidelines. Therefore the MAH cannot plan when a certain change can be implemented.

The risk is high to implement a type IA variation as long as the notification letter of the outcome has not been received, since the variation could still be rejected. Thus it is not a true tell and do procedure.

Nevertheless the introduction of type IA variations shortened the time between submission and the implementation of the change.

2.2.2.2 Impact on Industry and Authorities

Multiple Reviews by Authorities: Double or even multiple reviews by authorities are required, e.g. for changes to a Certificate of Suitability which are currently reviewed by the EDQM and the Health Authorities. If the respective active ingredient is part of several drug products several variations will be submitted and assessed.

Multiple Variations: Where several changes are to be made concerning one marketing authorisation a separate notification or variation for each change has to be submitted. Only if the changes are consequential a single variation can cover all changes. The consequential revision of the SPC, PL or labelling is considered as part of the variation (11). Bulk or group variations where the same change affects many marketing authorisations was not implemented (10). According to the regulations it is not foreseen to cumulate several changes concerning one product.

Extensive Paper Work: For variations concerning several strengths of a product several countries require one application form per strength. This means for example for a change for marketing authorisations in 10 Member States and 5 strengths there are 50 application forms of usually 5 pages to be filled in, which sums up to 250 pages for one variation!

The above mentioned aspects lead to an

a) Increased workload for the MAH, since instead of one dossier and application form for several changes and strengths, one dossier per strength and change has to be provided

b) Additional workload for authorities concerning validation, electronic tracking and archiving

In some Member States e.g. Germany as RMS it is possible to combine several type IA or IB changes in one variation dossier if the same part of the documentation is concerned while separate application forms for each strength has to be submitted. Other Member States as RMS accept several type I changes combined as one type II variation if all changes concern either the drug substance part or the drug product part of the dossier e.g. Sweden.

Type II Variations by Default: Since only type IA and type IB variations are specified all other changes, which are no line extensions or new applications, are type II variations by default. This leads to the following consequences even for minor changes not affecting the quality and safety of the product:

On authority side:

a) The RMS has to prepare an assessment report and all CMSs have to assess the dossier(s)

And on the industry side:

b) An amendment to the quality overall summary has to be prepared

c) The difference in time until the change is approved and can be implemented is notable:

	Type II without clock stop	3 ½ months minimum
versus	Type IA	2 weeks minimum or
	Type IB without clock stop	1 ½ month minimum

d) The fees are considerably higher for a type II variation in comparison with a type IB variation. As example a variation on quality for five strengths with Germany as RMS and as CMSs: Austria, Spain, Greece, France, Italy, The Netherlands, Portugal, Sweden and the United Kingdom is shown in the table below. The total expense of a type II variation is around 4.5 times higher than a type IA variation and more than 3 times higher than a type IB variation:

Table 3: Fee Calculation for a CMC Variation - Example (Source: IDRAC, personal information)

Country	**Fees for a type IA variation** **Euro**	**Fees for a type IB variation** **Euro**	**Fees for a type II variation** **Euro**
DE BfArM (RMS)	700 + 4 x 546 = **2,884**	700 + 4 x 546 = **2,884**	4,372* + 4 x 530 = **5,492**
AU (CMS)	400 x 5 = **2,000**	400 x 5 = **2,000**	1,600 x 5 = **8,000**
ES (CMS)	662.5 + 4 x 335.17 = **2,003.18**	1,142.43 + 4 x 335.17 = **2,483.11**	6,513.43 + 4 x 335.17 = **7,854.11**
EL (CMS)	500 x 5 = **2,500**	1,000 x 5 = **5,000**	2,000 x 5 = **10,000**
FR (CMS)	1,011 x 5 = **5,055**	1,011 x 5 = **5,055**	1,011 x 5 = **5,055**
IT (CMS)	600 x 5 = **3,000**	1,392 x 5 = **6,960**	8,352 x 5 = **41,760**
NL (CMS)	Fees covered by annual fee	Fees covered by annual fee	580 x 5 = **2,900** (simple variation)
PT (CMS)	797.94 + 4 x 271.10 = **1,882.34**	797.94 + 4 x 271.10 = **1,882.34**	1,585.65 + 4 x 511.50 = **3,631.65**
SE	Fees covered by annual fee	Fees covered by annual fee	540 x 5 = **2,700**
UK	264 + 4 x 132 = **792**	416 + 4 x 208 = **1,248**	1,096 + 4 x 548 = **3,288**
Total	**20,116.52**	**27,512.45**	**89,680.76**

*Mean of 2,454 and 6,290

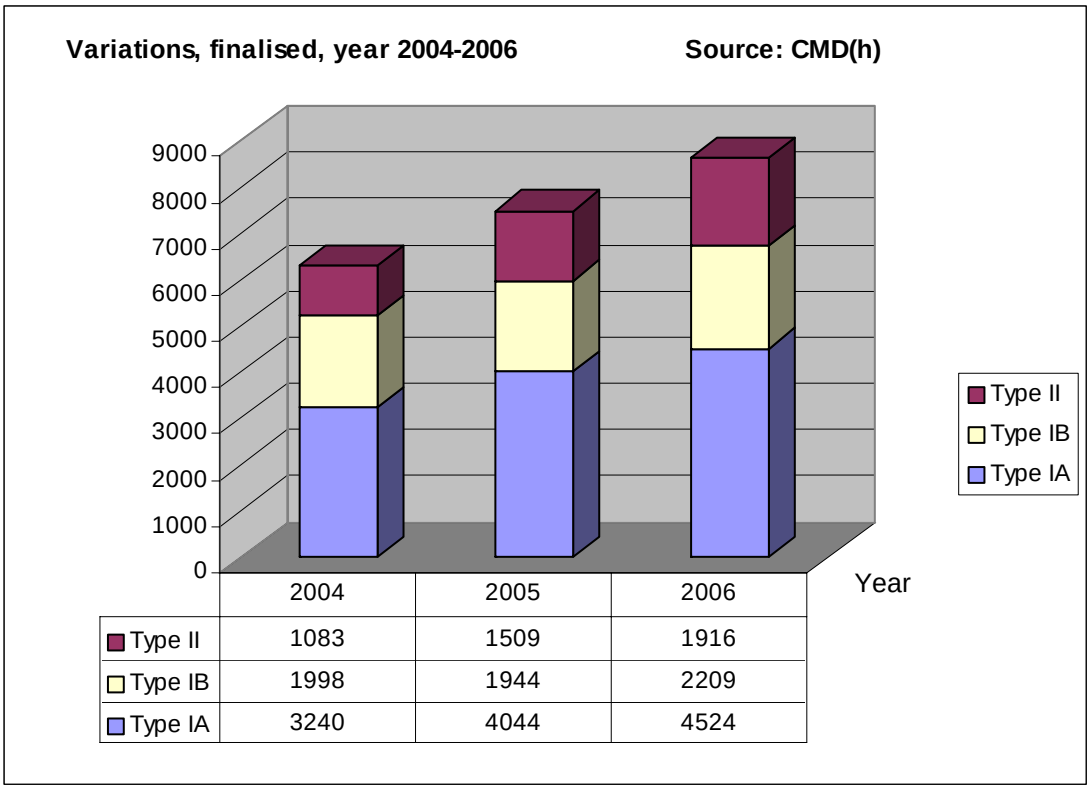
The fee systems from country to county vary considerably and are rather differentiated such as:

- Type I variations are covered by annual fees as in The Netherlands and Sweden

- Some give rebates on further strengths, as Germany, Portugal, Spain and UK
- Others differentiate type II variations according to their complexity, as UK, Greece
- Especially in Italy the difference of costs of one type IA or IB variation versus a type II variation is high.

Still Increasing Number of Variations: In October 2003 the current Variation Regulation came into force and in 1 May 2004 was the accession of the new European Member States. The total amount of variations has jumped from the year 2003 to 2004 by 51% and slowing down on 19% in 2005 and 15% in 2006.

Figure 2: MRP Variations from 2004 to 2006



	2004	2005	2006
Type II	1083	1509	1916
Type IB	1998	1944	2209
Type IA	3240	4044	4524

Table 4: MRP Variations from 2003 to 2006 (Source: CMD(h))

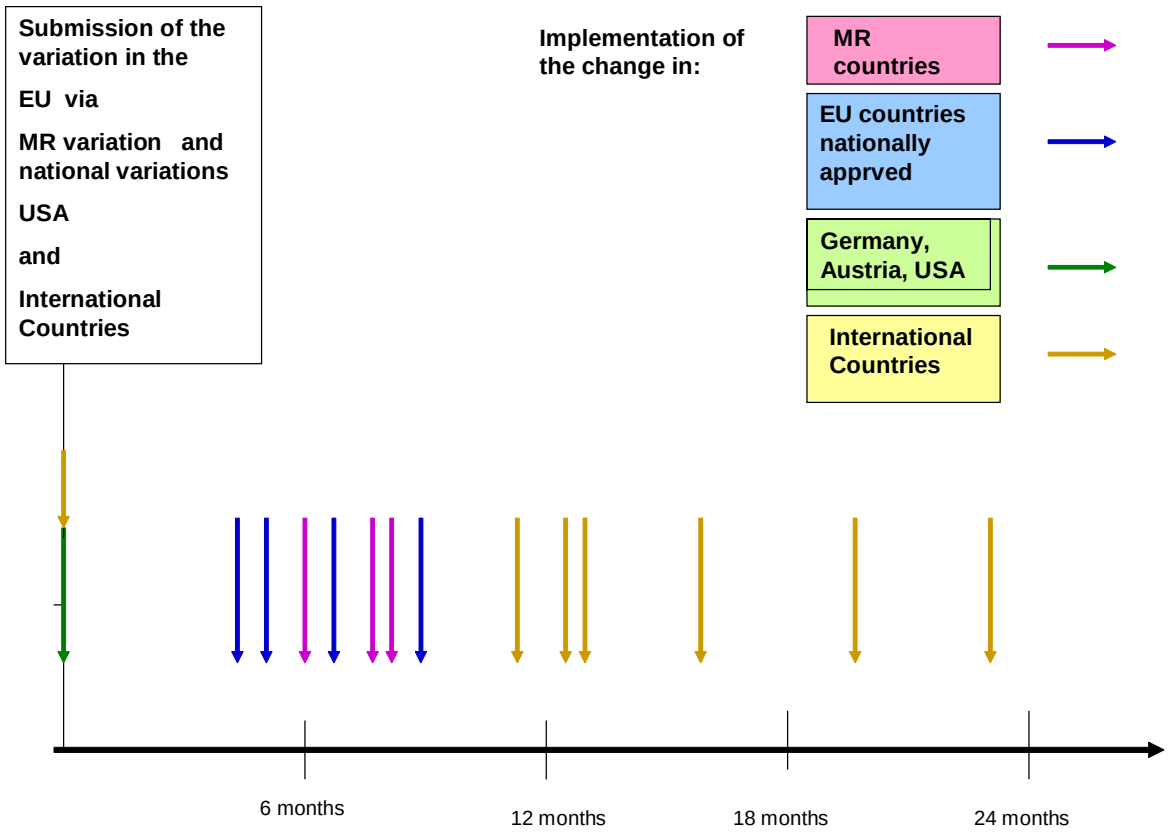
Year	New MRP/DCP approvals	Total amount of MRP/DCP approvals finalised since 1995	Annual Growth of approvals	Type IA	Type IB	Type II	Total	Total amount of variations compared with the previous year	Ratio amount of variations to procedures finalised until the year before
2003	529	2348		2473 + 230 + 94		754	3551		
2004	760	3108	32 %	3240	1998	1083	6321	51%	2.7
2005	954	4062	31%	4044	1944	1509	7497	19%	2.4
2006	592	4654	15%	4524	2209	1916	8649	15%	2.1

The table above shows that the amount of variations is still raising but the growths rate and the ratio of the amount of variations to the total of all procedures seems to be slowing down.

Point in Time, When a Change Can Be Implemented: A big challenge is the implementation of a change even for MR variations because of the differences from country to country. Although for the majority of the countries the variation can be implemented at the day of the end of procedure, for type II variations on CMC changes for example in Finland, France, Italy, Poland, Portugal and Slovenia the MAH has to wait for the national approval. In Italy even for IA and IB variations the local authorisation has to be published in the Official Journal first.

For international operating companies the implementation of a change is complex. For nationally approved products some European countries have similar regulations as Commission Regulation (EC) No 1084/2003 for example Sweden, Spain, France and the United Kingdom. Others have substantially different ones such as Germany and Austria. Countries outside the European Union follow other procedures, timelines and dossier requirements. Therefore an international operating company has to deal with many different requirements and unpredictable timelines, until a certain change finally can be implemented. Considerable efforts and resources are necessary for the change management. The example below demonstrates the situation:

Figure 3: Point of Time of the Approval of a Change in Different Countries: Type IB Variation for a product in the EU via MRP in further EU states nationally approved and marketing authorisations in the US and non ICH countries:



Any harmonisation of requirements and timelines within the European Union for products which are nationally approved or via MRP and further within the ICH region would simplify the process and changes could be implemented faster resulting in the prevention of product shortage, in a higher quality of products in an earlier stage or lower production costs.

2.2.3 Variations in the Centralised Procedure

2.2.3.1 Regulations and Guidelines

The new Variation Regulation - Commission Regulation (EC) No 1084/2003 replacing Regulation (EC) No 541/95 as amended is in force since 01. October 2003. It is binding for all EU-Member States, Iceland, Norway and Liechtenstein and applicable to all medicinal products, which are authorised according to Council Regulation (EC) No. 726/2004. (1)

The following documents give guidance on variations to centrally approved products:

- Notice to Applicants Volume 2A Chapter 5 - Variations (updated version - February 2004)
- Notice to Applicants Volume 2C :
    - Guidelines on Dossier Requirements for Type IA and Type IB Notifications (Updated version –July 2006)
    - Variation Application Form (Updated version – February 2007)
    - Guideline on the Categorisation of New Applications (NA) versus Variations Applications (V) (October 2003)
- EMEA Post-authorisation Guidance from August 2006
- European Commission, Note to Applicants, 19 February 2004

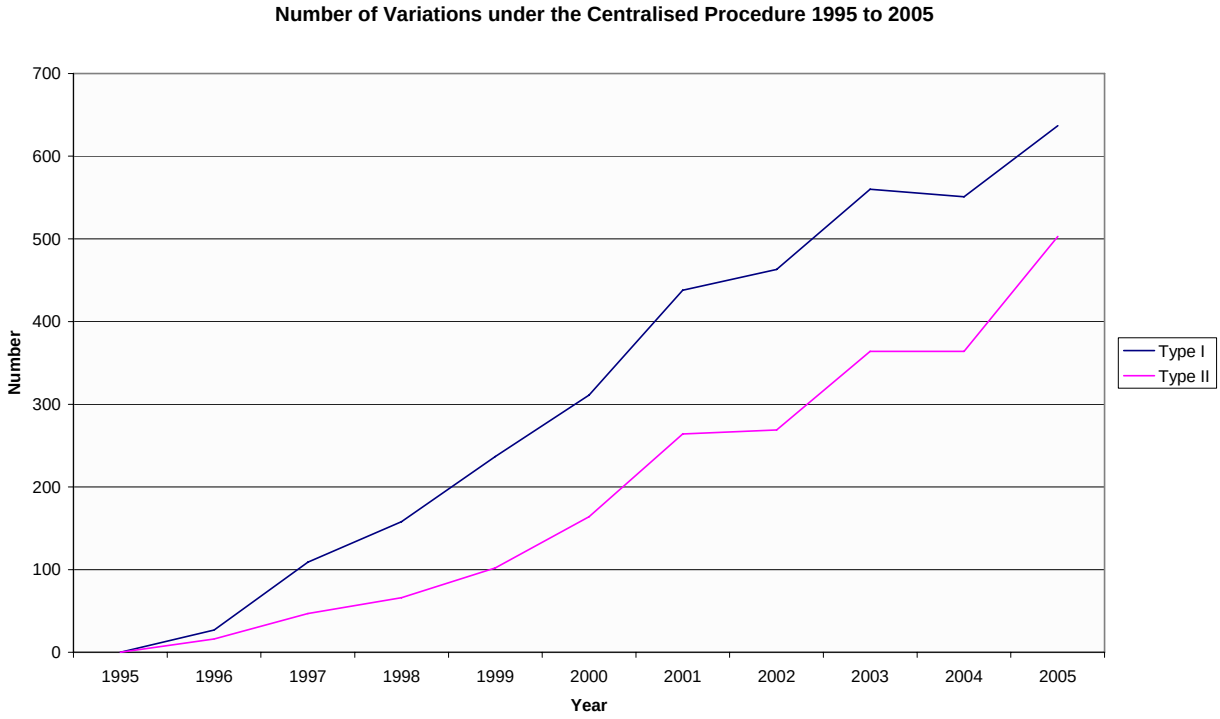
The changes are classified in the same way as for MR variations. (12, 14)
The variation dossier is sent to the EMEA and Rapporteur for information and for type II variations additionally to other CHMP members post validation. The timetables are similar to MR variations.

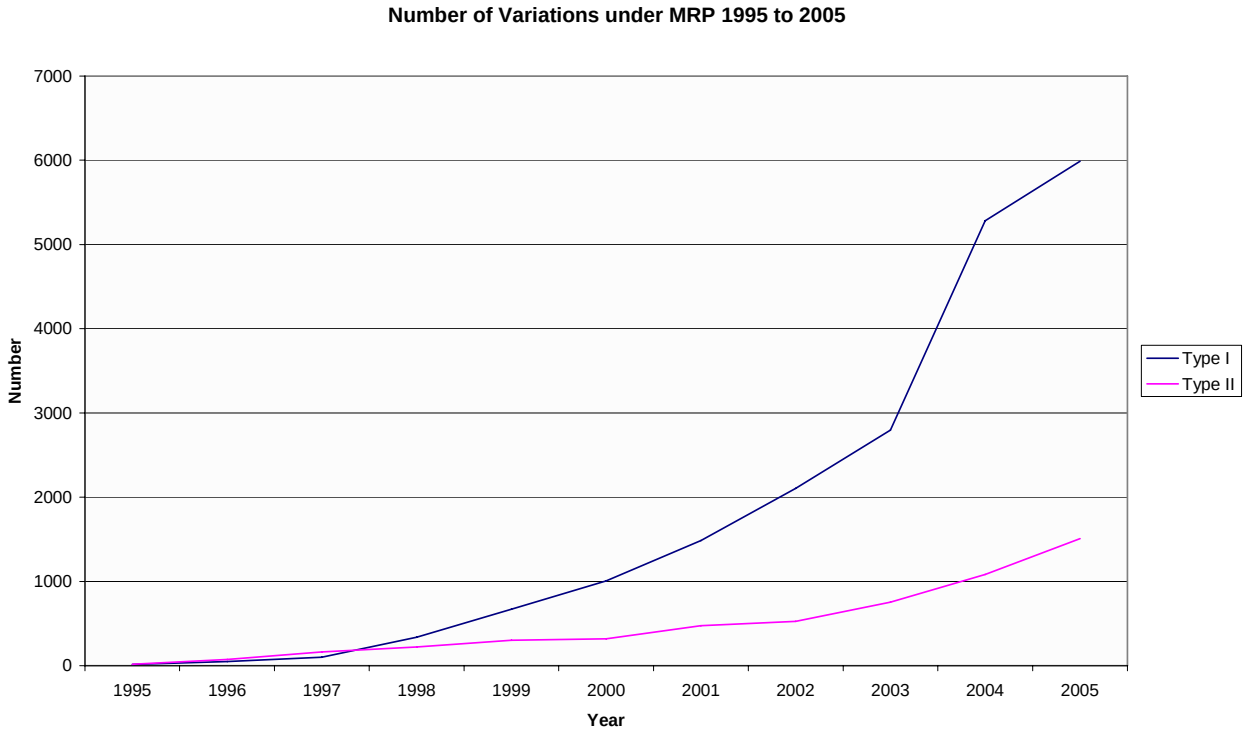
2.2.3.2 Impact on Industry and Authorities

For CMC variations each change per strength has to be submitted separately if the changes are not consequential. It is not accepted to combine several changes concerning the same documentation in one dossier. Separate application forms have to be submitted per strength and change.

Type II variations concerning the same documentation cannot be submitted in parallel. Therefore the sequences for the submissions have to be planned carefully. This is very critical since for biological medicinal products the vast majority of changes to manufacture and control are excluded from the usage of the type IA/IB notification submission route and are therefore automatically type II variations by default. The impact can clearly be seen in the proportion of type I versus type II variation applications in the Centralised Procedure CP compared with the MRP, see figures below. (13)

Figure 4: Number of type IA and IB Variations in the Centralised Procedure and Mutual Recognition Procedure (13)





The results are long assessment times leading to a delay of implementation of the changes as well as increased expenses on fees.

Centralised marketing authorisations are to be updated in respect of type IA and type IB variations every six months by the Commission. Within the Commission, a system of ´sweep´ decisions has been introduced, whereby updates related to type I variations are made either

through 6 months update or at the occasion of a Commission Decision for the concerned product, e.g. type II variation, transfer of the marketing authorisation, renewal etc, whichever is the earliest. This system is quicker and decreases the number of decisions. (14, appendix 2)

2.2.4. Further Aspects

A significant amount of new clinical data and if necessary new safety data have to be submitted usually for the application of a new indication via type II variation. For the addition of a new strength within the already approved dose range usually only quality data, for the addition of a new pharmaceutical form usually only new quality and bioequivalence data, for a new dosing regimen only new clinical and bioavailability data will be submitted but these applications are categorized as new applications. According to EFPIA/EVM/EBE´s opinion this is not justified (Appendix 1)

2.3 Objective of the EU Initiative "Better Regulation" Commission Policy

In March 2000 the European Council met in Lisbon and the "Lisbon Strategy" was launched. It aims at making the European Union (EU) the most competitive economy in the world and achieving full employment by 2010. This strategy, developed at subsequent meetings of the European Council, rests on three pillars (15):

- An economic pillar preparing the ground for the transition to a competitive, dynamic, knowledge-based economy. Emphasis is placed on the need to adapt constantly to changes in the information society and to boost research and development.
- A social pillar designed to modernise the European social model by investing in human resources and combating social exclusion. The Member States are expected to invest in education and training, and to conduct an active policy for employment, making it easier to move to a knowledge economy.
- An environmental pillar, which was added at the Göteborg European Council meeting in June 2001, draws attention to the fact that economic growth must be decoupled from the use of natural resources.

For the mid-term review in 2005 a report was prepared showing that the objectives had not been met. The results, which had been achieved, were unconvincing.

Therefore the ´Lisbon Strategy` had been renewed by the "Better Regulation" Initiative, which is a centrepiece of the European Commission's "Partnership for Growth and Jobs" and was launched in spring 2005. (16)

Better Regulation is a broad strategy to improve the regulatory environment in Europe - containing a range of initiatives to consolidate, codify and simplify the existing legislation and

improve the quality of the new legislation by better evaluating its likely economic, social and environmental impacts. (17) It aims to boost productivity and employment significantly, while continuing to take into account the social and environmental objectives. (18) Günter Verheugen, vice president of the European Commission, responsible for enterprise and industry, in his press conference „Better Regulation“ on 16 March 2005 emphasised the contribution of the Member States. According to a British study, 80% of the red tape (meaning extensive bureaucracy), does not come from Brussels but from the capitals of the Member States because EU Directives were implemented in an unnecessarily bureaucratic fashion. In this context the impact of the planned legislation will be assessed concerning promotion of growth and employment. (19)

The Better Regulation strategy is based on three key action lines:

- Promoting the design and application of Better Regulation tools at the EU level, notably simplification, reduction of administrative burdens and impact assessment.
- Working more closely with Member States to ensure that Better Regulation principles are applied consistently throughout the EU by all regulators
- Reinforcing the constructive dialogue between stakeholders and all regulators at the EU and national levels. (18)

In March 2006 the European Federation of Pharmaceutical Industries and Associations EFPIA and other industry organisations were informed by the European Commission that a process would be started to rework the Commission Regulation (EC) 1084/2003 and Commission Regulation (EC) 1085/2003.

2.4 ICH Guidelines Q8-Q9-Q10

The healthcare scene and its impact on the industry have been changing over the last decades: In the industrialised countries the ageing population is generating a need for new medicines and a greater use of pharmaceuticals. But increasing healthcare costs put high pressure to reduce the use and price of pharmaceuticals.

The pressure on the industry comes in many forms such as governmental agencies, shareholders, and speed to market, costs of goods, mergers, and continuity of supply and further more. (20) Today the pharmaceutical industry including biotech must cope with an increasingly difficult economic climate. Late-state failures, safety withdrawals and patent expiry have intensified the pressure on profit margins and sharpened the focus on operational efficiencies. (21) According to Janet Woodcock, FDA, but also to industry judgment such as CAMP, pharmaceutical manufacturing has not been ´state of the art´ with (20, 22, 23)

- Drug manufacturing costs as high as research and development costs at many companies because of low factory utilization, due to batch production processes (often a low 15%, and 30-40 % on average),
- Waste generation of more than 50% for some products,
- Unpredictable scale-up,
- Fragmented global operations,
- Low product yields,
- High operating costs,
- Long lead-times due to stage and final product testing and
- Because manufacturers often do not know the reasons for production failures.

The consequences are high manufacturing costs, low manufacturing efficiency, drug shortages and the need for intensive regulatory oversight. (8) According to FDA the pharmaceutical industry has six sigma products (3.4 defects per 1,000,000 opportunities) on the market but only three sigma processes (66,8 defects per 1,000,000 opportunities). Scientific manufacturing starting with the creation and transfer of robust processes from development into manufacturing lays the foundation for achieving six sigma performance in full-scale production. These concepts have been developed in extremely price driven high-tech industries such as the semiconductor industry and are now transferred to the pharmaceutical industry. (21)

The need for a change of paradigm such as building in product quality by design versus end control testing, and further more the development of a risk management and a quality system became obvious.

The three ICH guidelines Q8 Pharmaceutical Development, Q9 Quality Risk Assessment and Q10 Pharmaceutical Quality System are intended to provide a comprehensive scientific understanding of a medicinal product and its manufacturing process in order to guarantee the quality of a product throughout the lifecycle. The objective is to remove barriers to continuous improvement and the efficient use of resources by industry and regulatory authorities.

Since these new concepts are not considered in the current European Variation Regulations the new ICH Guidelines are a trigger for their revision.

2.4.1 ICH Q8 Pharmaceutical Development

The aim of pharmaceutical development is to design a quality product and manufacturing process in order to constantly guarantee the intended performance of the product.

With the adoption and implementation of the Common Technical Document dossier format CTD in the three ICH regions European Union, the United States of America and Japan the development of a harmonised guideline on Pharmaceutical Development became necessary. (25)

The guideline, which is in force in the European Union since May 2006 and has been adopted in Japan and the United States too, describes the suggested contents for the 3.2.P.2 Pharmaceutical Development section of the regulatory dossier in the CTD format. This section demonstrates a comprehensive scientific understanding of the product and manufacturing process for reviewers and inspectors, which was gained through the application of scientific approaches to the development of a product and its process development concerning the manufacturing process. (22, 26, 27)

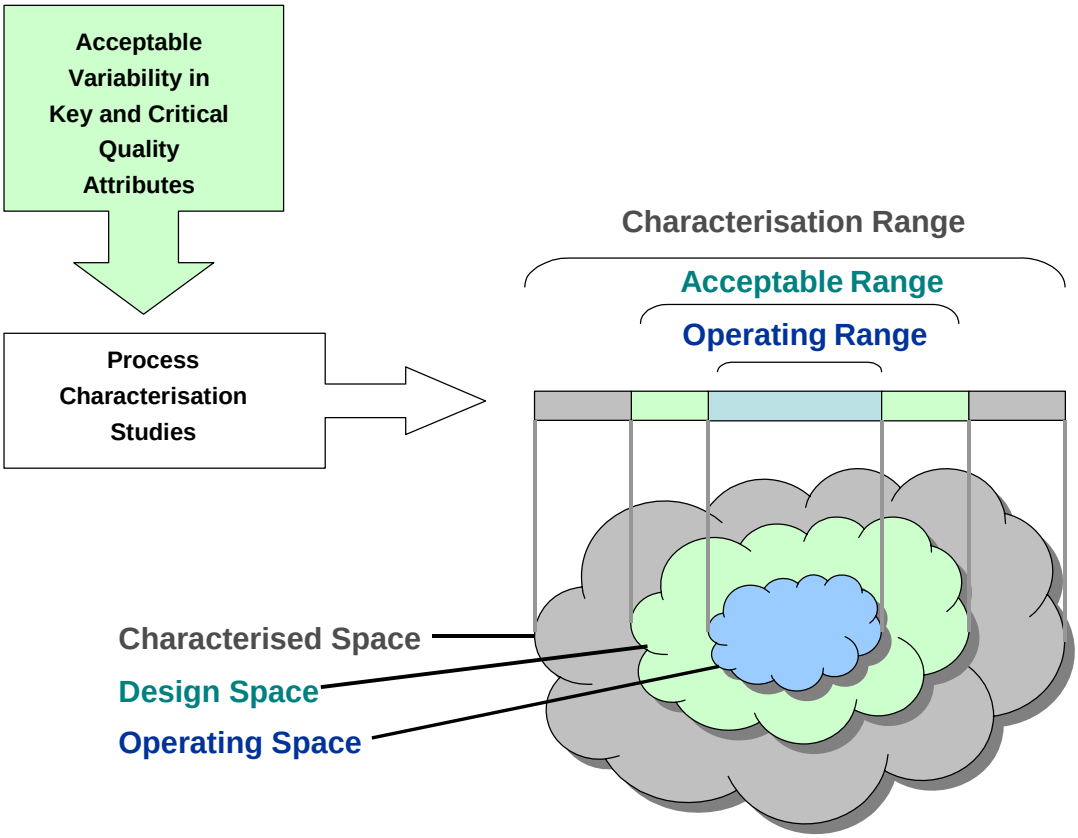
Pharmaceutical development studies are the basis for any further development activities for a drug product. They should contain the risk analysis of the suitability of a formulation and its manufacturing process, identifying any weak points and provide sufficient assurance that the product can be manufactured reproducibly in the specified quality. (25)

The quality of a product should be built into by design and well understood processes: Starting in the development phase and continuing throughout a product's life cycle (27):

- All critical sources of variability are identified and explained
- Variability is controlled by the process
- Product quality attributes can be accurately and reliably predicted over the Design Space established for materials used, process parameters, environmental and other conditions.

The term Design Space is introduced as the multidimensional combination of product design, manufacturing process design, manufacturing process parameters, formulation attributes and raw material quality that have been demonstrated to provide assurance of quality. (27, 28)
To determine the Design Space, first the acceptable variability in product quality and process performance attributes are established based on clinical exposure of the product, knowledge from other similar products, and general scientific understanding about the molecule. The next step is to perform the characterisation studies to explore the characterisation ranges and establish acceptable ranges for key and critical operational parameters. The characterisation studies should cover wide ranges for product quality and process performance attributes, extending beyond what is typically tested based on manufacturing logistics and practicability alone. The acceptable range for the critical parameters and its combination is defined by the assurance of quality and defines the Design Space. It is desirable to have the operating space nested comfortably within the Design Space as illustrated in the figure below. (29)

Figure 5: Illustration of the Creation of Design Space from Process Characterisation Studies and the Relationship between Design Space and the Characterized and Operating Spaces (29)



Movement within the Design Space is not considered to be a change, whereas movement out of the Design Space is considered to be a change and normally initializes a regulatory post approval change process. The Design Space is proposed by the applicant and is subject to regulatory assessment and approval. (26)

Information from pharmaceutical development studies can also be the basis for the Quality Risk Management. (26) The Pharmaceutical Development can create a basis of flexible regulatory approaches by reducing uncertainty and facilitates risk based regulatory decisions, continuous improvements without the need for regulatory reviews as well as ´real time´ quality assurance. (27)

Furthermore the pharmaceutical development describes the knowledge that the selected dosage form and the formulation are suitable for the intended use of the product.

At a minimum, all aspects, which are critical to the product quality concerning drug substances, excipients, container closure systems and manufacturing processes should be determined and control strategies established. These critical formulation attributes and process parameters are generally identified through an assessment to the extend to which their variations can have an impact concerning the quality of the product. (26, 30, 31)

In addition, further studies can lead to an enhanced knowledge and scientific understanding of product performance over a wider range of material attributes, processing options and process parameters leading to an expanded Design Space and facilitating for example:

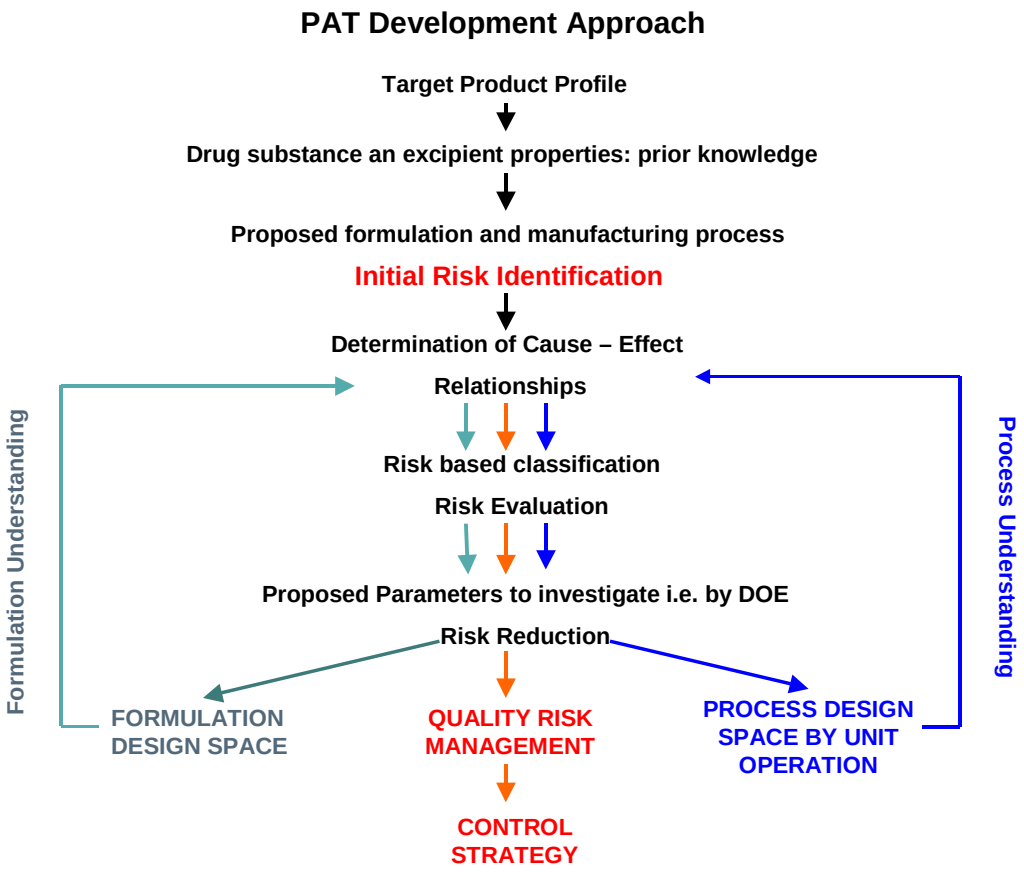
- Risk based regulatory decisions for reviewers and inspectors
- Manufacturing process improvements within the approved Design Space without further regulatory review
- Reduction of post-approval submissions
- Real-time quality control, leading to a reduction of end-product release testing.

This understanding can be gained by several different methods such as Process Analytical Technology PAT, formal experimental design, prior knowledge and/or experienced lifecycle knowledge. (26)

PAT is a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. The tools, which are used can be categorised in process analysers, process control tools, design of experiments and mulitvariant data analysis. An appropriate combination of some of these tools or all, may be applicable to a single-unit operation or to an entire manufacturing process. (5)

In the following figure PAT is used to develop Design Spaces for the formulation and manufacturing as well as the process and the control strategy for the product via Quality Risk Management.

Figure 6: PAT Development Approach (31)



The benefits of implementing PAT may include (32):

- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls
- Preventing rejects, scrap, and reprocessing
- Reducing costs dependent on inventory and time in storage
- Increasing automation to improve operator safety and reduce human error
- Facilitating continuous processing to improve efficiency and manage variability

At a given product quality it can be differentiated between ´baseline expectations´ and an enhanced understanding. Since PAT is not mandatory it is the applicant's decision how much resources to invest and at which time in a product's life cycle. (25)

Fritz Erni from Global Quality Operations, Novartis and member of the EFPIA PAT topic group, describes the desired state from the industry perspective as (31):

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes

- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- Ability to effect continuous improvement and continuous “real time” assurance of quality.

2.4.2 ICH Q9 Quality Risk Management

The guideline ICH Q9 provides a common understanding of what Quality Risk Management means and principles and examples of tools for Quality Risk Management. (33)

The ICH Q9 document on Quality Risk Management was adopted at step 4 at the ICH Steering Committee meeting in November 2005 and has been already adopted in Japan and the United States. Work is currently underway to determine the most appropriate way to adopt ICH Q9 into the European regulatory system. (33)

In the EU risk management is not a new concept in GMP or in the approach of the assessment of quality dossiers but no common understanding exists about what Quality Risk Management means and how it is applied in the pharmaceutical environment. (46)

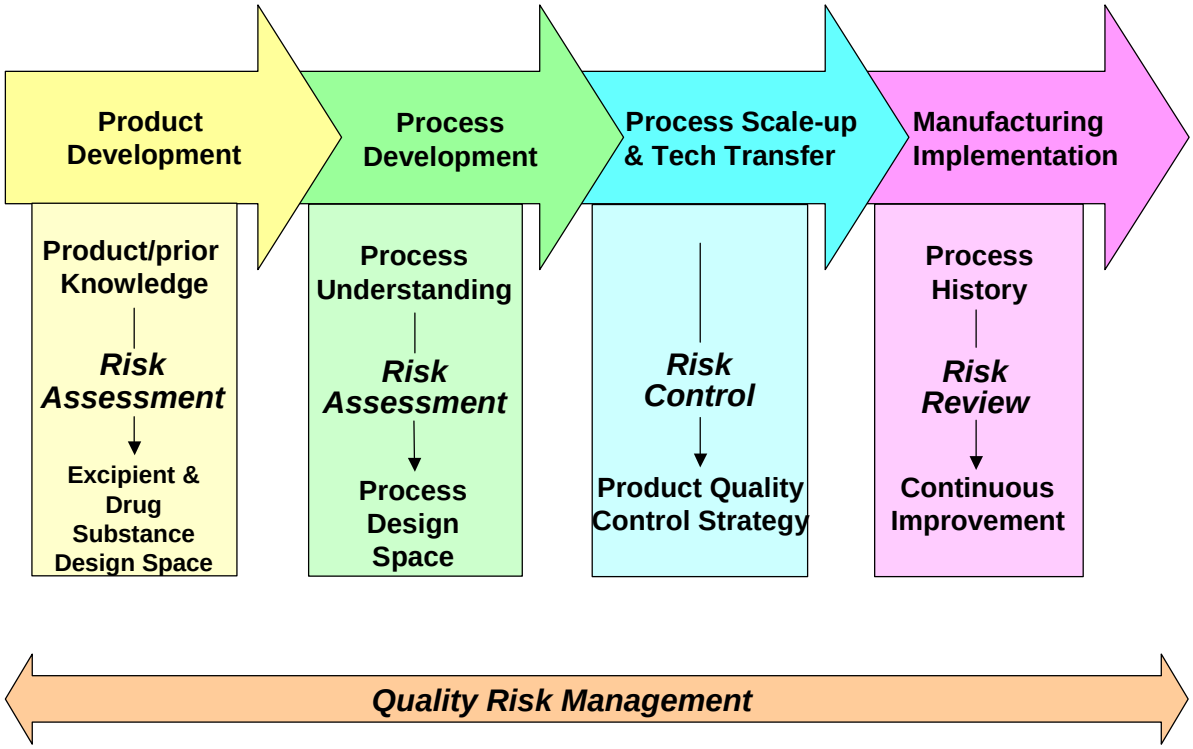
ICH Q9 provides an international standard, principles, tools and methods for Quality Risk Management. The level of risk should determine the extend of risk management. (70)

For the MAH the Quality Risk Management principles can be applied (36):

- During pharmaceutical development in order to develop the Design Space for the drug substance and excipients and to define the process Design Space
- In the manufacturing environment for process scale-up and technological transfer to define the product quality control strategy as well as for continual process improvement
- For the preparation of the quality part of the marketing authorisation dossier

The following figure demonstrates the role of risk management in the product life cycle (36):

Figure 7: Role of Risk Management in the Product Lifecycle (36)



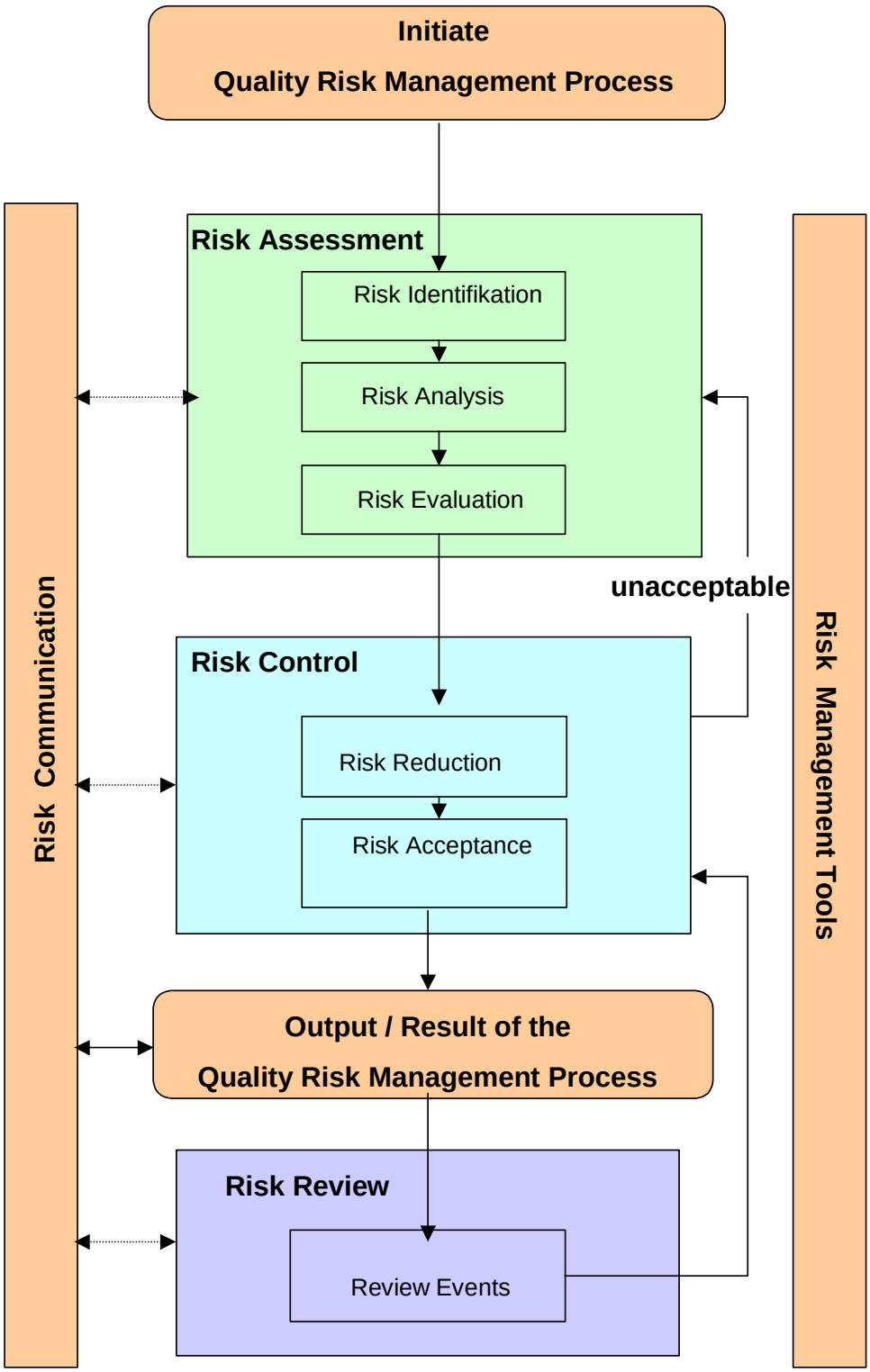
For the regulatory authorities Quality Risk Assessment applies in the fields of (33):

- The pharmaceutical assessment of the quality part of the marketing authorisation dossiers
- GMP inspections
- The handling of suspected quality defects

The application of Quality Risk Management by manufacturers is optional but it is expected to provide many benefits from identifying risks to analysing the risks, evaluating the consequences of a high-risk event occurring, and establishing policies for risk reduction or acceptance. (22) Risk management can help companies to identify the most essential areas, that require closer monitoring and evaluation and those areas that merit less attention. If a quality problem arises the use of Quality Risk Management can improve science-based decision-making, leading to better and more informed decisions. (37) Through the use of modern statistical and analytical methods, the critical sources of variability in a production system can be defined and appropriate quality controls can be established. Risk analysis can estimate probabilities of being outside or inside of design limits in various scenarios. (38)

According to ICH Q9 a typical quality risk management process shows the diagram below with the main steps of risk assessment, risk control and risk review:

Figure 8: Overview of a Typical Quality Risk Management Process (33)



The methods and tools described are already well-known and approved in other industries for example the semiconductor industry. They are amongst others Failure Mode Effects Analysis (FMEA), Failure Mode Effect and Critically Analysis (FMECA) and Fault Tree Analysis (FTA). (33)

In the pharmaceutical industry it is becoming evident that Quality Risk Management is a valuable component of an effective quality system. Since not every single tablet, capsule, injection etc. can be tested before administering to the patient an effective Quality Risk Management approach can further ensure the high quality of the product to the patient and lower the risk of product recalls for the industry.

For regulators it can provide greater assurance of a company's ability to deal with potential risks and the extend as well as the level of direct regulatory oversight can be beneficially affected.

As a conclusion Quality Risk Management can facilitate better use of resources by all parties. (22, 33, 37)

2.4.3 ICH Q10 Pharmaceutical Quality System

The Q10 guideline is based on ISO concepts, includes applicable Good Manufacturing Practice regulations and complements ICH Q8 Pharmaceutical Development and ICH Q9 Quality Risk Management. (39)

The guideline applies to pharmaceutical drug substances and products including biotechnology and biological products throughout the lifecycle from development, to technology transfer, manufacturing and finally to product discontinuation. (39, 40)

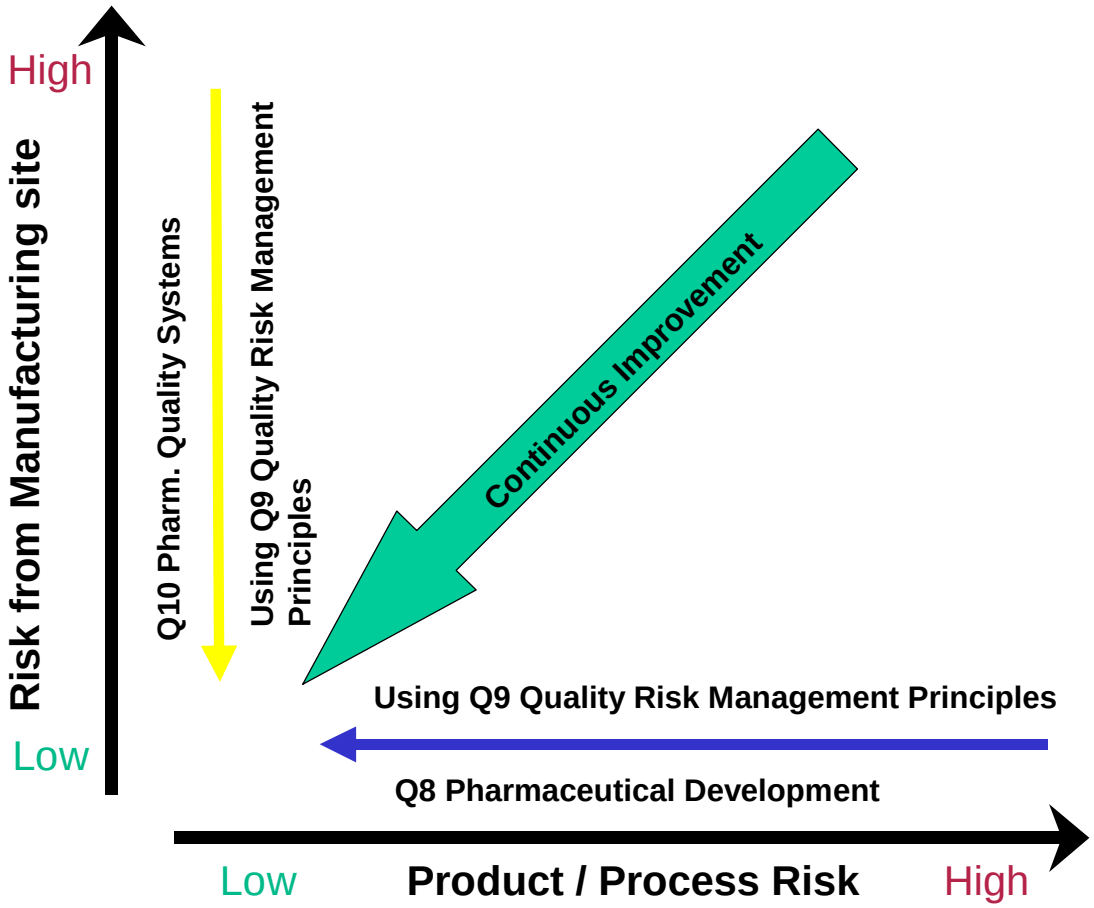
It is intended to describe a model for an effective quality system, which is needed to establish and maintain a state of control that can ensure the realization of a quality drug product and facilitate continuous improvement over the product life cycle (39, 40):

- Improve quality of pharmaceutical products
- Improve cGMP compliance
- Facilitate continual improvement
- Necessary for implementation and effective utilization of:
    - Quality by design (ICH Q8 Pharmaceutical Development)
    - Risk Management (ICH Q9 Pharmaceutical Risk Management)
    - Effective knowledge transfer
        - Corrective and preventive action CAPA
        - Change control
        - Review and inspection

- Demonstrating the state of control: Ability to manage movement within the Design Space.

The figure below demonstrates the links between Q8 Pharmaceutical Development, Q9 Quality Risk Management and Pharmaceutical Quality Management:

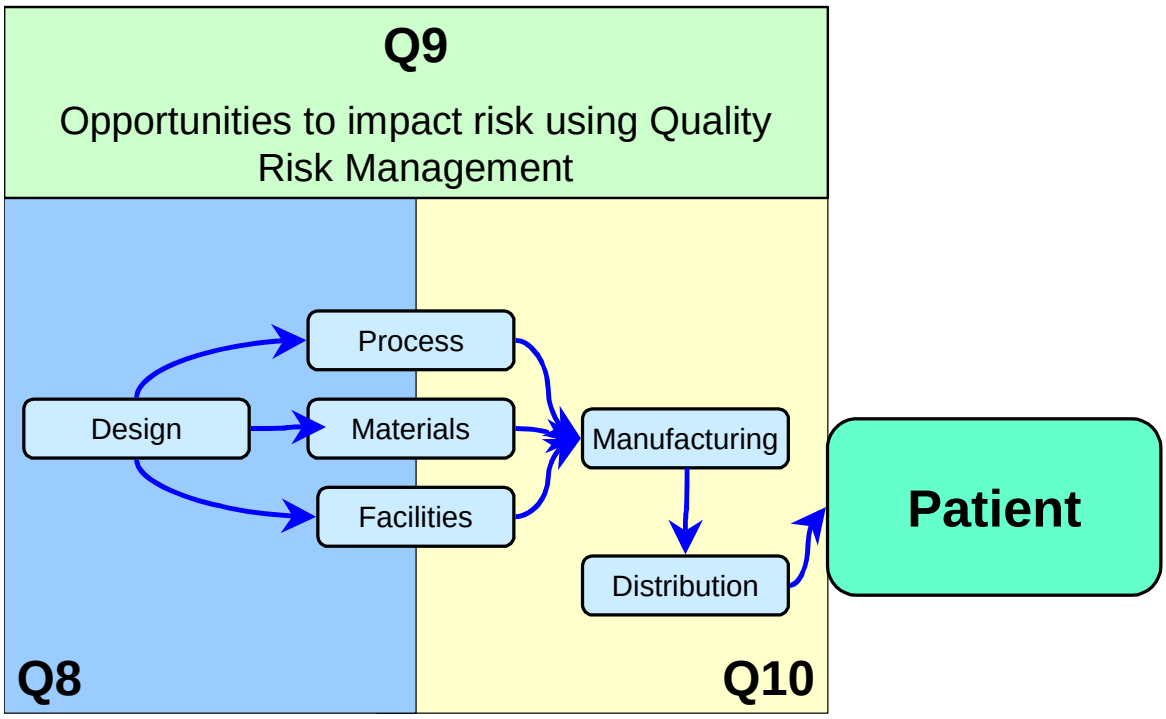
Figure 9: Links between ICH Q8, Q9 and Q10 (35)



Product and process risks can be lowered by a scientific Pharmaceutical Development and defining Design Spaces. Risk from manufacturing is controlled by Pharmaceutical Quality System.

Using Quality Risk Management principles and through continuous improvement of processes overall risks can be minimised for the patient, as shown in the figure below:

Figure 10: ICH Q8, 9 and 10 and Patient Risk (35)



The contents of ICH Q10 that are additional to current GMP requirements are optional. (44) A company might adopt certain or all elements of Q10 or even an alternative quality system, depending on the existing system. (37, 41)

The guideline is on step 3 of the ICH process. The step 2 version has been released for consultation on 9 May 2007. (42)

The role of management respectively senior management as having the ultimate responsibility to ensure that an effective quality system is in place is outlined. (39)

From industry perspective an ICH guideline on pharmaceutical quality systems is needed since there are divergent approaches to quality systems across regions leading to suboptimal deployment of resources by industry and regulators, inconsistent approaches to compliance inspections followed by potential delays in new product launches and availability of medicines. Furthermore the implementation of innovation and continuous improvement can be speeded up. (43)

2.4.4 Authority and Industry Initiatives

Linked to the ICH discussions in the ICH guidelines Q 8, Q 9 and Q10 several initiatives were launched by the health authorities in order to develop tools for their implementation. In the US

the initiative on Pharmaceutical Current Good Manufacturing Practices was started in 2002 to modernise the regulation of pharmaceutical manufacturing. Under this umbrella further initiatives were started to implement Q 8, Q 9 and Q10. Some of the tools, such as the use of Comparability Protocols and Regulatory Agreements have been taken up in the EFPIA/EVM/EBE proposal for the Revision of the Variation Regulations, see chapter 4.2 Impact of ICH Guidelines Q8, Q9, Q10 introducing the Comparability Protocol and 4.6 Regulatory Agreement. The relevant initiatives are described in the following.

2.4.4.1 Process Analytical Technology (PAT) Initiatives from FDA and EMEA

In the US the FDA PAT initiative was launched in November 2001. In September 2004 the Guidance for Industry PAT – A framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance was published.

In November 2003 the EMEA founded the PAT team consisting of four assessors and four GMP inspectors plus an observer from EDQM. (32) Its general objective is to provide a forum for dialogues and understanding between Quality and Biologics Working parties and Ad Hoc Group of GMP Inspection Services to prepare a harmonised approach in Europe on assessment of applications and inspections of products, systems and facilities for PAT, including quality by design principles and manufacturing science in the context of PAT. Further objectives are for example to review the legal and procedural implications on the EU regulatory system such as the revision of existing guideline and for new guidelines. The PAT team will review and assess mock submissions of applications using PAT and quality by design principles and develop a procedure for the assessment involving a co-ordinated approach by assessors and inspectors as well as identify their training needs. (44)

As a basis for the discussions with the EMEA PAT team EFPIA is developing mock submissions for the drug substance part of the dossier ´mock S2´ and for the drug product ´mock P2´.

In March 2006 the EMEA published a Reflection Paper on chemical, pharmaceutical and biological information to be included in dossiers when PAT is employed which is intended to assist companies already planning to file PAT-based submissions.

EMEA published a procedure for worksharing between the national Competent Authorities on quality variations in June 2006 in order to give a guidance for the submission of variations concerning Design Space and PAT for nationally authorised products. This document outlines timelines and the cooperation between national authorities. (45)

Further tasks of the PAT team include the harmonisation of the EU approach with USA and Japan and to act as a forum for informal presentations from drug companies. (32, 46)

2.4.4.2 FDA Initiative Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century and ONDC´s New Risk-Based Pharmaceutical Quality Assessment System, Comparability Protocol and Regulatory Agreement

As in the European Member States the Food and Drug Administration (FDA or the Agency) is facing similar challenges concerning their change system for medicinal products.

In August 2002, FDA announced a significant new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernise the regulation of pharmaceutical manufacturing and product quality — to bring a 21st century focus to this critical FDA responsibility. The initiative was intended to modernise FDA's regulation of pharmaceutical quality for veterinary and human drugs and selected human biological products such as vaccines. (47)

Due to increasing inspections and shrinking resources, which can be allocated for inspections FDA had to find a solution to insure the safety of the products. FDA identified efficient risk management as the primary way to be applied to the review, compliance, and inspections since it is less elaborate to inspect the risk management system of a company than the complete contents of the manufacturing facility qualification and process validation. (48)

As part of this initiative, both the pharmaceutical, as well as the chemistry, manufacturing, and controls (CMC) regulatory programs were evaluated with the following objectives in mind (47):

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities.

The final report was published in 2004. (47))

In July 2005 the FDA announced a pilot program involving the submission of chemistry, manufacturing, and controls (CMC) information consistent with a new pharmaceutical quality assessment system. CDER´s Office of New Drug Chemistry (ONDC) is responsible for reviewing the CMC section of new drug applications and post-approval CMC changes.

The challenges and difficulties include (49):

- Inconsistencies in application quality combined with a lack of adequate pharmaceutical development information prevent from taking full advantage of risk-based assessments. This leads to multiple CMC review cycles and a considerable increase in the number of post-marketing manufacturing supplements being submitted to the Agency (Supplements are applications for moderate or major changes. For details see chapter 3.2.).
- The need for an applicant to seek FDA prior approval through a supplement before effecting post-marketing CMC changes may be slowing down the introduction of new technologies and innovations into pharmaceutical manufacturing.
- A lack of process understanding on the part of the applicant and submission of insufficient product knowledge information in applications could lead to tight product specifications at the time of approval, resulting in unnecessary recalls and drug shortages if a product batch fails to meet the specification.
- As a result of a heavy Agency workload and lack of resources, there is insufficient scientific dialogue between CMC reviewers and applicants during drug development prior to the submission of new drug applications (NDAs).
- Reliance on a single chemistry reviewer to evaluate the entire CMC section of a drug application throughout the entire life cycle does not facilitate optimum use of ONDC's limited resources or available expertise.
- Many valuable resources are being used to generate comprehensive CMC summaries and analyze raw data in CMC submissions — tasks that could be done more efficiently by applicants.

As a reaction the ONDC was restructured to Office of New Drug Quality Assessment (ONDQA) in November 2005 and has started a pilot program for a new pharmaceutical quality assessment system. The new system focuses on risk-based assessments relying on available knowledge about the product and the manufacturing process and is intended to facilitate continuous improvement and manufacturing process optimization. The supplement review process is planned to be streamlined based on the degree of process understanding exhibited in the application and the extent of controls and quality systems that have been implemented throughout the applicant's manufacturing process. (36, 49, 51))

This approach is intended to (49):

- Reduce the frequency and extent of prior review of changes by FDA
- Accelerate the distribution of drugs produced using an improved manufacturing process and / or process optimization
- Permit the manufacturer to notify FDA of the change in an Annual Report

- Offer means to prevent or diminish drug supply disruptions or shortages

Comparability Protocol

The ONDC has proposed the use of Comparability Protocols to implement numerous CMC changes. A Comparability Protocol provides evidence that an applicant has a firm scientific, and technological understanding of the drug, the manufacturing process, the controls, the proposed change, and the potential effect of that change on the product quality. FDA's evaluation of a Comparability Protocol would include a determination of whether a change is made in accordance with that protocol and may be submitted under a reduced reporting category. Depending on the level of process and product understanding exhibited in the protocol, the change could be made with less prior review by FDA. (49) Several Guidances for Industry have been published on Comparability Protocols such as Guidance for Industry: Comparability Protocols-Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information 2003, Guidance for Industry: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process, 2005.

The role of the CMC reviewer is changing and linked much more to GMP inspections. ONDQC´s review staff is now more directly involved as a partner in inspections. (49)

In comparison with the US the European GMP system and also the documentation on Pharmaceutical development shows already a risk-based approach.

Regulatory Agreement

Moheb Nasr, director of FDA´s Office of New Drug Quality Assessment proposed creating a Regulatory Agreement between the FDA and the applicant to govern the chemistry, manufacturing, and controls (CMC) sections of new drug applications (NDAs) in 2005. (51)

According to Nasr the Regulatory Agreement is intended to cover critical CMC issues and to enable the applicant to share Quality by Design information without concerns about regulatory implications. It should be an opportunity for the applicant to build a regulatory framework for post-approval changes based on product and process understanding in order to afford appropriate regulatory flexibility and to facilitate product lifecycle management. Further it is intended to provide a mechanism for the applicant to propose a regulatory strategy specific to a product and process and allowing continuous improvement. (51)

The proposed content of the Regulatory Agreement is (36, 53, 66):

- Critical CMC information as formulation, Design Space, specifications, critical process parameters and their acceptance criteria, criteria for real time release and critical processes.
- Description of the manufacturing control strategy

- The criteria used to evaluate post-approval changes
- The proposed regulatory process to manage post-approval changes, such as no filing, CBE, PAS etc. in order to facilitate product lifecycle management.

The Pharmaceutical Research and Manufacturers of America PhRMA sees in the Regulatory Agreement besides Comparability Protocols, risk based guidances and Design Space a tool to reduce the number of supplements identifying life-cycle commitments based on quality by design. (54)

3. Concepts of Selected National Variation Systems

The national change procedures in Germany/Austria and the US follow different philosophies and procedures compared with the current EU systems. Industry and authorities have in the respective countries long-time experiences. Since these have influenced the industry proposal considerably they are described in the following chapter.

All change systems including the EU regulations differentiate between minor and major changes, line extensions or new applications. Minor changes in comparison to major changes have a very low potential to influence the quality and efficacy of the medicinal product.

The main characteristic of the Germany/Austrian system is the high responsibility born by the industry. In the respective laws only the criteria for major variations and new applications are laid down. All other changes fall into the category minor changes and can be implemented simultaneously with the notification to the authority. As new applications and line extensions major changes have to be approved.

The US change system defines the principles in the law (Code of Federal Regulation) and provides guidances for the details, which can be adapted to the evolving needs of authority and industry more easily. Minor changes can be implemented immediately and are submitted to the FDA only once a year as part of the Annual Report. Moderate changes follow a tell-and-do – respectively tell-wait-and-do-procedure. Major changes have to be approved. Also for the fee system the US could be a model: An annual fee has to be paid per product and manufacturing facility plus additional fees for each major variation. (55) As the EU, the US are currently adapting to the new ICH guidelines Q8 and Q9 and furthermore revising their regulatory review system and in connection their GMP system to a risk-based approach as shown in chapter 2.4.4.2.

3.1 Germany and Austria

The national procedures for variations are regulated in § 29 of the German Medicinal Products Act ´Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz-AMG)´ as amended and in § 24 the Austrian Árzneimittelgesetz-Novelle 185/1983 as amended.

Both laws differentiate between:

a) Minor variations (´meldepflichtige Änderungen´), which are changes requiring only a notification – tell and do notification procedure (Erlaubnis der Änderung mit Verbotsvorbehalt)

b) Major variations (´zustimmungspflichtige Änderungen´), requiring an official consent – tell, wait and do procedure (Verbot der Änderung mit Erlaubnisvorbehalt mit Genehmigungsfiktion)

c) Major variations (´zulassungspflichtige Änderungen´) requiring an official approval – explicit approval procedure (Verbot der Änderung mit Erlaubnisvorbehalt)

a) Minor Variations: In contrary to the EU regulations only the major variations are defined. All other changes fall by default under ´minor variations´. All changes, which are considered as minor variations can be implemented when the variation is submitted to the authority. The advantages are that the pharmaceutical company does not have to wait for an approval and the authority is not under time constraint to start a variation procedure: The change can be implemented immediately. The responsibility of the change and that it does not influence the quality of the product in a negative way is carried by the pharmaceutical company.

Nevertheless the authorities review the minor changes. Objections might be raised, which have to be answered in the given timeframe. If the responses are not satisfactory the authority can reject the change. In this case the MAH has to go back to the former status with all its negative impacts, e.g. if a change in methods or equipment is concerned or the up-scaling of a product. The pressure on the MAH is high in order to avoid a rejection.

b) Major changes, requiring an official consent: All major changes are listed in the German and the Austrian drug law. The lists of changes are partly identical.

Germany: The change can be implemented after official approval or 3 months after submission according to §29 (2a). (56) A variation can be refused because of reasons according to § 25 AMG. (57)

Austria: according to AMG § 24 (5) the change can be implemented after 6 months, if there is no rejection. (58)

c) Major changes, requiring an official approval: The cases in which a new marketing authorisation has to be applied for are listed in the respective laws:

Germany: See AMG §29 (3). (56)

Austria: See AMG § 24 (2). (58)

The lists of changes are partly identical.

The advantages of the German and Austrian system are the clear definitions of the major variations, which have a considerable impact on the quality, and safety of the medicinal product. For all minor changes the MAH has to take responsibility in the first line. Nevertheless the authorities can raise their objections and reject a variation if necessary. For the MAH the big advantage is that the majority of variations being minor can be implemented without delay and since the major changes are clearly defined there is no risk that a minor change could be categorised as major by default.

Furthermore several changes concerning one marketing authorisation can be cumulated and submitted within one variation. This reduces the workload for authorities and industry since only one dossier has to be prepared and reviewed.

A disadvantage to the EU Variation Regulation system is that a new indication means a new application in Germany and Austria versus a type II variation. (1, 56, 58) In Germany the introduction of genetic engineering to the manufacturing process for a non-biological drug substance with a certificate of suitability CEP is a new application versus a type Ia variation.

In total the German and Austrian variation system have considerable advantages compared with the EU Variation Regulations and the suitability is shown by long-term experience of a number of decades. These systems appear to be efficient, effective and safe.

3.2 USA

The US variation system differentiates between drugs (chemical entities) and biologics: The legal basis of changes to a marketing authorisation is the Code of Federal Regulations 21 CFR 314.70 for drugs (chemical entities) and 21 CFR 601.12. for biologics defining the principles of the system.

In order to give support in more detail and to categorize a change the FDA has published several guidances for industry such as

- Changes to an Approved NDA or NDA from 2004;
- Changes to an Approved Application: Biological Products, from 1997;
- Packaging and Post approval Changes PACPAC
- Several guidances for industry on Scale up and Post-approval Changes SUPACs, which are usually dedicated to specific dosage forms;
- Bulk Actives Post Approval Changes BACPAC I and II
- Questions and Answers on specific topics.

These guidances are recommendations and help to categorise a certain change as well as the information, which has to be submitted to support the change.

3.2.1 Current Variation System

The risk-based approach of the US system was codified in section 116 of the Modernization Acts 1997 and requires manufacturers to assess the effects of manufacturing changes on the identity, strength, quality, purity, and potency of a drug or biological product as those factors relate to the safety or efficacy of the product. (59).

3.2.1.1 Categories of Changes

Pursuant to 21CFR 314.70 and 21 CFR 601.12 the applicant must notify the FDA about each change in each condition and must assess its effects before distributing a product made with the manufacturing change. A supplement or Annual Report must include a list of all changes contained. (59)

According to Guidance for Industry: Changes to an Approved NDA or ANDA a change is categorised corresponding to its potential impact in four reporting categories:

- Major changes have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.
- Moderate changes/Supplement – change being affected in 30 days CBE 30: have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.
- Moderate changes/Supplement – change being effected CBE. Certain moderate changes which are identified by FDA can be implemented when FDA receives the supplement, see Guidance for Industry: Changes to an Approved NDA or ANDA
- Minor Changes reported in the Annual Report have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. (59, 60)

For all changes including the change via Annual Report FDA can ask for further scientific information from the applicant.

In case of disapproval of a CBE 30 or CBE FDA can order the manufacturer to cease distribution of the drug that has been made using the disapproved change. (60)

An applicant can submit protocols, for example a comparability protocol as a prior approval supplement to apply for the reduction of the reporting category. (59, 60, 61)

The table below gives an overview of the reporting categories, when an approval is necessary and when a change can be implemented.

Table 5: Overview of Reporting Categories (59, 60)

Reporting category	Reporting	Approval necessary ?	Implementation of the change
Minor change	Annual Report, Once a year	No FDA approval before implementation	During the year
Moderate change	Supplement - Change being effected CBE	Notification	At the time of notification
	Supplement - Change being effected in 30 days CBE 30	Notification	30 days after notification
Major change	Prior approval supplement	Yes	After approval

For biologics also three reporting categories exist: Minor, moderate and major changes with the difference that the moderate changes fall under “supplement – change being effected in 30 days”. (61)

3.2.1.2 New Applications

New drug applications NDAs or Biologics License Application BLAs are required for the change of active ingredients, routes of administration, dosage forms, strengths/concentrations, or excipients. (62)

3.2.1.3 Fees

According to the Prescription Drug User Fee Act (PDUFA) the FDA is allowed to collect additional resources in form of fees from the industry. PDUFA enables FDA to accelerate its drug evaluation process without compromising review quality. The Prescription Drug User Fee Amendments of 2002 extended PDUFA through September 30, 2007 (PDUFA III). (55) PDUFA IV is in preparation. (63)

The revenues are provided by a set of three fees (64):

- Application fees for the submission of certain human drug or biological applications;
- Annual establishment fees paid for each establishment that manufactures prescription drugs or biologics; and
- Annual product fees assessed on certain prescription drugs and biologics.(35)

The amount of prescription drug product fees is calculated every year and adjusted to account inflation and increased workload. The fees are published every year for the respective fiscal year starting on October 1 and ending on September 30 each year.

The application fees have to be paid with each application or supplement under PDUFA. Establishment and product fees are usually published by FDA in August. (65)

The following drugs are not included in the term ´prescription drug product (64)´:

- Whole blood or a blood component for transfusion.
- A bovine blood product for topical application licensed before September 1, 1992, an allergenic extract product, or an in vitro diagnostic biologic product licensed under section 351 of the PHS Act (Section 351 of the PHS Act provides the authority for regulating biological products. Biological products are regulated by the Center for Biologics Evaluation and Research.).
- A biological product that is licensed for further manufacturing use only
- A drug that is not distributed commercially AND is the subject of an application or supplement submitted by a State or Federal Government entity.
- A large volume parenteral drug product approved before September 1,1992.

3.2.1.4 Review Times

Under PDUFA the FDA published the objectives for review times. According to PDUFA III, covering 2003 to 2007 the goals are:

Table 6: FDA Goals of Review Times: Summary of Goals at the End of PDUFA I, II, and III (55)

Goal	PDUFA I	PDUFA II	PDUFA III
Complete review of priority original new drug and biologic applications and **efficacy supplements**	90 % in 6 months		
Complete review of standard original new drug and biologic applications and **efficacy supplements**	90 % in 12 months	90 % in 10 months	
Complete review of manufacturing supplements	90 % in 6 months	90 % in 4 months if prior approval needed. 6 months otherwise	
Complete review of resubmitted new drugs and biologic applications	90 % in 6 months	90 % of class 1 in 2 months and 90% of class 2 in 6 months	
Complete review of resubmitted efficacy supplements	No goal	90 % in 6 months	90% of class 1 in 2 months and 90% of class 2 in 6 months

Supplements for New Indications of Approved Drugs: Because new indications might have the potential to deliver important benefits for patients, these ´efficacy supplements´ are treated with higher review priority than other supplements. The Agency published the Guidance for Industry: Standards for the Prompt Review of Efficacy Supplements; Including Priority Efficacy Supplements, 1-May-1998 and the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May-1998 describing efficacy standards for supplemental indications.

The performance of FDA is reviewed regularly and published on the FDA homepage. Measures for improves e.g. of review times are discussed.

3.2.2 Current Discussions and Further Developments

The current variation system was established in 2004: In April 2004 FDA was amending its regulations on supplements and other changes to an approved application in order to implement the Manufacturing Changes Provision of the Food and Drug Administration Act of 1997 (Modernization Act). This rule was effective 22 June 2004. It requires that the manufacturers assess the effects of changes on the identity, strength, quality, purity, and

potency of a drug or biological product as those factors relate to the safety or effectiveness of the product. To accommodate future technological advancements, section 116 of the Modernization Act and this rule provide that FDA may change the designation of a particular category of a change from major to non-major or vice versa, by regulation or guidance. This concept of an evolving risk-based approach to manufacturing changes is consistent with the agency´s Good Manufacturing Initiative: Pharmaceutical cGMPs for the 21st Century, see 2.4.4.2. The goals of this initiative are among others to strengthen public health protection by implementing risk-based approaches, continuous improvement and innovation in manufacturing by allowing manufacturers to make certain types of changes in their processes without prior FDA approval. (59)

As in Europe the industry and FDA have the target to reduce manufacturing supplements and a revision of 21 CFR 314.70 is in discussion. In February 2007 during a FDA Public Meeting the FDA announced that the manufacturing supplements should be reduced drastically by introduction of the ´Design Space´-concept. One of the goals is to limit supplements to major changes, e.g. development of a new formulation and end supplements for the vast number of modifications and improvements that occur within predefined parameters. (22)

3.2.3 Differences to the European Variation System

Compared with the EU the US variation system is more flexible: There is not one list categorising certain changes in a regulation. The categorisation is done via several guidances, which are dedicated to certain topics and can be changed more easily.

In the current EU regulations is no room given to use further knowledge gained through experiences for example on the manufacturing process and to switch reporting categories: In the US a switch from CBE 30 to CBE is possible. The rule ´Supplement and Other Changes to an Approved Application´ from 2004 provides for a mechanism of continuous improvement through the guidance process that might provide for less burdensome documentation of certain changes as manufacturing processes and pharmaceutical science develop. (59) In the EU if a change is not listed, it is automatically a type II variation - no matter, if it has a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. There is no possibility to switch from a type IB to type IA variation.

Similar to the German and Austrian system the responsibility of the applicant is considerably higher compared with the current EU regulations.

In the US, the restructuring of the ONDC to ONDQA is creating a strong link between GMP inspections and the regulatory process. (59)

Similar to Germany and Austria the US variation system allows submitting several changes per product in one supplement and naturally in the Annual Report.

4. Industry Proposals and Consultation Paper from the EU Commission

In March 2006 the EU Commission informed EFPIA and other industry associations that the process on reworking the Commission Regulation (EC) 1084/2003 and Commission Regulation (EC) 1085/2003 would be started.

From the position of the EU Commission the revision became necessary due to the following aspects:

- Adoption of the ICH guidelines Q8 (step 5), Q9 (step 4) and Q10 being in preparation (step 3): After discussion with the Heads of Medicines Agencies it was decided that ICH Q8, Q9, and Q10 cannot be implemented without the revision of the Variation Regulations.
- Experiences of the different stakeholders (authorities and industry) with the current Variation Regulations.

In September 2006 EFPIA jointly with the European Biopharmaceutical Enterprises EBE and European Vaccine Manufacturers EVM (EFPIA/EBE/EVM) sent the industry proposal to the EU Commission (Appendix 1).

The EU Commission published the Consultation Paper: Better Regulation of Pharmaceuticals: Towards a Simpler, Clearer and more Flexible Framework on Variations in October 2006 (Appendix 2).

On 12 December 2006 a workshop of the EU Commission with industry associates was held to receive industries feed-back on the Consultation Paper. EFPIA/EVM/EBE sent their final response to the EU Commission and EMEA on 20 December 2006 (Appendix 3).

In March 2007 EFPIA/EVM/EBE forwarded the Immediate Notification List (Appendix 4).as well as the Major Change List to the EU Commission (Appendix 5).

During the meeting of the Pharmaceutical Committee of the EU the Commission presented results of the consultation of its strategy paper. The outcome of the consultation will be taken forward in the preparation of the draft legal texts, which is planned to be published for public consultation in the course of 2007. (67)

On 10 July 2007 the EU Commission published for consultation on the ´co-decision´ part the Draft Proposal for a Directive of the European Parliament and of the Council amending Directive 2001/82/EC and Directive 2001/83/EC as regards amendments to the terms of marketing authorisations for medicinal products. The Commission intends to consult all stakeholders on a proposal to modify the legal basis of the Variations Regulations, so that all authorised medicinal products are subject to the same criteria for the evaluation, approval and administrative handling of variations, regardless of the procedure under which those

medicines have been initially authorised. The public consultation does not address the aspect of the review, which can be implemented through ´comitology´, and it was announced that these aspects would be addressed in another round of consultation. (4)

The EFPIA/EVM/EBE proposal starts from the current variation system in the EU keeping what is running well and looking for improvements for critical areas and trying to implement the new requirements deriving from the ICH guidelines Q8, Q9, Q10 as well as taking up experiences from national variation systems such as Germany/Austria and the US. The overall target is to improve flexibility, to avoid unnecessary burden for industry and Competent Authorities and facilitate improvements of manufacturing, quality and safety of medicinal products.

In the following chapter the point of views of the industry proposals, proposals respectively discussion papers from EFPIA/EBE/EVM, APIC dated August 2006, AESGP from 19 December 2006 and Bundesverband der Arzneimittel-Hersteller from Germany BAH from 22 January 2007, as well as the EU Commission Consultation Paper will be discussed.

The central documents are the EFPIA/EVM/EBE proposal and the EU Consultation paper, which are outlining the future variation system. EFPIA represents 32 European national pharmaceutical industry associations as well as 44 companies undertaking research, development and the manufacture in Europe of medicinal products for human use. The companies are mainly international operating companies. (50) The discussion papers of the other industry associations represent the dedicated interests of the active ingredient manufacturers (APIC), the self-medication industry (AESGP) and more European or nationally operating companies in Germany (BAH). (Appendices 6, 7 and 8)

4.1 Introduction and Principles

According to EFPIA/EVM/EBE, the proposed variation system should be applicable to all marketing authorisations regardless of the route of registration such as centralised, mutual recognition, decentralised or national in order to improve the harmonised implementation for all variations and to make the processes and timelines more predictable for all changes. (Appendix 1) Similar to the US system it is proposed that the lists of details on minor and major should be developed as separate Commission guidelines to allow the flexibility to be easier adapted according to experience. (Appendices 4 and 5)

All industry associations consider the German and Austrian change system as an appropriate model for the discussion of the revision of the European Variation Regulations.

The APIC position paper presents a preferred system, a minimum option and suggestions for interim improvements for the current in their eyes malfunctioning system. The main issue is that due to the current variation systems improvements concerning active ingredients are often

blocked by the MAH since the circumstances are difficult to handle: Filing variations in different countries, for different formulations, via different procedures with different approval times with full approval for implementation of the change may only be obtained after several or many years. (Appendix 8)

From the AESGP point of view it should be agreed on the general approach before discussing the details of an harmonised system in the centralised, mutual recognition/decentralized and national procedures. Since the systems in Germany and Austria have been used satisfactorily nearly 30 years without any reported public health concerns they are proposed as a model. For non-prescription medicines the United Kingdom has started the development of Better Regulation for Over the counter Medicines Initiative BROMI, which is in line with the above-mentioned systems. (Appendix 7)

The BAH, representing numerous German based companies with national marketing authorisations, agrees with the Design Space concept but sees a harmonisation of European variations and national systems only attractive, if it would be as pragmatic as the current German/Austrian system. They have reservations with view to a harmonisation of marketing authorisations via the variations system. For international operating companies the harmonisation of national authorisations via article 30 procedure is recommended. (Appendix 6)

The EU Consultation Paper includes the veterinary medicinal products to the new variation concept. (Appendix 2) This essay focuses on medicinal products for human use only.

4.2 Impact of ICH Guidelines Q8, Q9, Q10

The EFPIA/EVM/EBE proposal includes a risk and science based approach including the concept of self-management of changes where appropriate. Innovation and continuous improvement of pharmaceutical manufacturing processes, and the rapid implementation of changes that have no potential impact on patient safety or that reduce any potential risk would be encouraged.

The same science and risk-based concepts should be applicable to all products: Small molecules, biological medicinal products including biotechnology products and vaccines as well as herbals.

The new Variation Regulations should reproduce the text from Q8 defining a Design Space and its implications for changes. The use of Quality Risk Management tools as described in Q9 should be encouraged to assess the impact of a proposed change and to facilitate its assignment to a type I or type II variation. Q10 focuses on quality systems to be applied throughout the product life cycle, including process development, technology transfer and routine manufacturing. (Appendix 1)

All industry associations promote ICH Q8, 9 and 10 and especially the Design Space concept in general. (Appendices 6, 7 and 8) AESGP does not see the relevance of Design Space at the moment for their sector and proposes to be optional. (Appendix 7) APIC has a similar view concerning already marketed products. Similar to the US approach the system should be supported by a verification system through inspections by the authorities. (Appendix 8)

The EU Commission Consultation Paper introduces the Q8 concept of Design Space in the Variations Regulations as well. In spite of the ICH guideline stating “Working within the Design Space is not considered as a change” these changes would be notified to the Competent Authorities through an annual reporting system. (26, appendix 2) The impact on industry and authorities would be the need of additional resources although a Design Space had been submitted and approved before.

The EFPIA/EVM/EBE response argues against the annual notification of changes within the Design Space. For example for adaptive manufacturing processes, which can be adjusted to accommodate variability in input materials, each batch may be processed slightly different depending on particular attributes of the raw materials in order to minimise the variability of the output. And adjustments might even be performed during the process. According to the Commission proposal each of these changes would have to be notified. EFPIA/EVM/EBE sees a huge increase in complexity and workload for industry and regulators.

The EU Commission proposes the application of the Design Space as well as the changes outside the Design Space to be categorised as major changes or line extensions. EFPIA/EVM/EBE does not agree to the line extension.

According to EFPIA/EVM/EBE the Commission had not fully appreciated the intentions of the ICH guidelines, nor their implications. Significant and specific incentives should be provided to applicants who have developed enhanced product and process understanding, to use the principles of Q8, Q9 and Q10. EFPIA/EVM/EBE recommends that these incentives should include the self-management of changes to approved Design Spaces, and the more general shift of changes from currently requiring pre-approval towards notifications via Annual Report. The concepts of Comparability Protocols could be applied for example for changes widening the Design Space in order to categorise them as a notification as long as the amendment demonstrated to meet pre-approved quality criteria. EFPIA/EVM/EBE proposes the introduction of Regulatory Agreements, which would summarise the applicant’s compliance commitments and post approval change strategy, see 4.6, which the FDA is actively promoting in pilot studies, see 2.4.4.2. (22, Appendix 3)

4.3 Variation Categories

According to EFPIA/EVM/EBE the variation categories should apply to all types of medicinal products and without specific requirements for biological medicinal products.

In the proposal the current categories and the criteria for allocation are changed:

4.3.1 Type I Notifications for Minor Changes

The EFPIA/EVM/EBE proposal revises the categorisations of the IA and IB variations. A type I variation applies to a minor change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as they may relate to the safety or the risk–benefit profile of the medicinal product.

I. Type IA: Immediate Notifications

Immediate notifications are required for changes, which are necessary for the Competent Authority to fulfil its legal obligation for effectively supervising the industry and for information which needs to be kept current for patient safety or sourcing issues. These changes are typically amendments to the administrative information of the EU application form, e.g. name and/or address of the MAH, name of the medicinal product, name and/or address of a manufacturer of the medicinal product. They do not require validation or assessment however the MAH would require acknowledgement of receipt from the Competent Authorities. Furthermore changes are included to this category, concerning the product information, which have been assessed by the Competent Authority before, for example changes following a renewal or an assessment of a PSUR, implementation of class labeling statements from new or revised core SPCs, Article 31 referral procedures, adaptation to QRD templates where the MAH fully complies with the request. No further data would be submitted.

Procedure and Timelines: The notification should be submitted and the change would be implemented simultaneously. A letter and replacement pages for the MA dossier would be sent as documentation.

In Appendix 4 a list of immediate notifications, which was sent to the EU Commission in March 2007, is provided. EFPIA/EVM/EBE proposes that such a list could be developed as a separate Commission guideline to allow the flexibility to be adapted easier according to experience and knowledge.

II. Type IB: Periodic Notifications

Type IB notifications mean minor changes to a MA dossier not requiring a submission or prior approval before implementation. They would be recorded in an annual notification and submitted to the relevant Competent Authority on a regular basis. The

Annual Notification should contain the type and date of implementation of each change.

The following principles were proposed:

a. A single report for each product defining and summarising the quality and non-quality changes introduced in the previous 12 months
b. Submitted to the relevant Competent Authorities on an annual basis
c. The birth date of the annual notification should be determined by the MAH in agreement with the Competent Authority
d. Replacement pages for the relevant sections affected by the changes would be included in the annual notification
e. The Competent Authority/agency would acknowledge the receipt of the annual notification

All type IB changes concerning the quality section of the dossier would be managed under a company's change management system and involve appropriate quality and technical assessment and validation and/or stability studies where appropriate. (Appendix 1)

AESGP supports the suggestions to group the necessary notifications in an Annual Report and proposes to send the immediate notification for administrative purposes via e-mail. (Appendix 7)

APIC recommends the replacement of the current type I variation list with a limited list of major type II variations. All ´non-type II´ variations should cover all non-major changes being notified through biennial reporting. (Appendix 8)

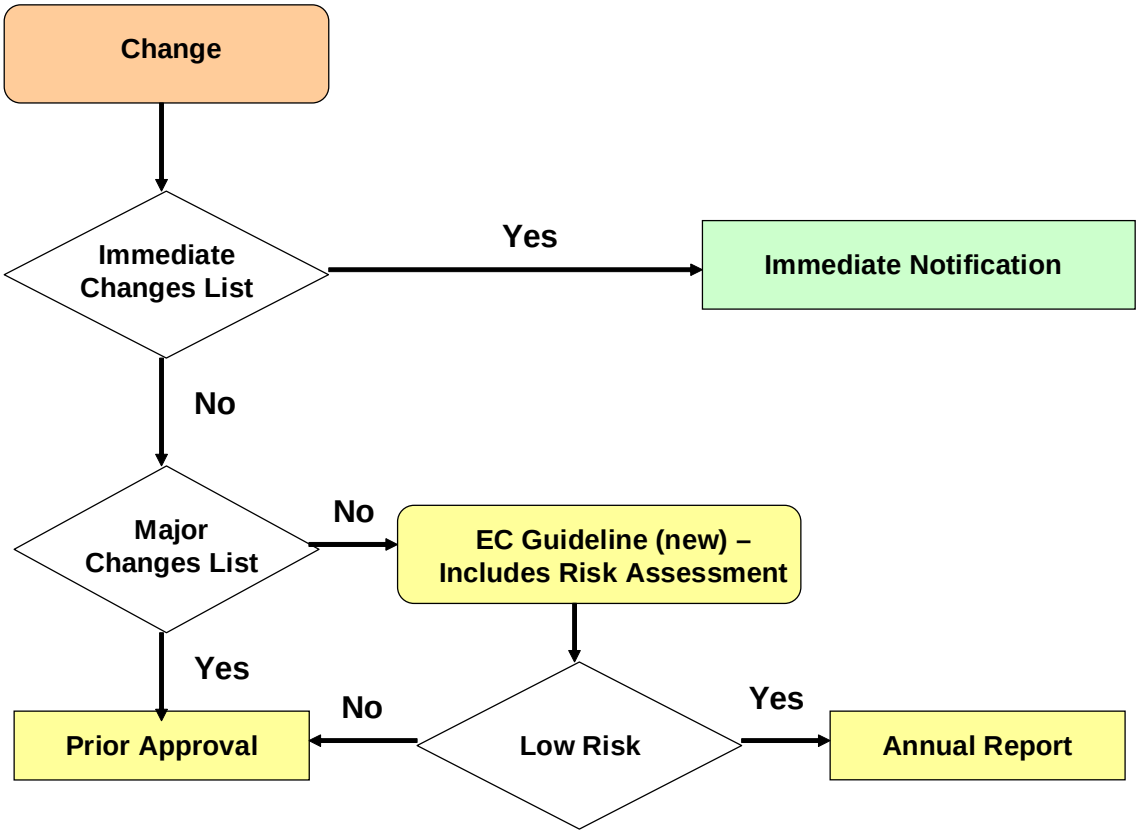
The EU Commission Consultation Paper follows the proposal on the change of the current type IA variations to be implemented into an Annual Report in order to reduce the tremendous amount of this type of variation submissions being the majority of variations and to change from the current Tell and Do procedure to a Do and Tell procedure. The EFPIA/EVM/EBE differentiation of type IA and type IB variations, as mentioned above is not followed. But specific administrative changes where Competent Authorities need to be informed rapidly e.g. changes in the name/ address of the MAH or the manufacturer of the active substance to be submitted immediately are mentioned in a foot note. The MAH would have the option to group Annual Reports so that one joint document was submitted per Competent Authority, outlining all minor changes for the relevant medicinal products. The Consultation Paper introduces the possibility for the concerned Competent Authorities to request all regulatory information related to the type IA change from the date of implementation from the MAH. (Appendix 2)

The current type IB variations as a change requiring prior approval, is kept. The EU Commission Paper introduces the use of the type IB procedure by default to changes which

are not listed in the Appendixes to the Variation Regulations to be handled by default as type IB variations and no longer as type II unless the concerned Competent Authorities considers that, due to the potential impact of the proposed change on the quality, safety or efficacy of the product, the variation should be processed as a type II variation. Biologics should not be handled in the same way as chemical entities. Some more changes are now classified as type I A/B variations and included in the list. (Appendix 2)

EFPIA/EVM/EBE demands a listing of minor changes, which should be reported as immediate notification. Immediate notifications of labeling changes, which are the implementation of previously agreed changes with no further required scientific assessment and the update of annexes to the MA dossier in line with the most current QRD template should fall under this category. Concerning the type IB procedure by default EFPIA/EVM/EBE agrees that an automatic default to a type II variation is not appropriate. Nevertheless they insist on the proposed categories as minor and major changes with two lists to be created defining immediate notifications and major changes. The type IB variation category needing prior approval is objected. The proposed decision tree on procedures concerning variation categories of changes is shown below:

Figure 11: Decision Tree for Variation Categories (Appendix 3)



The appropriateness of company decisions controlled through inspections and/or limited checks of Annual Reports. (Appendix 7)

The BAH rejects the type IB default procedure for changes, which are not listed as type IA or II, because this would lead to single case decisions with insecure outcome and complicating the procedure. The applicant should be able to categorise his change type according to clear criteria. (Appendix 6)

AESGP agrees with the EU Commission proposal on a Type IB procedure and proposes for the type IB Tell-Wait-Do procedure the submission of the variation dossier to the RMS and after 30 days to be implemented by the applicant. In case the RMS requests additional documents for approval, the clock stop may be used to provide additional data by the applicant. The change will be submitted to the other Member States as part of the Annual Report. If the RMS considers the proposed change to have a major impact on quality, safety or efficacy the variation should be processed as type II with all Member States involved. (Appendix 7)

4.3.2 Type II Variations: Prior Assessment for Major Changes

According to EFPIA/EVM/EBE this category applies to a major change which has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as they may relate to the safety or the risk –benefit profile of the medicinal product and requires approval by the Competent Authority prior to implementation.

Similar to the German variation system, it is proposed to develop a list of such major changes. A change not included in the list would automatically default to a type I notification (IA or IB).

Procedure and Timelines:
The currently existing review times of 30, 60 and 90 days shall be kept with some adjustments to the specific types of changes allowing one clock-stop with a specified time limit in order to allow a predictable overall evaluation time of the variation. The MAH should have the right to appeal if the outcome of the procedure is not agreeable.

60-day procedure: For changes on quality and SPC the 60-day procedure would be applied as default procedure:

- Changes to the quality dossier.
- Changes to the clinical particulars in the SPC not covered by the 90- or 30-day procedures (e.g. changes to section 4.2 Posology and Method of Administration alone).
- In case an accelerated review is granted for an indication extension the 60-day procedure should be followed

30-day procedure: For all safety related product information changes, for example:

- Changes to product information following an Urgent Safety Restriction.
- Changes to the safety-related information in the SPC (sections 4.3-4.9[*]), initiated by the MAH.
- Changes made at the request of Competent Authorities (e.g. product information changes following the assessment of a PSUR or renewal application; implementation of class labelling statements from new or revised core SPCs or Article 31 referral procedures), where the MAH does not comply fully with the request and/or submits further data.[*]

90-day procedure: Addition or change to therapeutic indications, addition of a new strength, of a new pharmaceutical form or a new route of administration.

Currently the addition of a new strength within the current approved dose range, a new pharmaceutical form or a new dosing regimen falls under an application for line extension whereas a new indication falls under a type II variation for which usually extensive new clinical and maybe additional safety data have to be evaluated. Therefore it is proposed to include the addition of a new strength, of a new pharmaceutical form or a new route of administration into the type II variations category since the amount of new data to be provided and evaluated is even lower. (Appendix 1)

APIC proposes a fast track approval system for changes with clear quality, environmental or safety benefits to accelerate the implementation of these kinds of improvements. (Appendix 6)

The EU Commission Consultation Paper does not refer to any timelines. (Appendix 2)

In March 2007 EFPIA/EVM/EBE sent a list of type II major variations, see appendix 5 and proposed that such a list as for the type I immediate notifications would be developed as a separate Commission guideline to allow the flexibility to be easier adapted according to experience. The purpose of the guideline is for reviewers and industry to conduct appropriate risk assessments, which enable them to classify prior approval changes from notifications. It is not intended that the list will be exhaustive. The list distinguishes Quality Related Changes from Regulatory Changes concerning SPC changes. The Quality Related Changes contain furthermore a list of specific Type II changes for biological products. Regulatory changes differentiate on review times proposing normally a 60 days review timeline for type II variations. An extended period of 90 days is proposed for changes to, or addition of therapeutic indications, adding a new strength, dosage regimen, pharmaceutical form or route of administration. A reduced 30 days period should be foreseen for changes, which are made at the request of the Competent Authority, where the MAH does not comply fully with the

[*] 4.3 Contraindications 4.4. Special warnings and precautions for use 4.5 Interactions with other medicinal products 4.6 Pregnancy and lactation 4.7 Effects on ability to use machines 4.8 Undesirable effects 4.9 Overdose

request and/or submits further data, for example product information changes following the assessment of a PSUR or renewal application and for changes to the safety-related information in the SPC sections 4.3-4.9 initiated by the MAH.

4.3.3 Extension Applications

EFPIA/EVM/EBE proposes to apply a 120 days assessment period versus the current 210 days. (Appendix 1)

Again the EU Commission Consultation Paper does not refer to any timelines. The introduction of a new Design Space or changes to an approved Design Space are proposed to be evaluated as variation or line extension, see above chapter 4.2. (Appendix 2)

4.4 Worksharing Procedure for Type II Variations to Nationally Authorised Products

Since one of the major problems experienced by the industry are the varying approval times, different national variation procedures and different scientific criteria for the evaluation of changes for nationally approved products, EFPIA/EVM/EBE proposes that type II changes should be assessed via an optional Mutual Recognition process available to the MAH. A single Agency would assess the variation on behalf of the other concerned agencies in a work sharing procedure and the outcome would be implemented nationally via type IA/IB notification. A Rapporteur and Co-Rapporteur would be appointed. Furthermore this optional procedure is proposed to be applicable to ´related´ variations, see below, in which a single change or a small group change is applicable across a number of national authorisations.

The proposed procedure consists of three phases:

I. Pre-submission to CMD:

In this phase the validity of the procedure to the changes required is accepted, including the agreement that the differences between the dossiers in the Member States would not impede approval. The Rapporteur and Co-Rapporteur is appointed at this step.

II. Assessment

The Rapporteur and Co-Rapporteur assesse the submitted variation dossier on behalf of all concerned national agencies, resulting in the adoption of a final Assessment Report and, where appropriate, proposed product information wording to be included into the national product information.

III. Implementation in the national authorisation

Following the adoption of the final Assessment Report the variation should immediately be implemented. The legal approval of the change should be defined in the legislation as being the date when the variation procedure has been finalized in step II. The

implementation and revision of the national documents in step III is only an administrative step. For changes affecting product information, the submission of the translations to the national Competent Authority should occur 5 days after finalisation of step II. If the MAH has not received any justified objections on the translations within 10 days, he may proceed with the implementation

The impact on industry would be the harmonisation of the change implementation Europe-wide. This procedure would save resources considerably for authorities, since duplicate assessment by every Competent Authority would be avoided, without requiring full harmonisation of the dossiers across all Member States. Nevertheless the MAH would have a strong motivation to harmonize the quality section of dossiers. (Appendix 1)

The EU Commission Consultation Paper recognises the negative effects for globally operating companies having to deal with different requirements from authorities and the impact on the delay or even preventing the implementation of certain changes as well as logistical issues. Since the majority of marketing authorisations are national a significant effect would be achieved by the harmonisation of the legislative framework. The suggestion would require a change in the co-decision legal basis of the Variations Regulation in order to include the purely national licenses. A 2-steps approach was suggested and a transitional period, e.g. 2 years. Furthermore a voluntary worksharing between national authorities for the assessment of certain quality variations has been elaborated in the context of an agreement by the Heads of Medicines Agencies concerning the introduction of PAT and Design Space. (68) The worksharing was also proposed for a change concerning several medicinal products as it is already in place for Vaccine Antigen Master Files and Plasma Master Files. It would apply for type IB and type II changes and for several marketing authorisations owned by the same MAH. Each Member State would have to agree to participate in the worksharing procedure and for the Member States, who do not agree, the variation would have to follow the standard procedure. The authority for assessment would be the EMEA in case of one centrally authorised product was involved. If no centrally authorised product is involved the MAH could chose among the involved Member States. The Use of the CMD (h) or (v) could be also used for coordination. All involved authorities would be given the opportunities to comment on the assessment before it is finalized. The finalized assessment would be the basis for the update/ amendment of the relevant marketing authorisations but it is not binding and Member States would retain the right not to agree with the assessment. (Appendix 2)

The consultation on the Directive amending Directive 2001/83/EC has been started and the Draft Proposal for the Directive amending Directive 2001/83/EC has been published on 10 July 2007 in order to modify the legal basis of the Variations Regulations so that all authorised medicinal products including the purely nationally approved ones are subject to the same

criteria for the evaluation, approval, and administrative handling of changes, regardless of the procedure under which these products have been initially authorised. (4)

The EFPIA/EVM/EBE concern is that the worksharing procedure is optional for national authorities. The fact that authorities have to confirm their participation prior to each variation will have a negative impact on the timelines. Therefore the worksharing procedure should not be optional for National Authorities. Furthermore EFPIA/EVM/EBE proposes that objections must be based only on potential serious risk to public health grounds. Legal obstacles to the mandatory national implementation of the outcome of the worksharing procedure are recognized and the Commission is encouraged to explore ways of using the co-decision procedure. If at all the right of Member States not to agree with the assessment should be expressed before the assessment is finalised and not afterwards. (Appendix 3)

4.5 Related and Grouped Variations

4.5.1 Related Variations

EFPIA/EVM/EBE: A related variation application concerns one change relating to several products, for example the change in the active ingredient specification or the addition of common adverse event information to the SPC.
If the change relates to products, which have been approved via different procedures (centralized, mutual recognition or national) it would be desirable to have a mechanism to include all products in one variation application. At minimum it should be possible to apply for a related variation within one route (centralized, mutual recognition or national). In the case that several RMSs are involved the process should allow to agree on one RMS to lead the assessment. (Appendix 1)
The EU Commission does not refer to the term ´related variations´ explicitly, but includes this concept in its proposal of the worksharing procedure, see 4.4.

4.5.2 Grouped Variations

EFPIA/EVM/EBE: Grouped variations concern several changes for a single marketing authorisation beyond being consequential, for example addition of information to different sections of the SPC; multiple, separate improvements to an analytical procedure and a production process to be implemented at the same time. (Appendix 1)
Currently this is possible for variations, which are nationally approved for example in Germany, Austria or the US. Again it saves resources on authority's as well as industry's side, since only one variation dossier has to be submitted and assessed.

The EU Commission does not respond to the possibility of the submission of several changes concerning a single marketing authorisation in general but mentions them for the annual reporting system specifically for changes to CEPs. (Appendix 2)
According to EFPIA/EVM/EBE it should also be possible to combine related and grouped variations. (Appendix 1)

4.6 Regulatory Agreement

EFPIA/EVM/EBE proposes that a Regulatory Agreement should be an optional product specific document being used to define the applicant's post-approval change strategy for the quality section of the marketing authorisation application dossier. The agreement between authority and applicant should cover all critical-to quality attributes, parameters and procedures. It would outline the regulatory flexibility at the highest level and allow these companies to self-manage the majority of quality changes, without needing to seek prior approval.
The following components could form part of the Regulatory Agreement:

- Listing of critical-to quality attributes, critical process parameters and boundaries of Design Space
- Reproduction of the defined control strategy including specifications and analytical methods, together with other compliance-related aspects such as composition.

A Regulatory Agreement could operate on several levels, for example:

- Lowest level: Statement of the specific quality elements of the dossier with which the company had to comply. Compliance requirements e.g. composition, specifications etc. are separated from the supporting scientific and technical knowledge
- Highest level: Demonstration of product and process understanding and quality system based on the implementation of ICH Q8, Q9 and Q10. The post-approval change requirements should be based on the Regulatory Agreement defining principles concerning their possibility to impact the quality of the product: such as changes requiring notification as well as prior approval. The agreement could also include such concepts as change management protocols including Comparability Protocols.

Within the Regulatory Agreement the applicant could provide a list of changes, which could now be implemented via a type I notification instead of a type II variation, including changes for which comparability criteria for a specific change were approved, for example the expansion of Design Space complying with a pre-agreed protocol. Where experiments to a pre-agreed protocol were necessary to show the validity of the proposed change, a type II variation would have to be submitted.
It would be up to the applicant to describe the applied Quality Risk Management principles referencing to ICH Q9 in order to qualify changes as part of the variation application.

The applicant would submit the application for a Regulatory Agreement for:

- Future marketing applications as part of the initial dossier. The Regulatory Agreement would be part of the approval.
- Existing marketing authorisations: Submission as type II variation using the 60 days review timeline. The submission of the Regulatory Agreement should not be used to make an immediate change itself. It should be only used for the approval of manufacturing commitments in the future. (Appendix 1)

APIC also suggests the Regulatory Agreement concept. (Appendix 8)

The EU Commission Consultation Paper does not take into consideration the possibility of a Regulatory Agreement.

4.7 Fees System

EFPIA/EVM/EBE: The fees system would have to be adapted to the revised variation system. (Appendix 1)

4.8 Further Suggestions

4.8.1 Variations Conditions: Type IB to Type IA

The EU Commission Consultation Paper proposes to change the category of some changes from type IB to IA as listed in the attachment of the Consultation Paper. (Appendix 2)

EFPIA/EVM/EBE welcomed the proposal on type IA notifications (immediate notifications) and has provided its own proposals in March 2007 for type IA but as immediate notifications. (Appendix 4)

4.8.2 Variation Conditions for Biologicals

The EU Commission Consultation Paper provides a list of changes, which are reclassified from type II to type I. (Appendix 2)

The EFPIA/EVM/EBE agrees that a number of changes are major changes for biologicals, but minor changes for chemical entities. (Appendix 3) A list on type II variations has been provided in March 2007. (Appendix 5)

4.8.3 Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF)

The EU Commission Consultation Paper proposes, supported by EVM to clarify the legal applicability of the Variation Regulations to the VAMF/PMF and the ´2nd step´-inclusion of a new PMF/VAMF in a given MA dossier as a type IB variation and the inclusion of an updated/amended PMF/VAMF as a type IA. (Appendix 2 and 3)

4.8.4 Coordination Group for Mutual Recognition and Decentralised Procedures (CMD)

The EU Commission Consultation Paper proposes, supported by EFPIA/EVM/EBE, to introduce the appropriate references to CMD concerning the initiation of an arbitration procedure in case a Concerned Member State does not agree with the assessment of the Reference Member State. (Appendix 2 and 3)

4.8.5 Monographs and Certificates of Suitability and Changes to Active Ingredients in General

According to the EU Commission Consultation Paper the following changes would be grouped and reported through the annual reporting system (Appendix 2):

- Change of the certificate due to a new version of the European Pharmacopeia without any technical change
- Renewal of the certificates without any technical change
- Administrative change applied for by the holder of the certificate

EFPIA/EVM/EBE proposes further.(Appendix 3):

- Since new versions of a CEP based on technical changes are issued by the EDQM after scientific assessment the submission should also be considered as administrative and qualify for a ´do and tell´ procedure
- Changes in the specifications or impurity profile of the active substance should be an annually reportable change if it is an obvious improvement. Currently it is a type II variation.
- Communication between the EDQM and the national health authorities should be improved in order to allow EDQM assessors to state in general if the change in the active substance has the potential to negatively influence certain types of pharmaceutical formulations, in order to avoid multiple assessments of the technical details of a new CEP.
- The timelines for assessment of CEP related submissions and the issue of CEPs should be similar as for variations via the Decentralised Procedure.

Representing the interests of the active ingredients manufacturers APIC proposes to exclude the majority of API changes from the requirement to be submitted by the MAH. According to APIC MAHs block sometimes changes in order to avoid variations. The API manufacturer should submit these changes and a supplementary submission by the MAHshould not be required. This would especially apply to changes that do not have a significant potential to adversely impact the safety or efficacy of the medicinal product. The necessary strong relationship between API manufacturer and MAH should be enforced through inspections by

the authorities. APIC is referring to good experiences of the CEP system operating before the introduction of the revised Variation Regulation in 2003 when minor changes did not result in a variation to the MA. A second good example was the dedicated API approval system in the US (Abbreviated Antibiotics Drug Applications for bulk). Its deletion had been an unintended side effect of the FDA Modernization Act. (Appendix 8)

4.8.6 Clarification of Deadlines

The EU Commission proposes to introduce a fixed deadline for national authorities to update/amend the marketing authorisation following approval of a variation, e.g one month. (Appendix 2) EFPIA/EVM/EBE proposes a maximum period of 15 days since the process is mostly of administrative nature. For labeling changes the submission of final translations would have to be submitted 5 days after finalization of the assessment and the authorities would have another 5 days to notify justified revision requests to the translated texts. If there is no reaction within this period the translated texts would be considered approved. An update of the marketing authorisations is not warranted to occur before implementation of the change. (Appendix 3)

APIC proposes a legally binding approval time for all variation systems: National, MRP, Decentralised and Centralised. (Appendix 8)

4.8.7 "Sweep" Mechanism to Update Centralised Authorisations

The EU Commission proposes supported by EFPIA/EVM/EBE to introduce the ´sweep´ mechanism in the Variations Regulations, and to increase the periodicity of the update from 6 months to one year. In addition EFPIA/EVM/EBE encourages other Competent Authorities to introduce such a mechanism for updating their national authorisations. (Appendices 2 and 3)

4.9 Viewpoint of the National Competent Authorities

EFPIA/EVM/EBE is cumulating the viewpoint of the Competent Authorities on the review of the Variation Regulation as collected during discussions with the national industry organisations. So far the opinions from Belgium, Bulgaria, Denmark, Finland, France, Germany, Ireland and Sweden have been published. (69)

All authorities support the simplification process. The following critical points, which have been expressed towards the national industry organisations are:

An increasing workload should be avoided e.g. by level of inspections are expressed by Belgium, Denmark. Sweden forms its opinion more general and opts against any new requirement e.g. Annual Reports for changes within the Design Space.

The annual notification of minor variations would lead to the involvement of higher resources according to France and it might become delicate to provide a negative opinion after implementation of a change. Germany would have to change the current German Law in order to adopt an annual fee. Sweden agrees in principle but considers it not applicable to all type IA changes.

The extension of the EU variation legislation to nationally authorised products is welcomed by Ireland given the proposed two-years transitional period. France agrees the harmonisation of assessment.

Design Space: France prefers Design Space versus the Regulatory Agreement principle since they are not confident with this concept. Sweden agrees to the Design Space concept if it does not increase workload.

Predefined type II variations list: Although the experiences concerning the safety of the medicinal products Germany expressed concerns with the new concept of a predefined type II variation list and having all other minor changes not listed. Their main concern relates to the by default procedure since the authority would like to check in advance whether a change is minor or major.

Grouped and related variations are supported by Germany and Sweden including a "Pharmacovigilance Master File" change procedure.

Worksharing procedure: Sweden agrees that it could be used for major changes of innovative nature but if it should be performed in a more formal way appropriate procedures should be in place and the administrative burden should not be increased.

Type IB procedure by default is not recommended by Sweden. Germany would like to check in advance whether a change is minor or major.

Recommendation for the further proceedings: Germany recommends a two-step approach:

- Implement all provisions which are not controversial and which can be done under the current legislative framework, e.g. related and group variations
- All other parts should be further discussed without any time pressure, e.g. paradigm change in the variation system, inclusion of national marketing authorisations, Design Space

Position followed by the majority of Member States: Bulgaria

The above mentioned comments from national Competent Authorities show clearly that the proposals need to be further discussed and worked out in detail including their pro and cons to authorities and industry.

4.10 Key Changes to the Current System and Their Impact on Industry and Competent Authorities

The following chapter outlines the key points of the industry proposals and the EU Commission Consultation Paper investigating their impact on industry and Competent Authorities.

Harmonisation of the Variation System and Worksharing Procedure

The central aspect of the discussions is the harmonisation of the variation system EU wide for all medicinal products independently if they were nationally approved, via MRP, DCP or CP. This change system should include procedures, assessment criteria and timelines until a change can be implemented. A key aspect is the worksharing procedure as proposed by EFPIA/EVM/EBE: In order to result in a true improvement the participation and the outcome must be mandatory for the Member States. In addition it must be possible that after a positive outcome of a variation procedure the change can be implemented in all Member States concerned immediately. If a national phase needs to follow, e.g. when the SPC has to be changed according to the outcome of the procedure the time spans for the different steps should be fix, for example: The translations of the product information should be sent out within 5 days and the MAH should proceed with its implementation within 10 days if he has not received any justified objections according to the EFPIA/EVM/EBE proposal.

The worksharing procedure would streamline the whole review process. Authorities would be unburdened considerably since a Rapporteur / Co-Rapporteur from one authority would take the lead. Since the review criteria were harmonised neither national Competent Authorities nor the industry would have to proceed with two or even several tracks. The industry could focus the resources on a certain change since the objections would be received in a certain time span and could plan the implementation reliably. Especially for the application of Design Spaces identical review criteria are important. In order to have all involved authorities provide the Rapporteur / Co-Rapporteur a rotation system could be developed e.g. in alphabetical order of the country abbreviation. For example if Germany DE, Austria AT, Poland PL and Spain ES were involved in a worksharing procedure the Rapporteur for the first variation would be from AT, for the second from DE, for the third from ES and so on.

If the participation of authorities in the worksharing procedure was only optional the applicant would have to contact each Competent Authority and receive confirmation of its participation first before the variation could be submitted. Depending on how many authorities were involved and how fast the decision would be made a variation would be submitted with considerable delay. The discussions before submission could turn out to be especially time-consuming in combination with the adoption of the type IB procedure by default since it is foreseeable that not all involved authorities would form the same opinion. It could happen that

the MAH would end up submitting a type IB variation to some authorities and type II variations to others.

If the outcome of the worksharing procedure would be not binding the change could not be implemented at the same time in all countries. The planning of a variation would be more incalculable than it is now and the efforts are even higher.

Annually Reportable Notification System

The introduction of an annually reportable notification system would unburden authorities and industry considerably especially when the nationally approved products were included, since the reported 4524 type IA MR variations are only the tip of the iceberg with over 80 % nationally approved products. On the other side a new reporting system would be introduced but still the effort would be lower since the changes could be grouped. A second big advantage is that the change could be implemented immediately. Industry and EU Commission comply on this proposal.

Types of Variations

Due to the positive experiences in Germany and Austria the industry associations proposed a list for immediate notifications and major changes of type II variations. The changes are categorised in a simple system: minor or major changes.

The difference between the proposed notification of minor changes via an annual reporting system compared with the German / Austrian system is that the German and Austrian authorities are informed of a minor change at the time of its implementation whereas in the industry proposal the authorities are informed some time after the implementation of the change. The appropriateness of company decisions could be controlled through inspections and/or checks of Annual Reports. As shown in chapter 3.2.1.1 the current US change system with its three change categories being the most differentiated foresees the possibility of a tell-and–do-procedure concerning moderate changes as well. As in the EU FDA also aims to limit supplements to major changes and announced that the manufacturing supplements should be reduced drastically by the introduction of the Design Space concept.

The EU Commission kept the current concept of defined type IA and IB changes and introduced the default IB procedure where the RMS has the possibility to re-categorise the IB to a type II change.

This would lead to uncertainties for the industry and to loss of time as described above. It is also difficult to keep the lists up to the current state of the art especially for biologicals making the system very inflexible and focusing on changes which have little impact on quality, safety and efficacy of the medicinal product instead of defining the critical changes.

The EU Commission did not apply the same change criteria for chemical entities to biologicals but revised certain changes to the type IA/B list. Since experiences with biologicals are still much less extensive compared with chemicals re-categorisation of certain changes from time to time seem to stay necessary.

The proposed revision of the classification of some extension applications to a type II variation such as the addition of an additional strength would reduce the effort for the necessary contend of the dossier and its review to the relevant changes. It would speed up the implementation especially when nationally approved products are involved and the worksharing procedure (industry proposal) would be applied.

Introduction of Group and Related Variations

Group and related variations would further reduce the number of submissions and dossiers. For biologicals the continuous improvement process could be speeded up since several variations could be combined whereas currently parallel type II variations concerning the same documentation are not possible. Especially related variations would enable the authorities and the EDQM to avoid multiple assessments of the same change. The condition is the closer cooperation between Competent Authorities and EDQM. The EU Commission did not explicitly mention the term ´related variation´ but described it in the worksharing procedure for the authorities.

ICH Q8, Q9 and Q10

The concepts of ICH Q8 Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality Management provide tools and potential to further save resources and costs. The implementation is optional and its extend should be evaluated case by case.

An approved Design Space reduces the amount of variations. Changes within the Design Space for example up-scaling, movement between different sites can be implemented immediately. If and when a Design Space might be developed for a product is influenced by factors as the complexity of the processes, the sales potential of the product, its safety profile, since how long it is on the market and others. For a pharmaceutical company the development of a Design Space needs to be evaluated and decided case by case taking all aspects into consideration. To have older and mainly nationally approved products benefit from this concept, the application of the Design Space needs to be harmonised within the EU through the worksharing procedure in the mode proposed by EFPIA/EVM/EBE.

ICH Q9 Quality Risk Management and ICH Q10 Pharmaceutical Quality System provide international standards, principles and tools at least in the ICH area. Standardised procedures have the advantage that they can be applied systematically. Risk management and quality systems can be implemented according to the level of risk and can be of great benefit for big

but also smaller pharmaceutical companies since amongst others they can show the potentials to streamline processes, facilitate real-time release, ease decision making during product and process development, improve the quality and save costs. In case the supply is a rate-limiting factor process understanding can help to accelerate the time new products take to reach their sales peak. Thus increases the overall amount of revenue generated over their lifecycle. An example is Roche´s FUZEON (21) For regulators and GMP inspectors it is easier to assess a company's risk management and quality systems than complete contents of facility qualification and process validation. (48)

Comparability Protocols and Regulatory Agreements provide industry and authorities another tool to further streamline the change processes.

The implementation of the ICH Q 8, Q 9 and Q10 concepts, the proposed Comparability Protocols and Regulatory Agreements require the industry to take over more responsibility. Regulatory assessors, GMP inspectors and for the active ingredients the EDQM on the authority's side will have to cooperate closely in order to adequately control industry operations. Authority's personnel will have to be qualified according to their new tasks. The situation seems similar as in the US: With the reorganisation of the ONDC to ONDQA FDA needs to recruit pharmaceutical scientists, chemical engineers and industrial pharmacists to complement current review staff. (29)

A mutual understanding EU wide and a common approach across EU Member States has to be created leading to consistent decisions by assessors and inspectors on very different applications (European and national) across Europe. (3)

If a company implements completely or parts of the ICH Q8, Q9 and Q10 concepts the incentives should be provided accordingly.

The EU Commission proposes by the industry and the application of a Design Space. The difference is that according to the EU paper a change within the Design Space should be notified via Annual Report. This would mean a notification of every adjustment within the Design Space in the annual reporting. As laid down in EFPIA/EVM/EBE´s response, this would lead to such an increase in complexity and workload for industry and regulators that the flexibility gained through the Design Space would be levelled out, see chapter 4.2.

Furthermore the EU Commission Consultation Paper considers the application for a Design Space and also the change of a Design Space as a major variation or extension application. Currently a line extension means a new marketing authorisation application according to the current procedures (DCP, national MA followed by MRP, CP) with submission of a dossier respectively a module 2 and complete CMC part as a minimum from the applicant. The implementation of the Design Space would be delayed considerably minimising again the incentive for its application.

Under these circumstances the advantages of the application of a Design Space seems questionable for the industry as well as for authorities.

The fact that the EFPIA/EVM/EBE proposals on the introduction of Comparability Protocols and Regulatory Agreements have not been taken up by the EU Commission paper seems to indicate that further discussions are necessary on the implementation of the Q8, Q9, Q10 concepts in respect to the variation system and to develop ways to use them efficiently to reduce the administrative burden and to work out the advantages for industry and authorities leading to product improvements in the end. These discussions should include solutions concerning the efficient cooperation between the regulatory assessors and GMP inspectors.

The FDA as well as PhRMA sees in the application of the Comparability Protocols and Regulatory Agreements tools to reduce the number of post approval supplements.

Fee System

As indicated in chapter 2.2.2.2 for a MR variation the current fee system of the different authorities are very different especially taking the fees into consideration for the national variations. With the introduction of the annual reporting system, grouped and related variations the fee systems of each country needs to be adapted.

It is very important that this issue needs to be solved and that it does not influence the discussions on the other points in a negative way.

Further Considerations

The standpoints from industry and EU Commission currently show some essential differences. These issues should be further discussed and the impacts of each on all stakeholders carefully worked out in order to meet the agreed objectives.

Overview

In order to give an overview the key changes proposed by EFPIA/EVM/EBE and by the EU Commission are listed in the following table. (Appendices 1, 2, 6)

Table 7: Comparison EFPIA/EVM/EBE Proposal and EU Commission Consultation Paper

EFPIA/EVM/EBE Proposal	**EU Consultation Paper**	**Impact**	**Compliance + / -**
National variation systems are to be included within the scope of the Variations Regulations for all aspects (timeframes, principles and requirements)	Harmonisation EU-wide. Precondition: Change in the co-decision legal basis of the Variation Regulations	Implementation of a change EU-wide	+
Work sharing at EU level for type II variations to national MA with Member States legally obliged to implement at the conclusion of the assessment phase	Worksharing procedure for type IB and II variations. Optional for Member States, agreement before the variation procedure. Outcome not binding for the Member States.	Negative impact on timelines for submission. In combination with the default IB procedure some CA might categorise a variation as type IB others as type II Implementation of the change is uncertain.	+ – –
The elimination of additional national approval steps outside of those required by the Regulation for changes to MAs approved via MRP/DCP and national procedures	No comment	The implementation of a change could be reliably planned.	–
The introduction of a notification system for immediately notifiable type IA or annually reportable minor changes type IB. List for type IA variations. List for type II variation.	Annual Report for minor changes (type IA), exceptions for specific administrative changes to be notified immediately. No differentiation in immediate notifications and periodic notifications. Type IA and IB variation definitions are kept in principal and via a list. Introduction of type IB variations by default. No definite list for type II variations.	Considerable reduction of submissions especially since one Annual Report to a CA can content all notifications on all products Type IB variations need submission and approval and cannot be implemented immediately Focus on critical changes to quality, safety and efficacy	+ – –

EFPIA/EVM/EBE Proposal	EU Consultation Paper	Impact	Compliance + / -
The same concepts should be applicable to all products, irrespective of whether they are based on small molecules, or are biological medicinal products (including biotechnology products and vaccines) or herbals.	For biologics some type IB changes have been re-categorised to IA, but in general the differentiation between chemical and biological entities has been kept.	Many changes, which are currently type II variations for biologicals will stay.	–
Revision to classification of some extension applications to type II (a change or addition of a new strength, a new pharmaceutical form or new route of administration)	No comment	Reduction of the extend of the dossiers to be submitted and reviewed. Earlier implementation of the change especially if nationally approved products involved (worksharing procedure acc. to industry proposal)	–
Introduction of: Group variations Related variations	 No comment but considered within the annual reporting system Includes this concept in the suggestion of the worksharing procedure for Competent Authorities	 Reduction of submissions Avoid multiple assessments of the same change	– +
Possibility to fully utilise ICH Q8, 9, 10 concepts Changes within the Design Space do not have to be notified Proposal of the use of Comparability Protocol and Regulatory Agreement Disagreement to introduce a change of Design Space as Line Extension	Introduction of Design Space concept Changes within the Design Space have to be notified via the annual reporting system	Reduction of submissions Immediate implementation of a change Time to approval of the Design Space prolonged	+ – –
Fee system to be adapted	No comment	National systems need to be adapted. National law might have to be changed. Issue could influence the other points of discussion in a negative way.	–

5. Conclusion and Outlook

The current revision of the Variation Regulations has a great potential to contribute to the EU Commission's objective in strengthening Europe's economic power insuring high quality medicinal products and being still affordable, their availability and continuous improvement, as well as putting the pharmaceutical industry into a position to develop new products for a growing population of the elderly. This applies to every single EU state and citizen.

The attempts to streamline the change system in the past were not able to reduce the overall number of variations. On the contrary they kept rising. The main reasons are that every change is subject to a separate variation, the same change is reviewed multiple times by many authorities (e.g. CEP changes), grouped variations are not accepted and the inflexible system of defined minor change lists which are fixed by the Variation Regulations. The national change systems (procedures, timelines and assessment criteria) were not included in the former revision. (Chapter 2.1 and 2.2)

At present the Competent Authorities are unable to meet the procedural timelines (EFPIA survey from 2005) since they are obviously working above capacity.

The current revision of the Variation Regulations is influenced by

- The German and Austrian change systems, defining major changes and allowing grouped variations (Chapter 3.1),
- The concepts of ICH Q8 Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality Management providing tools and potential to further save resources and costs (Chapter 2.4) and
- The US approach showing how minor changes can be dealt with in a more efficient way by a do-and-tell-procedure and how the ICH Q8, 9 and 10 concepts can be implemented in respect to the variation system (Chapter 3.2).

The trigger of the revision of the Variation Regulations was the EU initiative "Better regulation" commission policy, which is aiming to reduce bureaucracy in order to strengthen the European industry.

The industry proposals with the key document from EFPIA/EVM/EBE introduce a radical change of the European variation system whereas the Consultation Paper of the EU Commission follows a more moderate approach. The main changes are the harmonisation of the EU variation systems and the worksharing procedures between EU Member States, an annually reportable notification system, the shift from defining minor to major changes and immediate notifications, the introduction of the Design Space concept, Comparability Protocols and Regulatory Agreements (Chapter 4). The standpoints from industry, EU Commission and

national health authorities currently show some essential differences. These issues should be further discussed and the impacts of each on all stakeholders carefully worked out in order to meet the set objectives.

The discussion in chapter 4.9 shows the impact on industry and health authorities.

The major challenges are:

- To harmonise the EU change systems (national, MR and CP) and introduce the mandatory participation in the worksharing procedure of all national Competent Authorities concerning assessment criteria, procedures, timelines including the national phase in cases where a change of the product information is involved
- To define immediate notifications and major changes
- To introduce group and related variations
- To establish appropriate national fee systems
- The implication of ICH Q8 Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality System concepts

Discussions on the details how Q8, Q9, Q10 can be used to streamline the variation processes seem necessary.

To adjust the variation system to new innovative medicinal products and processes in the future the regulatory framework should be set by regulations and the details by guidelines which can be adapted more easily.

Besides the overall number of variations the publication of review times by the Competent Authorities themselves could be an indicator for the efficiency of the variation system.

The challenging objectives can be achieved by overcoming a typical EU problem where many Member States have to cooperate and give up their individuality to a certain extent. Common assessment criteria, procedures and timelines including another authorities assessment would have to be accepted also for the nationally approved products.

The revision of the Variation Regulations facilitates the switch from a huge amount of single variations of minor changes leading to authorities operating above their capacities towards focusing on continuous improvement of medicinal products and major changes in the context of the implementation of ICH Q8, Q9 and Q10.

6. Glossary

Comparability Protocol: A Comparability Protocol provides evidence that an applicant has a firm scientific, and technological understanding of the drug, the manufacturing process, the controls, the proposed change, and the potential effect of that change on the product quality. FDA's evaluation of a Comparability Protocol would include a determination of whether a change is made in accordance with that protocol and may be submitted under a reduced reporting category. Depending on the level of process and product understanding exhibited in the protocol, the change could be made with less prior review by FDA. (49)

Formal Experimental Design: A structured, organized method for determining the relationship between factors affecting a process and the output of that process, also known as ´Design of Experiments´. (26)

Global Marketing Authorisation: When a medicinal product has been granted an initial marketing authorisation, any additional strengths, pharmaceutical forms, administration routes, presentations as well as any variations and extensions shall also be granted an authorisation or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation. Therefore the global marketing authorisation contains the initial authorisation and all variations and extensions , as well as any additional strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures and under a different name, granted to the marketing authorisation holder of the initial authorisation. Where a product is initially authorised nationally and, subsequently, an additional strength, pharmaceutical form, administration route or presentation is authorised through the Centralised Procedure, this shall also be part of the same global marketing authorisation. (70)

Grouped Variation: Grouped variation s concern several changes for a single marketing authorisation beyond being consequential, for example addition of information to different sections of the SPC; multiple, separate improvements to an analytical procedure and a production process to be implemented at the same time. (Appendix 1)

Process Analytical Technology (PAT): A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. (26)

Related variation: A related variation application concerns one change relating to several products, for example the change in the active ingredient specification or the addition of common adverse event information to the SPC. (Appendix 1)

Regulatory Agreement: The Regulatory Agreement is used to define the applicant's post-approval change strategy for the quality section of the marketing authorisation application dossier. The agreement between authority and applicant should cover all critical-to quality attributes, parameters and procedures. It should outline the regulatory flexibility at the highest level and allow these companies to self-manage the majority of quality changes, without needing to seek prior approval. . (Appendix 1)

Six Sigma: Set of practices originally developed by Motorola to systematically improve processes by eliminating defects. A defect is defined as nonconformity of a product or service to its specifications. Six Sigma asserts continuous efforts to reduce variation in process outputs is key to business success, manufacturing and business processes can be measured, analyzed, improved and controlled and further succeeding at achieving sustained quality improvement requires commitment from the entire organization, particularly from top-level management The term "Six Sigma" refers to the ability of highly capable processes to produce output within specification. In particular, processes that operate with six sigma quality produce at defect levels below 3.4 defects per (one) million opportunities (DPMO). Six Sigma's implicit goal is to improve all processes to that level of quality or better. (71)

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Appendix 1

EFPIA/EVM/EBE PROPOSAL FOR A SYSTEM FOR POST APPROVAL CHANGES TO A MARKETING AUTHORISATION

September 2006

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1. INTRODUCTION

We welcome the opportunity to provide a proposal for a system for post approval changes to the Marketing Authorisation (MA) for human medicinal products in the European Union (EU). This proposal has been prepared based on the underlying principle that the continued protection of patient safety is paramount.

This proposal builds on the aspects of the existing system that have operated successfully and offers proposals to address the challenges the current system raises.

It is EFPIA's position that the future variations system must allow for a much greater level of self-regulation for minor changes and, in the future, the use of ICH Q9 and Q10 to expand this concept to apply to more substantial changes.

In order to reach this goal EFPIA's proposal is based on changes to the variations system that can be implemented in the near term (e.g. introduction of a 'do & tell' mechanism for minor changes) and those which will require implementation over a longer period of time (e.g. implementation of ICH Quality Guidelines Q9 and Q10).

Although this proposal has been prepared in the context of the existing European legislative framework, some adjustments would be needed to encompass some of the new concepts outlined in this proposal and more specifically to Directive 2003/63/EC amending Directive 2001/83/EC.

We also propose that the revision of the Variation Regulations will be part of the European Commission's "better regulation" initiative and investigate the possibilities to more appropriately define compliance relevant information versus that required for the initial assessment.

Finally, due to the increasing globalisation of the pharmaceutical industry, it is important that the revision acknowledges all the harmonisation initiatives being examined within ICH and capitalises on the Q8, Q9 and Q10 guidelines.

2. PRINCIPLES

a. General Principles (applicable to all types of changes)

This proposal will aim to **focus the resources of both stakeholders, Industry and Regulatory Authority, on major changes** whilst recognising the need for minor changes to be appropriately recognised and registered both within the company and with the Regulatory Authorities.

In addition, we would like to emphasise that the proposed new variation system should be **applicable to all marketing authorisations regardless of the route of registration** (centralised, mutual recognition, decentralised or national) to improve the harmonised implementation of the general rules for all variations and to make the processes and timelines more predictable for all changes.

b. Quality Specific Aspects

Our proposal includes a **risk and science based approach** including the concept of self-management of changes where appropriate. This would allow the competent authorities to focus their resource on those variations that have the potential to impact product safety and/or efficacy. This should encourage and enable **innovation and continual improvement** of pharmaceutical manufacturing processes, which in turn will facilitate the rapid implementation of beneficial changes that have no potential to impact on patient safety or that reduce any potential risk (See Annex I).

We believe that the same science and risk-based concepts should be applicable to all products, whether they be based on small molecules, biological medicinal products (including biotechnology products and vaccines) or herbals.

c. Summary of Key Procedural Aspects

The main improvements that are going to be discussed in this proposal are summarised below:

i. General

- Maintenance of some elements of the current variations classification system and proposing significant changes to the implementation system:
    - Type I notifications for minor changes that will not need prior Competent Authority approval for immediate implementation. Type I A variations which are immediately notified to the competent authorities and Type I B variations reported uniquely through a new document - an **"Annual Notification "**
    - Type II variations for major changes that will require prior Competent Authority approval before implementation and a 30, 60 or 90 day evaluation period depending on the nature of the change
    - Reduction in scope for compulsory extension application and duration of assessment period of these applications.

- Introduction of the concept **"Related Variations"** for one identical change which affects more than one MA that would be submitted in one procedure.

- Introduction of the concept **"Grouped Variations",** allowing the submission of a single variation application for multiple changes to one MA. This would improve the process for introducing multiple changes to the SPC or linked changes to the Quality section of the dossier. Consequential changes would be included in the concept of "grouped variations".

- Optional use for the MAH of a proposed system for "**European Variation Assessment"** for the evaluation of major variations to MAs that have followed the National procedure and affect several competent authorities, within the context of the CMD and the nomination of a single Agency acting as Rapporteur for the assessment of the Type II variation

- Introduction of an **Annual Maintenance Fee** for processing Type I variations and a payment of an **additional separate fee** for assessing Type II variations.

ii. Quality Aspects

- Introduction of the concept of Regulatory Agreement for facilitating the management of Quality changes. A "Regulatory Agreement" may be proposed by the applicant, which would be used to define and agree the applicant's post-approval change strategy for the Quality section of the MAA.

3. VARIATION CATEGORIES

This proposal is for all types of medicinal products and there should be no specific requirements for biological medicinal products.

a. Type I Notifications for minor changes

Type I variations are minor changes which require only a **notification** to the Competent Authority.

A **minor change** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness or the risk-benefit profile of the medicinal product.

i. Type IA: Immediate Notifications

Principles & Definition

Immediate Notifications or Type IA are required for specific changes that impact the ability of a Competent Authority to fulfil its legal obligations with respect to effective supervision of the Industry and need to be kept current for patient safety or sourcing issues. These types of changes are mainly amendments to the administrative information included in the EU application form and examples are listed in Annex IV.

Such changes do not require validation or assessment, however Industry would require acknowledgement of receipt from the Competent Authorities.

In addition, changes in the product information (SPC, PIL, Label) that have been previously assessed by the competent authority through procedures other than variations, should also be treated as "immediate notifications".

For example, changes made at the request of competent authorities (e.g. product information changes following the assessment of a PSUR or renewal application; implementation of class labelling statements from new or revised core SPCs or Article 31 referral procedures or adaptation to QRD templates), where the MAH fully complies with the request and submits no further data do not require further scientific evaluation. In addition, product information changes which are a consequence of changes to the quality of the product (e.g. shelf life extension) belong to this category.

EFPIA believes that changes which have already been discussed and agreed with authorities do not need to be re-evaluated.

Procedure & Timelines

The notification would be sent simultaneously with the implementation of the change. The agency would immediately acknowledge receipt of the notification.

A letter and replacement pages for the MA dossier should be provided as documentation.

The concept of periodic updates to the Decision by the European Commission following Type IA and IB variations, currently applicable to centrally authorised products, is one which should be applied for the updating of marketing authorisation particulars following immediate notifications for all procedures (i.e. MR/DCP, Centralised and National). It should be made clear in the legislation that these changes can be implemented before the Decision or national authorisation is revised and the updated product information is published by the EMEA/National Competent Authority.

ii. Type IB: Periodic Notifications

Principles & Definition

A 'Type IB notification' means a minor change to the MA dossier which does not require a submission or prior approval but is recorded in an annual notification and submitted to the relevant competent authority on a regular basis.

EFPIA believes that this would be the most efficient mechanism for providing a competent authority with relevant information on changes and updated MA information, which do not require prior approval or immediate notification before implementation.

We would envisage the following principles to apply to the use of an annual notification (see Annex V):

- A single report developed for each product, defining and summarising the Quality and non-Quality changes introduced in the previous 12 months
- Submitted to the relevant competent authorities on an annual basis
- The birth date of the annual notification should be determined by the MAH, in agreement with the competent authority
- Replacement pages for relevant sections of the Quality dossier or other documentation, affected by the changes, would be included as part of the annual notification
- The competent authority/agency acknowledges the receipt of the "Annual Notification"

All Type IB changes impacting the Quality section would be managed under a Company's Change Management system and involve appropriate quality and technical assessment and, where appropriate, validation and/or stability studies.

b. Type II: Prior assessment for major changes (see Annex III and VI)

Principles & Definition

A Type II Variation means a major change to the MA dossier which requires prior submission and **approval** by a competent authority before it can be implemented by the MAH.

A **major change** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a medicinal product as these factors may relate to the safety or effectiveness or risk-benefit profile of the medicinal product.

A pre-defined list of examples of such major changes should be developed. A variation not included in this list would automatically default to a Type I notification, which would be

reported to a competent authority either in an annual notification only, or as an immediate notification.

A major change would require the submission of a Type II variation dossier for review and approval by a competent authority. Procedural aspects, including timelines for review and approval, would depend upon the nature of the change.

It is worth pointing out that this principle has been used in Germany for national variations for a number of decades (cf. Article 29 of German AMG). During this period, the system has proved to be efficient and effective and has not resulted in any serious public health issues.

Procedure & Timelines

The existing review times (30, 60 and 90 days) should be applied, with some changes to their applicability to specific types of changes (see below). The procedure should allow for one clock-stop with a specified time limit in the event that supplementary information is requested from the MAH, and the MAH should in addition have the right of appeal if they disagree with the outcome of the procedure.

For Quality changes once the assessment period of 60 days has elapsed, unless a negative assessment conclusion has been reached and a rejection letter dispatched, the MAH should be able to introduce the proposed change(s) without having to wait for a formal approval prior to implementation.

Clock-stops should only be allowed for pre-specified timelines in all procedures to allow a predictable overall evaluation time of the variation.

The changes for which Type II variations would be applicable include, but are not limited to:

- 60-day procedure:
  The 60 days procedure would be the default procedure for changes to the Quality section and the SPC which are not specified as falling under the 30- or 90-day procedure.

  - Changes to the quality dossier.
  - Changes to the clinical particulars in the SPC not covered by the 90- or 30-day procedures (e.g. changes to section 4.2 alone).
  - In case accelerated review is granted for an indication extension this should follow 60 days

- 30-day procedure:
  The 30 days procedure would be applicable for all safety related product information changes, for example:

  - Changes to product information following an Urgent Safety Restriction.
  - Changes to the safety-related information in the SPC (sections 4.3-4.9), initiated by the MAH.
  - Changes made at the request of competent authorities (e.g. product information changes following the assessment of a PSUR or renewal application; implementation of class labelling statements from new or revised

core SPCs or Article 31 referral procedures), where the MAH does not comply fully with the request and/or submits further data.
  - Other changes that would benefit from a shortened assessment, taking into account the urgency of the matter.

- 90-day procedure:

  - Changes to, or addition, of therapeutic indications, adding a new strength, a new pharmaceutical form or a new route of administration alone or as a consequence of a new indication.

EFPIA believes that adding a new strength, a new pharmaceutical form or a new dosing regimen alone or as a consequence of a new indication, should be handled through a Type II variation procedure as well.

The approval of a new indication usually requires the evaluation of a significant amount of new data resulting from a clinical program and maybe additional safety data. We therefore propose that it is not justified that the addition of a new strength (usually only new quality data), or the addition of a new pharmaceutical form (generally quality data and bioequivalence data), or a new dosing regimen (clinical and bioavailability data justifies a lengthier evaluation time than allocated for a new indication.

In addition the possibility for having accelerated review for innovative indication extension should follow a timetable of 60 days

This does not prohibit the MAH to apply for any additional strengths, pharmaceutical forms, administration routes or presentations as stand alone MA under a separate name.

c. Extension Applications

We recommend that extension application should not be subject to a 210 days assessment period as for a full MAAs, we propose that extension application be assessed within a 120 days assessment period.

New strength within the currently approved dose range would be handled as Type II variations (90 days).

4. OPTIONAL 'WORKSHARING' PROCEDURE FOR TYPE II VARIATIONS TO NATIONALLY AUTHORISED PRODUCTS

For products with authorisations issued via the national procedure (non MRP) in multiple countries Type II changes should be assessed based on an optional mutual recognition process available to the MAH. Although the procedural details may need to be different for Type II Variations on Quality changes as compared to Labelling Changes, the same principles would apply, based on an assessment by a single Agency on behalf of the other concerned Agencies in a **work sharing procedure**. The outcome of the assessment would be implemented nationally via Type IA/type IB notification. Details including timelines of the proposed options are included in the Annex III.

5. RELATED AND GROUPED VARIATIONS

a. Related variations

A related variation application is one which concerns a change which impacts across several products e.g. change in active ingredient manufacturing process and specification, or addition of common adverse event information to the SPC or for single agent and combination products containing the same active ingredient or changes to vaccine active ingredients, i.e. antigens.

Where the same change concerns products approved via different procedures (Centralised, MRP/DCP or national), it would be desirable to have a mechanism that allows for all these products to be included in the same application. Should this not be possible, a "related variation" application would be required for each route. In the case of MRP/DCP products with different RMSs, the process should allow for discussion between the RMSs and applicant prior to submission of the variation in order to agree on a single RMS to lead the assessment.

Related variations may also be combined with grouped variations.

b. Grouped variations

Grouped variations differ from related variations as they only pertain to a single MAA, though they may collectively also comprise a related variation. Under the current system, submission of multiple non-consequential changes under a single variation is not generally permitted. Currently the possibility for a single application to cover several changes is limited to the submission of "consequential variations. (A consequential variation is a change, which is an unavoidable and direct result of another change, and not simply a change that occurs at the same time.)

This leads to a significant increase in the administrative burden for both MAH and regulators, as separate variations must be prepared, submitted and assessed for each change. Examples of such changes include: addition of information to different sections of the SPC; multiple, separate improvements to an analytical procedure and a production process that the MAH has decided to implement at one time.

All changes would be listed on a single variation application form. Replacement pages for relevant sections of the Quality dossier or other documentation, affected by the changes, would be provided, with an indication of which data support which change(s).

6. REGULATORY AGREEMENT (See also Annex II for more details of this concept)

The post-approval change requirements for the Quality section of an MAA could, optionally for the MAH, be based on a **Regulatory Agreement**. A 'Regulatory Agreement' would refer to the specific components of the marketing authorization application, which would be changed only through a variation. These components should be defined taking into account the potential for change to impact the quality of the product. The agreement could be extended to additionally summarise the applicant's proposals for management of post-approval changes. A Regulatory Agreement is proposed by the applicant and

approved by regulatory authorities. A regulatory agreement, where established and approved, therefore, can be used to define and agree specific change strategies for the product thereby providing an efficient notification framework and process.

- A Regulatory Agreement could be envisaged operating at a number of levels. These might commence with a straightforward statement of the specific Quality elements of the dossier with which a company had to comply. In this situation, the agreement separates compliance requirements (e.g. composition, specifications, etc.) from the supporting scientific and technical knowledge. At the highest level, the agreement for companies demonstrating an appropriately enhanced level of product and process understanding and Quality Systems (based on implementation of ICH Q8, Q9 and Q10) would allow these companies to self-manage the majority of Quality changes, without the need to seek prior approval.

7. FEES SYSTEM

The future fees system would have to be adapted to the revised post approval changes system to ensure that the Competent authority receives appropriate fee for service.

8. CONCLUSIONS

In conclusion the key changes to the current regulatory environment pertaining to variations that EFPIA is proposing include the following:

- National variation systems are to be included within the scope of the Variations Regulations for all aspects (timeframes, principles and requirements)
- The introduction of a notification system for immediately notifiable or annually reportable minor changes
- The inclusion in the scope of any new Regulation text of the possibility to fully utilise the concepts outlined in ICH Q8/9/10 guidance documents as these concepts are developed and implemented
- The elimination of additional national approval steps outside of those required by the Regulation for changes to MAs approved via MRP/DCP and national procedures
- Allowing group and related variations to be submitted via a single submission.
- Revision to classification of some extension applications to Type II (a change or addition of a new strength, a new pharmaceutical form or new route of administration)
- Work sharing at a EU level for Type II variations to national MA with Member States legally obliged to implement at the conclusion of the assessment phase
- The same concepts should be applicable to all products, irrespective of whether they are based on small molecules, or are biological medicinal products (including biotechnology products and vaccines) or herbals.

ANNEX I: Implications of ICH developments

Introduction

Currently ICH is in the process of completing 3 guidelines intended to realise a vision to *"Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science."* These guidelines are Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Quality Systems (Q10). Part of the agreed business case supporting the development of these guidelines is to reduce the number of post approval changes requiring regulatory approval. While many of the ideas expressed in these three guidelines are optional, any new Variations Regulations need to be constructed so that companies taking advantage of the opportunities described in the ICH guidelines can achieve a higher degree of self-management of changes.

Further developments within the ICH Expert Working Groups have been discussion on the potential usefulness of a revised Quality Overall Summary and a Regulatory Agreement that could form an adjunct to achieving this goal.

Q8: Pharmaceutical Development

ICH guideline Q8 encourages companies to develop an enhanced scientific understanding of their products and processes. Where scientific understanding is demonstrated by the applicant, then the intensity of oversight for subsequent changes should be reduced significantly: These concepts and intentions are described within this guideline.

In addition, Q8 defines the concept of Design Space. The guideline explicitly states that working with the design space is not considered to be a change. Therefore any modifications of processes or products that are contained within the approved design space are not required to be captured in a periodic report nor do they require any regulatory approval. We recommend the new Variations Regulations should reproduce the text from Q8 defining a Design Space and its implications for changes.

Q9: Quality Risk Management

Q9 describes tools for Quality Risk Management. A new Variations Regulation should encourage the use of the Q9 tools by the MAH to assess the impact of a proposed change and facilitate its assignment to a Type I or Type II variation.

Q10: Quality Systems

Q10 (currently at Step 1 at the time of writing this proposal) describes expectations for robust quality systems.
Q10 will focus on quality systems that facilitate implementation of Q8 and Q9, thus enabling the realization of the full benefits of the concepts contained within these two guidelines. This guideline is intended to apply to pharmaceutical drug substances and drug products throughout the product lifecycle, including process development, technology transfer and routine manufacturing.

In the Q8/Q9/Q10 environment an annual notification provides the ideal route for submission of substantial change information that now can be judged not to require assessment because the company has the three essential components to facilitate self-management of change: enhanced product and process understanding, demonstrable ability to apply quality risk management tools, and robust quality systems.

ANNEX II: The Regulatory Agreement

A Regulatory Agreement is proposed which would be used to agree and define the applicant's post-approval change strategy for the Quality section of the MAA.

The Regulatory Agreement should be an **optional** product specific document and it may include a company specific component in relation to strategies for Change Management. We currently recommend it be placed in Module 1. (It may be that the Regulatory Agreement could be harmonised through the ICH process in which case there is an argument that it could then be placed in Module 2: however we would not want any revision of the Regulations to be dependent on potential harmonisation.) The Regulatory Agreement should cover all critical-to-quality attributes, parameters and procedures. For example, the following components could form part of the regulatory agreement:

- Listing of critical to quality attributes, critical process parameters and boundaries of design space when submitted;
- Reproduction of the defined control strategy including specifications and analytical methods, together with other compliance-related aspects such as composition.

A Regulatory Agreement could be envisaged operating at a number of levels. These might commence with a straightforward statement of the specific Quality elements of the dossier with which a company had to comply. In this situation, the agreement separates compliance requirements (e.g. composition, specifications, etc.) from the supporting scientific and technical knowledge.

At the highest level, for companies demonstrating an enhanced level (see ICH Q8) of product and process understanding, the post-approval change requirements for the Quality section of an MAA should be based on a Regulatory Agreement. It should define principles based on their possibility to impact the quality of the product. The agreement could include such concepts as change management protocols (including comparability protocols). In addition the agreement could form the basis for measuring compliance. A Regulatory Agreement, where established and approved, can be used to define and agree specific change strategies for the product. These may include changes that require notification, as well as those changes that require prior approval, thereby providing an efficient notification framework and process.

This document would, therefore, outline the regulatory flexibility proposed and subsequently approved, it could include comparability and stability protocols for supporting change and propose/agree reduction in change category for specific scenarios where generated data meet the criteria laid down in the relevant comparability/stability protocols.

Within the Regulatory Agreement, the Applicant could provide a list of changes that would otherwise be submitted as Type II variations. However the criteria for successful implementation of these changes would have already been agreed by authorities, so the company would be free to implement them via the Type I (notification only) mechanism described in more detail earlier within this proposal. Changes appropriate for this category include changes for which comparability criteria were approved within the Regulatory Agreement for that specific anticipated change. For example, expansion of design space against data complying with a pre-agreed protocol may deserve a lower

change classification, e.g. Type II to Type I. Where experiments additional to those described in a pre-agreed protocol are required to demonstrate the validity of the proposed change, then the change would revert to a standard Type II variation.

It would be up to the applicant to describe how they have applied Quality Risk Management principles to classify changes as part of their application (e.g., by reference to tools and processes described in ICH Q9).

For future marketing applications, the Regulatory Agreement (which would remain optional) would be submitted as part of the initial marketing application and the approval of the MA would mark its acceptance as the basis of future changes. The transition to a Regulatory Agreement-based system for future applications would be a straightforward process.

For existing products, applicants may continue to submit variations as provided for within the current/future variations system. Where a company chooses to instigate it, the Regulatory Agreement itself would be submitted as a Type II variation as provided for within the current variations framework, and utilising the same review timeline (60 days standard) and system applicable to the associated application (i.e. MRP, centralized review). The submission of the Regulatory Agreement should not be used to make an immediate manufacturing or control change itself, but should only be used for approval of manufacturing commitments for the future, based on the currently operating process and current product and/or process knowledge. The submission of the Regulatory Agreement for an existing product may be used to reduce the number of reporting obligations from those currently required by law and to propose reduced reporting categories from those specified in the existing variations regulation. After approval of the content of the Regulatory Agreement through the current Type II variation mechanism, future manufacturing changes would be made as designated within the approved Regulatory Agreement.

ANNEX III: Optional "Work Sharing" Procedure for Type II Variations to Nationally Approved Products

Industry has expressed concern that one of the major problems experienced is with the varying approval times and different Variations procedures applicable to nationally approved products. The following proposal is intended to facilitate the reduction of regulatory burden for both the CA's and Industry without requiring full harmonisation of the dossiers across Member States.

The proposal is developed from the concepts for work sharing across the National Competent Authorities and thus has some precedents from Periodic Safety Update Reports, Paediatric data submission, and for elements of Process Analytical Technology. The certificate of the European pharmacopoeia (CEP) procedure is a further example of successful harmonisation and work sharing.

The proposal describes an approach in which Type II variations for the same (or very similar [1]) nationally authorised product are assessed in a defined timescale by a single Member State prior to a simplified formal National procedure. The principal aim of this work sharing arrangement is to avoid duplicate assessment of variations by several Member States and so avoid the waste of resources this entails.

It is further proposed that the optional procedure be applicable to "related' variations in which a single change or a small group of changes is applicable across a number of National Authorisations.

The existing CMD should resolve outstanding difficulties and encourage the efficient sharing of the workload.

The procedure consists of 3 phases:

- Pre-submission to CMD including appointment of Rapporteur/ co-Rapporteur **as appropriate**
- Assessment of the data and final AR
- Implementation in national authorisations

1. Pre-submission to CMD:
This phase results in acceptance of the validity of the procedure to the changes required, including agreement that the differences between the filings in Member States would not impede approval. The Rapporteur and Co-Rapporteur would be appointed at this step.

2. Assessment
This phase includes the technical assessment of the submitted variation dossier by the Rapporteur and Co-Rapporteur on behalf of all concerned national agencies, resulting in the adoption of a final AR and, where appropriate, proposed product information wording to be included into the national product information. This step is similar to MRP/DCP variations.

3. Implementation in the national authorisation
Following the adoption of the final assessment report, the variation should immediately be implemented. Similar to MRP/DCP variations, the legal approval of the change should be defined in the legislation as being the date when the variation procedure has been finalized in step 2, and the implementation and revision of the national documents

in step 3 is only an administrative step. Hence, implementation of the change occurs immediately after finalizing the major variation procedure. For changes affecting product information, the submission of the translations to the national competent authority should occur 5 days after finalisation of step 2. If the MAH has not received any justified objections on the translations within 10 days, they may proceed with the implementation.

A potential impact of this procedure may be to encourage Marketing Authorisation holders to harmonise the Quality sections of Dossiers where this is appropriate. For products authorised through both National and Mutual Recognition Procedures it is proposed that the RMS acts as the Rapporteur to ensure harmonised decision making for all products registered through MRP and nationally.

Footnote 1
The degree of similarity of the different national files, which would be considered acceptable for CAs to agree to initiate an optional work sharing procedure, will need to be expressed in guidance documents.

	Timing			Activity	
	30 days	***60 days***	***90 days***	***Variation impacting Quality***	***Variation impacting Safety & Efficacy***
PRE-SUBMISSION	-30 days			MAH contacts CMD to request a work sharing procedure and proposes Rapporteur In the case of mixed MR/National authorisations RMS naturally takes lead.	
				Rapporteur from the country in which manufacture or first import takes place. This facilitates link between Inspections and Assessment Over time should facilitate development of the expertise in that NCA with that particular product (or range).	
				It may be necessary to involve a co-rapporteur in some instances e.g. min case of complex applications for which a large amount of new clinical trials data or other data will have to be assessed..	
	-10 working days			Rapporteur appointment and adoption of timetable	
				MAH assembles the variation application	
				Any existing differences in the contents of the relevant parts of the national dossiers that have a potential impact on the assessment should be clearly communicated with justifications and proposed solutions to the Rapporteur in order to support harmonized assessment. *The submission dossier will include, listed by each NCA, the Authorisations affected, and the impact on the National Marketing Authorisations*	
				In addition, the site or sites of manufacture and/or importation and release is identified.	*If applicable, the responsible person for Pharmacovigilance will need to be named for each MS.*
	- 5 working days			MAH submits the variation application to Rapporteur (Co-Rapporteur), and notifies concerned NCAs (application form only). *Validation step by the Rapporteur includes confirmation of receipt of application form, necessary fees are paid and acceptance of the principle that assessment will be made by work sharing arrangements.*	

	Timing			Activity	
	30 days	***60 days***	***90 days***	***Variation impacting Quality***	***Variation impacting Safety & Efficacy***
ASSESSMENT	Day 0	Day 0	Day 0	<u>Start of Assessment Procedure</u> Rapporteur informs the MAH of the start date and timetable, and circulates timetable to NCAs	
				Rapporteur may wish to consult with sub groups of NCA staff from other Authorities if particular expertise is required (e.g. PAT group). *For changes impacting a range of products (bulk changes) assessment of the impact of the change on each product affected should be facilitated by the MAH using principles of science and risk management*	*Rapporteur may wish to consult with sub groups of NCA staff from other Authorities if particular expertise is required.* *For changes impacting a range of products (bulk changes) assessment of the impact of the change on each product affected should be facilitated through the application of benefit/risk management principles*
	By Day 15	By Day 40	By Day 70	[1] Rapporteur circulates Preliminary Variation Assessment Report (PVAR) to NCAs and to the MAH *for information only* The PVAR contains Rapporteur's position (i.e. approval or refusal or, Request for Supplementary Information (RSI))	
	By Day 20	By Day 55	By Day 85	[2] Rapporteur receives opinion or comments on PVAR from NCAs. Rapporteur prepares RSI where necessary.	
	By Day 21	By Day 59	By Day 89	Raporteur sends the approval or refusal or the RSI to MAH and copy NCAs.	
	Clock stop	Clock stop	Clock stop	Applicant clock stop (specified time limit) MAH prepares and submits its responses to Rapporteur	
	NMT 10 days	NMT 60 days	NMT 90 days	RSI responses assessment Rapporteur liaises with the MAH as necessary (clarification of questions or responses) Rapporteur prepares the Final VAR (FVAR) as soon as the responses have been submitted	
	By Day 22	By Day 60	By Day 90	Rapporteur circulates the FVAR to the NCAs and to the MAH *for information only* [3] Rapporteur gives the NCAs a set timeframe to respond for deciding whether a breakout has to take place	
		Around Day 75	Around Day 105	Hold break-out meeting when needed, in case discussion is required between NCAs to come to harmonised decision	

<table>
<tr><td rowspan="3"></td><td>By Day 27</td><td>By Day 85</td><td>By Day 115</td><td colspan="2">Rapporteur receives confirmation from NCAs of acceptance/non-acceptance of FVAR
If disagreement between Rapporteur and NCAs, referral to the CMD(h)
In case of refusal, the MAH may appeal in the first instance to the CMD(h)
MAH transmits to Rapporteur highlighted and clean versions of the agreed product information</td></tr>
<tr><td rowspan="2">By Day 30</td><td rowspan="2">By Day 90</td><td rowspan="2">By Day 120</td><td colspan="2">Rapporteur finalises the assessment and notifies NCAs and MAH of final position</td></tr>
<tr><td>For Variations impacting the manufacturing and supply chain, a satisfactory assessment should permit the MAH to immediately implement the change</td><td>For Variations impacting the product information, a satisfactory assessment should permit the MAH to implement the change.</td></tr>
</table>

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	Timing			Activity	
	30 days	***60 days***	***90 days***	***Variation impacting Quality***	***Variation impacting Safety & Efficacy***
NATIONAL	**The outcome of the assessment will be included in the national authorisation via Type IA/Type IB notification**				
	By Day 31	By Day 91	By Day 121	MAH implements changes if no impact on product information (no translation required), the agreed change will be included in the next annual notification (Type IB)	
	By Day 35	By Day 95	By Day 125	MAH submits to NCAs translation of product information in national language or other notifiable information as applicable (Type IA)	
	By Day 45	By Day 105	By Day 135	MAH implements product information changes if it has not received any justified objections on the translation NCA issues amended national decision	

For 30 Days variations, translations occur in parallel with the variation (as is the case currently in Centralised Procedure).

ANNEX IV: Type IA Examples of Immediate Notifications

Proposals for Minor Changes requiring Immediate Notification
(Note: This list is not exhaustive, but is intended to exemplify the sort of changes that should be considered as Type IA notifications)

- Change in the name and/or address of the MAH (formerly 1)
- Change in the name of the medicinal product (formerly 2)
- Change in the name and/or address of a manufacturer of the finished product (formerly 5)
- Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product (formerly 7)
- Change to batch release arrangements and quality control testing of the finished product (formerly 8)
- Change in the name and/or address of a manufacturer of the active Substance (formerly 4) including:
  Submission of a European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance from a manufacturer (replacement or addition) that was not previously named in the submission (formerly 15 in part)
- Submission of a new or updated European Pharmacopoeia TSE certificate of suitability for an excipient sourced from a TSE relevant species from a new manufacturer (replacement or addition) for a Substance in a veterinary medicinal product for use in animal species susceptible to TSE (formerly 15 21 22)
- Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules (formerly 39)
- Change of dimensions of tablets, capsules, suppositories or pessaries (formerly 40)
- Change in pack size of the finished product outside the range of the currently approved pack sizes (formerly 41a)2)
- Change in the fill weight/fill volume of multidose products (formerly 41b but embracing all multidose products – including parenteral products -formerly Type II)
- Change in the summary of product characteristics of an essentially similar product following a Commission Decision for a referral for an original medicinal product in accordance with Article 30 of Directive 2001/83/EC or Article 34 of Directive 2001/82/EC (for Mutual Recognition Procedure only, Regulation 1084/2003)
- Change in the summary of product characteristics, labelling and package leaflet/insert as a consequence of a final opinion in the context of a referral procedure in accordance with Articles 31 and 32 of Directive 2001/83/EC or Articles 35 and 36 of Directive 2001/82/EC (for Centralised Procedure only, Regulation 1085/2003)
- Deletion of: a pharmaceutical form, a strength, or a pack-size(s) (for Centralised Procedure only, Regulation 1085/2003) (formerly 47)
- Changes to the summary of product characteristics already assessed and approved by other competent bodies (e.g. change of ATC code following adoption by WHO; change in name of product following agreement from EMEA Invented Name Review Group).

ANNEX V: Type IB Annual Notification

The annual notification should contain the following information on Quality changes:

- Type and date of implementation of each change
- Replacement pages to the relevant sections of CTD of the MAA, where appropriate

ANNEX VI: Type II

Validation

The assessment timelines described below must be adhered to regardless of the regulatory procedure followed (Centralised, MRP/DCP, national). In addition, for Type II variations, a short, fixed validation period of no longer than 5 days should be specified in the Regulations, in order to avoid problems with validation delays encountered with some variations under the current system, particularly for MRP/DCP /National approved products.

List of Type II variations related to Quality changes

We would propose that the list of Type II major variations is not included as an Annex to the revised Variation Regulation, but is developed as a separate Commission guideline to allow flexibility and easier adaptation, once experience is gained with the new Variation System.

As well as listing the categories of major variations, the Guideline should also contain conditions to be fulfilled and documentation to be supplied for each major variation.
Below are examples of Quality changes, which would require the submission of a type II variation unless notification procedure has been proposed and approved (via Regulatory Agreement).

- Change in specification of drug substance:
  - Removal or widening of quality indicating parameters
  - Addition of a quality indicating parameter(s) driven by a quality issue of potential relevance to efficacy or safety
- A change in analytical procedure for drug substance when it requires a widening in specification(s)
- Major change in manufacturing process of drug substance
- Addition of, or extension to, design space for an existing drug substance, when not pre-agreed through a comparability protocol
- Replacement or addition of a manufacturing site for part or all of the manufacturing process for the drug product, where the site requires verification of GMP status
- Change in formulation for a modified release dosage form
- Change in specification of a drug product
  - Removal or widening of quality indicating parameters
  - Addition of a quality indicating parameter(s) not driven by a commitment
- Major change in manufacturing process of drug product
  - Changes to Critical Quality Attributes and Critical Process
  - Changes to principles of manufacturing technology e.g. wet to dry granulation, change in sterilization process
- Change to less protective primary packaging materials
- Change to shelf life or storage conditions beyond parameters defined in submitted protocol

- Addition of or extension to design space for an existing drug product, when not pre-agreed through a comparability protocol

- Change to elements of the agreed change control strategies within a Regulatory Agreement.
- Establishment of a Regulatory Agreement where none was previously provided in the marketing authorisation.
- Addition of a new strength within the currently approved dose range.

Translations & Implementation:

- MRP/DCP: The legal approval of the change should be defined in the legislation as being the date when the variation procedure has been finalized by the RMS, and the issuing of the national documents is only an administrative step. Hence, implementation of the change occurs immediately after finalizing the major variation procedure. For changes affecting product information, the submission of the translations should occur 5 days after finalisation. If the MAH has not received any justified objections on the translations within 10 days, they may proceed with its implementation.

  EFPIA requests that the high quality and good faith translations of the approved labelling text are the responsibility of the MAH and agency resources for checking translations can be easily saved.

- The same would apply to the CP. However, while the current legislation indicates that the update of the Commission Decision may take up to 45 days, it is our experience that this activity can be completed in 30 days. We propose that the legislation be amended to reflect this shorter timeline.

Lack of consensus among Agencies in MRP/DCP variations:

- Consistent with the procedures for new applications in MRP and DCP, referral should be made to the CMD in the first instance, and only to the CHMP if the CMD fails to reach agreement. A CMS referral to the CMD in the case of a variation must only be made strictly on grounds of a potential serious risk to public health (in contrast to the current variations regulation, which stipulates no grounds for CMS referral to the CHMP other than the CMS being of the opinion that the variation cannot be accepted). Taking into account the different nature of variations and new applications, a shorter period for conclusion of CMD referral of a variation should be implemented: 30 days seems appropriate.

  EFPIA believes that the current possibility for the MAH and CMS to refer a Type II variation to the CHMP for arbitration should be modified and adapted to the accepted regulatory framework.

ANNEX VII Annual Variation of Influenza Stain – Amendment to Legal Text

Commission Regulation 1085/2003 (Centralised procedure)

Article 7
Human influenza vaccines

1. With regard to variations to the terms of the marketing authorisations that are required in order to achieve the annual update of ~~for~~ human influenza vaccines, (i.e. change of active substance(s) as recommended by WHO and EMEA) the procedure set out in paragraphs 2 to 6 of this Article shall apply.

2. Within 45 days following the date of the receipt of a valid application that contains the administrative and quality information, the Agency shall give its opinion on the quality documents referred to in Module 3 of Annex I to Directive 2001/83/EC as amended, based on an assessment report.

3. Within the period laid down in paragraph 2, the Agency may request the holder to provide supplementary information.

4. The Agency shall address forthwith its opinion to the Commission.
The Commission shall adopt a decision updating the marketing authorisation that has been granted pursuant to Article 6~~10~~ of the Regulation (~~E~~EC) No ~~2309/93~~ 726/2004.

This decision shall be implemented on condition that the final opinion of the Agency as provided for in paragraph 5 is favourable. The decision would be given after submission and assessment of clinical data, if appropriate.

The updated marketing authorisation shall be notified by the Commission to the holder.

5. ~~The clinical data and w~~Where appropriate, the clinical data and those concerning the stability of the medicinal product shall be addressed by the holder to the Agency at the latest 12 days following the end of the time limit laid down in paragraph 2.

The Agency shall evaluate these data and shall give its final opinion within 10 days of the reception of the data referred to in the first subparagraph. The Agency shall address the final opinion to the Commission and to the marketing authorisation holder within the three following days.

6. The Community Register of Medicinal Products provided for in Article 13 ~~12~~ of Regulation (~~E~~EC) No ~~2309/93~~ 726/2004 shall be updated as necessary.

Rationale: *The aim of this revision is to clarify that the Commission decision will be granted before the final opinion of the CHMP on clinical data is given. The clinical data will be provided by the MAH, if appropriate. In this respect, there are discussions with authorities on whether annual flu clinical trials are relevant.*

Article 8

Pandemic situation with respect to human diseases

In case of a pandemic situation with respect to the human influenza virus, duly recognised by the World Health Organisation or by the Community in the framework of Decision 2119/98/EC of the European Parliament and of the Council (1), the Commission may exceptionally and temporarily consider the variation to the terms of the marketing authorisation for human influenza vaccines to be accepted after an application has been received and before the end of the procedure laid down in Article 7. Nevertheless, ~~complete~~ clinical safety ~~and efficacy~~ data ~~can~~ shall be later on submitted ~~during the procedure~~ and the Decision of the Commission will be granted after those data have been assessed and have been granted a positive opinion by the Agency only.

In case of a pandemic situation with respect to human diseases other than the human influenza virus, the first paragraph and Article 7 may be applied mutatis mutandis.

Rationale: *In the event of a pandemic, mass vaccinations will most likely take place after a positive opinion from the CHMP is obtained but before clinical data is available EMEA Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (CHMP/VEG/4717/03). The Commission marketing authorisation should only be given after the clinical data is available. In a pandemic situation, the focus of the trials should be to obtain appropriate safety data rather than efficacy data.*

Commission Regulation 1084/2003 (MRP)

Article 7

Human influenza vaccines

1. With regard to variations to the terms of the marketing authorisations that are required in order to achieve the annual update of ~~for~~ human influenza vaccines, (*i.e. change of active substance(s) as recommended by WHO and EMEA*) the procedure set out in paragraphs 2 to 5 of this Article shall apply.

2. Within 30 days following the date of the start of the procedure, the competent authority of the Reference member State shall prepare an assessment report on the basis of the quality documents referred to in module 3 of annex 1 to Directive 2001/83 as amended and a draft decision which shall be addressed to the other competent authorities concerned.

3. Within the period laid down in paragraph 2, the competent authority of the reference member State may request the holder to provide supplementary information. It shall inform the other competent authorities of the Member States concerned.

4. Within 12 days of receipt of the draft decision and the assessment report, the other competent authorities of the member States concerned shall recognise the draft decision and inform the competent authority of the reference Member State to this effect.

5. ~~The clinical data and,~~ Where appropriate, the clinical data and those concerning the stability of the medicinal product shall be addressed by
the holder to the competent authority of the reference Member State and to the other competent authorities of the Member States concerned, at the latest 12 days following the end of the time limit laid down in paragraph 4.

The competent authority of the reference Member State shall evaluate these data and draft a final decision within 7 days of the receipt of the data. The other competent authorities shall recognise the final draft decision and, within 7 of the receipt of the draft final decision, adopt a decision in conformity with the final draft decision.

6. If, in the course of the procedure laid down in paragraph 2 to 5, a competent authority raises a question of public health which they consider poses an obstacle to the mutual recognition of the decision to be taken, the procedure referred to in ~~Article 35(2) of directive 2001/83/EC~~ Article … of Directive 2004/27 shall apply.

Rationale: *There are discussions with authorities on whether annual clinical trials are relevant.*

Article 8

In case of a pandemic situation with respect to the human influenza virus, duly recognised by the World Health Organisation or by the Community in the framework of Decision 2119/98/EC of the European Parliament and of the Council (1), competent authorities may exceptionally and temporarily consider the variation to the terms of the market authorisation for human influenza vaccines to be accepted after an application has been received and before the end of the procedure laid down in Article 7. Nevertheless, ~~complete~~ clinical safety ~~and efficacy~~ data ~~can be~~ shall be later on submitted ~~during this procedure~~ and authorization should be granted, according to the Mutual Recognition/Decentralised Procedure.

In case of a pandemic situation with respect to human diseases other than the human influenza virus, the first paragraph and Article 7 may be applied mutatis mutandis.

Appendix 2

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

CONSULTATION PAPER

BETTER REGULATION OF PHARMACEUTICALS:

TOWARDS A SIMPLER, CLEARER AND MORE FLEXIBLE FRAMEWORK ON VARIATIONS

Version: 20 October 2006

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary proposal. The suggestions contained in this document do not prejudge the form and content of any future proposal by the European Commission.

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Table of contents

1. INTRODUCTION

Medicines are regulated throughout their entire lifetime. Changes subsequent to their placing on the EU market (*e.g.* change in the production process, change in the packaging, change in the address of the manufacturer etc.) are handled according to a specific Community legislative framework: the 'Variations Regulations'[1].

The handling of variations requires significant administrative and regulatory resources, both for competent authorities and for the industry. While regulating changes in pharmaceuticals is essential to ensure that EU medicines remain of good quality, safe and efficacious, it is also important that such regulation does not hinder but rather stimulates the introduction of changes that are beneficial to patients in particular, and to society in general. In other words, the framework on variations must strike the right balance between protecting health and supporting innovation. It is equally crucial that the administrative workload entailed by the framework still enables competent authorities to focus on the substantial issues, related to the scientific monitoring of medicines and the protection of public health.

The last round of revision of this framework occurred in 2003-2004. A global review of the Community pharmaceutical legislation (the 'Pharma Review') was adopted in 2004, while the Variations Regulations were revised in 2003. The principal objective of this last revision was to **simplify the system** without compromising human and animal health.

After about three years of experience, it now appears appropriate to assess how far this objective has been achieved, and to reflect on possible improvements of the variations framework. Elements to be taken in consideration in this context include:

– Feedback from Member States' competent authorities, the European Medicines Agency (EMEA), the European Directorate for the Quality of Medicines (EDQM) and the industry on the operation of the current system;

– Internal experience within the Commission.

Furthermore, regulatory developments at international level, notably the elaboration of the Q8-Q9-Q10 guidelines of the International Conference on Harmonization (ICH) on medicinal products for human use, have led to the establishment of new concepts which have an important impact on the regulatory handling of post-authorisation changes.

Simplification lies at the core of the **'Better Regulation'**[2] Commission policy initiative, whose primary goal is to ensure -whenever possible- that Community legislation is made clearer, simpler and more flexible. A reflection on further simplification of the Variations Regulations provides a concrete illustration of this policy in the area of pharmaceuticals.

The purpose of this Consultation paper is not to outline detailed legal amendments. It provides a basis for discussion on key items where possible improvements of the

[1] Commission Regulation (EC) No 1084/2003, OJ L 159, 27.6.2003, p.1; Commission Regulation (EC) No 1085/2003 OJ L 159, 27.6.2003, p.24.

[2] Ref.: http://ec.europa.eu/enterprise/regulation/better_regulation/index_en.htm

legislative framework have been identified, in the light of the abovementioned policy. This list of items is also not meant to be exhaustive[3].

2. KEY ITEM 1: APPLICATION TO NATIONAL AUTHORISATIONS

2.1. Today's picture

The current Variations Regulations apply to changes to marketing authorisations granted under the centralised and decentralised procedure, but not to changes to national authorisations granted without any mutual recognition (hereby referred to as 'purely national' authorisations). Consequently, changes affecting purely national authorisations are handled according to national rules, which can vary among Member States (although in certain countries they nevertheless follow the Variations Regulations by analogy).

Purely national marketing authorisations represent the vast majority of authorisations in the EU, both in the human and veterinary sector. While they are granted according to Community law[4], changes to these authorisations are at present not subject to harmonised Community rules. For example, critical changes such as the introduction of a new therapeutic indication, or of a new pharmaceutical form, may be handled differently in Member States in terms of regulatory classification, administrative procedures, timelines and criteria for scientific assessment.

As consequences of this situation:

– Competent authorities must follow different requirements, depending whether they are dealing with changes to a purely national authorisation or with a mutual recognition (or centralised) procedure;

– Companies, who very often operate globally but on the basis of purely national authorisations, may be confronted with different rules in different countries. This legal uncertainty can delay, impair or even prevent the introduction of certain changes. It also raises logistical issues for the actual implementation of changes.

In certain cases, 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.

Last but not least, the current disharmonised situation does not appear justified from a public health perspective. Indeed:

– Why should a change affecting an excipient be scientifically assessed and administratively approved in a different way, depending whether the concerned medicinal product is authorised at purely national level or not?

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[3] In particular, other suggestions for technical amendments to the Annexes to the Variations Regulations and to the variations conditions may be proposed in the future.

[4] Directive 2001/83/EC (medicinal products for human use) and 2001/82/EC (veterinary medicinal products).

– Why should the approval of a given route of administration be subject to Community harmonised rules where this route is submitted as part of a marketing authorisation application (including purely national applications), and to non-harmonised, national-specific rules where this route is submitted as a change?

Nonetheless, it is also recognised that a number of competent authorities and companies 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 on stakeholders.

2.2. Suggestions for improvement

Today's regulatory situation as regards changes to purely national authorisations is an area where significant simplification could be achieved through harmonisation. This would be all the more beneficial as purely national licenses represent the vast majority of marketing authorisations in the EU.

In the light of the above, the following suggestions are proposed:

(1) to include purely national authorisations within the scope of the revised Variations legislative framework, so that all authorised medicinal products are subject to the same criteria for the approval and administrative handling of changes, regardless of the procedure under which those medicines have been authorised (purely national, mutual recognition, centralised);

(2) to provide for a transitional period (*e.g.* 2 years) during which changes to purely national authorisations would remain subject to existing national rules, in order to facilitate stakeholders' adaptation to the new system.

However, it is important to note that given the 'co-decision' legal basis on which the Variations Regulations are currently established[5], the scope of these Regulations is limited to variations to marketing authorisations under the mutual recognition or centralised procedure. The current scope does not include variations to purely national licenses. The above suggestions would therefore require a change in the co-decision legal basis of the Variations Regulations, so that variations to purely national licenses can be included within the scope. However, this should not delay the implementation of the other suggestions provided in this Consultation Paper. Thus, a 2-steps approach would have to be envisaged: first, implementation of the suggestions which do not require a change in legal basis; second, change in legal basis and subsequent implementation of the above Key Item 1.

[5] Article 35 of Directive 2001/83/EC, Article 39 of Directive 2001/82/EC and Article 16 & 41 of Regulation (EC) No 726/2004.

3. KEY ITEM 2: ICH Q8-Q9-Q10

3.1. Today's picture

At present, the Variations Regulations are based on a rather 'prescriptive' approach:

– any change/amendment to the contents of the marketing authorisation dossier must be registered as a variation or a line extension[6]. The procedure for the assessment and approval depends on the type of change.

– Minor variations are listed in an exhaustive manner. Variations which cannot be deemed to be minor are considered, by default, as major variations.

The ICH Q8 guideline[7] introduces the notion of 'design space' in the context of pharmaceutical development[8]. Design space is defined as *"the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality"*. Examples of relevant parameters include for instance starting materials variables like particle size distribution, specific surface area, process operations variables such as water content of mass/granule over time, blending profile over time, etc. ICH Q9/Q10 guidelines provide, amongst other aspects, the tools –risk management and quality systems- to properly implement this notion.

Design space is proposed by the applicant as part of the marketing authorisation application and is subject to regulatory assessment. Importantly, working within an approved design space is not considered a change to the terms of the marketing authorisation dossier, while movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process, *i.e.* a variation or an extension of the marketing authorisation.

The introduction of the 'design space' concept therefore creates the basis for a less prescriptive, relatively more flexible regulatory approach, whereby changes within an approved design space would not be considered to require a variation application. Besides, the establishment of a robust 'design space' goes together with an approach on quality which does not only rely on end-testing of finished products, but rather on quality built in by design.

3.2. Suggestions for improvement

On this basis, it is proposed to formally introduce the notion of 'design space' in the Variations Regulations:

(1) Changes within an approved design space would not trigger any variation approval procedure, but would be notified to competent authorities through an annual

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[6] with the sole exception of *"updated monographs of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the marketing authorisation dossier"* (Introductory Statements, Annex I to the Variations Regulations).

[7] Ref.: http://www.emea.eu.int/pdfs/human/ich/16706804en.pdf

[8] Section 3.2.2.2. (Pharmaceutical Development) of Annex I to Dir. 2001/83/EC.

reporting system similar to the one outlined in Section 4. Conversely, movement outside the design space would still be considered a change and would hence trigger either a variation or a line extension;

(2) The design space would be established and reviewed either (i) as part of the initial marketing authorisation application, or (ii) later, independently;

(3) Introduction of a new design space or changes to an approved design space would be evaluated as variations or line extensions;

(4) Although ICH Q8-Q10 apply to medicinal products for human use only, the related concepts are expected to be also useful in the context of veterinary medicinal products. It is therefore proposed that the design space concept is made applicable to both human and veterinary sectors, regardless of the type of marketing authorisation (purely national, mutual recognition, centralised).

The introduction of the 'design space' concept is expected to bring more flexibility in the regulatory approach to changes by further reducing variations submissions, thereby facilitating continuous and increased understanding during product lifecycle of material attributes, as well as manufacturing processes and controls. It is also expected to better address the 'out of compliance *vs.* out of business' dilemma that manufacturers may face.

However, it should be borne in mind that, although the design space concept may be applicable to any medicinal product, companies may in practice be less likely to invest in such an approach for old products. The concept may therefore not be sufficient to address the issue of non-implementation of improvements in the manufacture and pharmaceutical development of old medicinal products.

4. KEY ITEM 3: "DO AND TELL" PROCEDURE

4.1. Today's picture

In the current system, the simplest variation procedure is the Type IA notification. It is a "Tell and Do" system: competent authorities (or the EMEA) are notified by the marketing authorisation holder, the reference Member State (or the EMEA) acknowledges receipt of the notification within 14 days, and the relevant authorisations are updated accordingly. The change is implemented ("Do") only after the notification is made ("Tell").

The Variations Regulations lay down that these minor Type IA changes *"do not affect the approved quality, safety or efficacy of the product"*[9]. In actual fact, a number of those variations are of purely administrative nature (*e.g.* change in the name/address of the manufacturer of the finished product). However, these minor changes still account for a large number of variation procedures, both in the veterinary and human sector, and hence represent a considerable regulatory workload.

[9] Recital (5) of Regulation (EC) No 1804/2003 and Recital (4) of Regulation (EC) No 1085/2003.

4.2. Suggestions for improvement

In order to further reduce the overall number of variations procedures and to enable competent authorities to focus on those changes that have a genuine impact on quality, safety or efficacy, the following is proposed as regards Type IA variations:

(1) Type IA variations would not require any prior approval. They would be processed through a "Do and Tell" (no longer "Tell and Do") procedure: the marketing authorisation holder implements the change first, and notifies the concerned Member States competent authorities or the EMEA/Commission afterwards;

(2) The notification of the change would be done on the occasion of an annual report[10], compiling all "Do and Tell" changes made in the last twelve months. The annual report would be submitted to all concerned competent authorities. The corresponding marketing authorisations would be updated, if necessary, within a certain period of time following reception of the annual report (*e.g.* 2 months);

(3) Applicants would have the option –but not the obligation- to group annual reports so that one joint document is submitted per competent authority, outlining all "Do and Tell" changes for the relevant medicinal products;

(4) From the date of its implementation, all regulatory information related to a given "Do and Tell" change would be available without delay to the concerned competent authorities, upon request to the marketing authorisation holder;

(5) The system would apply equally to medicinal products for human use and to veterinary medicinal products, regardless of the type of marketing authorisation procedure (purely national, mutual recognition, centralised).

Thus, variations would *in fine* fall in two categories:

– Changes requiring prior approval, whose approval procedure depends on the level of health risk (*i.e.* line extensions, Type II or Type IB);

– Changes not requiring any prior approval (*i.e.* Type IA or changes within design spaces –see Section 3), which would be processed under the "Do and Tell" procedure outlined above.

[10] Except for specific administrative changes where competent authorities need to be informed rapidly, *e.g.* changes in the name/address of the marketing authorisation holder or of the manufacturer of the active substance.

5. KEY ITEM 4: SINGLE EVALUATION OF COMMON CHANGES

5.1. Today's picture

In the current system, there are two cases where a change that jointly affects several, independent marketing authorisations is nevertheless processed according to the 'one variation procedure per authorisation' rule:

(a) Where the change concerns one given medicinal product that is authorised at purely national level in several Member States. In that case the same variation is submitted in all the concerned Member States and assessed independently, although the change is the same in all cases and concerns the same medicinal product;

(b) Where the change is common to several, distinct medicinal products (*e.g.* change concerning a common excipient, change to test procedure of common solvents used, etc.).

As regards case (a), a procedure for voluntary worksharing between national competent authorities for the assessment of certain quality variations has been elaborated, in the context of an agreement by the Heads of Medicines Agencies[11]. A pilot phase is already ongoing. This example illustrates the benefits of worksharing, not only to reduce the burden imposed on competent authorities' assessors and to avoid redundant evaluations, but also to pool available expertise in case of changes of major and innovative nature.

As regards case (b), the concepts of Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF) have already shown that a single evaluation of certain quality aspects that are common to several medicinal products is feasible and can significantly reduce workload both for competent authorities and companies. As an example, the first PMF certificate concerned more than 80 medicinal products in 25 countries.

5.2. Suggestions for improvement

In the light of the above, it appears appropriate to provide for provisions that facilitate worksharing in the two aforementioned cases. The following is therefore proposed:

(1) Where the same Type IB or Type II change affects the terms of several marketing authorisations (should they correspond to the same medicinal product –case (a)- or to distinct products –case (b)) owned by the same marketing authorisation holder, that holder may request that this change is evaluated only once, *i.e.* by one single competent authority, for all or part of the concerned products;

(2) Each concerned Member State would have to confirm its agreement to participate in this 'worksharing' procedure. In Member States who do not agree to participate, the variation would follow the standard Type IB or Type II procedure;

(3) As regards the choice of the competent authority in charge of the evaluation of the change, two options are proposed:

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[11] Ref.: http://www.emea.eu.int/Inspections/docs/12045706en.pdf

– At least one of the concerned products is authorised centrally: in such a case, the EMEA would be in charge of the evaluation. This would ensure, through the operation of the EMEA network, that all Member States concerned are properly involved, as well as facilitating pooling of expertise;

– No centrally-authorised product is concerned. In this case, the authority in charge of the assessment would be chosen amongst the involved Member States, by the marketing authorisation holder. Use of the Coordination Group for Mutual Recognition and Decentralised Procedures (CMD, human and veterinary) to coordinate this worksharing procedure could also be explored in this context.

(4) All involved competent authorities would be given the opportunity to comment on the assessment before it is finalised;

(5) The finalised assessment would form the basis of the update/amendment of the relevant marketing authorisations. This task would obviously remain a competence of the concerned Member States. In any event, those Member States involved in the procedure would retain the right not to agree with the assessment carried out;

(6) The system would apply equally to medicinal products for human use and to veterinary medicinal products;

(7) The system would not apply to minor -Type IA- changes, which do not normally require any scientific assessment and are subject to the "Do and Tell procedure" (see Section 3);

(8) The system would not apply to line extensions, which are in most cases highly product-specific and therefore cannot be evaluated at once for several products.

6. KEY ITEM 5: USE OF THE TYPE IB PROCEDURE BY DEFAULT

6.1. Today's picture

At present, a change which is neither a 'line extension' nor a Type IA/IB change is by default a Type II variation. This implies, in particular, that any change not clearly foreseen in the Annexes to the Variations Regulations is subject, by default, to the lengthiest and most complex variation procedure.

In practice, this means that certain changes which may not raise any major health issue and could be handled in a simple manner still require a Type II procedure for legal reasons, solely because they were not foreseen in the abovementioned Annexes.

6.2. Suggestions for improvement

In order to avoid the contradictory situation outlined in Section 6.1, the following is proposed:

(1) Changes which, in the Annexes to the Variations Regulations, are explicitly laid down as neither being Type IA/IB nor a line extension, would remain handled as Type II variations;

(2) Changes which are not laid down in the Annexes would be handled, by default, as Type IB variations (and no longer as Type II), unless the concerned competent authorities consider that, due to the potential impact of the proposed change on the quality, safety or efficacy of the product, the variation should still be processed as a Type II.

It should be noted that the Type IB procedure ("Tell, Wait and Do"), which is proposed as the default procedure, preserves the ability of competent authorities:

– to judge whether the submitted application should indeed be a Type IB (see paragraph (2) above);

– if it is a Type IB, to request additional scientific information for the purpose of evaluating the application.

7. OTHER SUGGESTIONS

Other proposals are suggested below, in order to clarify certain aspects of the Variations framework and to further smoothen its operation:

7.1. Variations conditions: Type IB to Type IA

The classifications of certain changes as Type IB may appear questionable given the nature of these changes and their unlikely impact on quality, safety or efficacy of the product. Those changes, outlined in the Annex to this Consultation Paper (see Section 8.1), may therefore be cases for reclassification as Type IA.

7.2. Variations conditions for biologicals

In the current Variations Regulations, most of the changes affecting biological medicinal products or biological substances are processed as major (Type II) variations, although an identical change affecting a chemical substance would be handled as a Type I. This may appear questionable in certain cases, outlined in the Annex to this Consultation Paper (see Section 8.2). Those cases are therefore proposed to be reclassified.

7.3. Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF):

Regulation (EC) No 1085/2003 applies not only to variations to the terms of centralised marketing authorisations, but also to "*variations to the terms of a plasma master file and of a vaccine antigen master file*"[12]. However, this 'extrapolation' may not appear entirely clear from a legal point of view, since the term 'variation' is defined as an amendment to the marketing authorisation dossier, and not to the PMF/VAMF.

It has also been questioned whether the incorporation of a new or varied PMF/VAMF in the marketing authorisations of the concerned medicinal products (the so-called '2nd step') triggers in itself a variation procedure. In certain cases, it has been argued that since this incorporation is not explicitly foreseen in the Annexes to the Variations Regulations, it needs to be processed as a Type II variation. However, this would undermine the overall

[12] Article 1(2) of Regulation (EC) No 1085/2003.

objective of the VAMF/PMF mechanism, which is precisely to reduce the number of redundant evaluations and simplify variations procedures.

It is therefore proposed to clarify the legal applicability of the Variations Regulations to the VAMF/PMF, and to introduce the following mechanism for the handling of the '2nd step':

– The '2nd step' inclusion of a new PMF/VAMF (for the first time) in a given marketing authorisation dossier would be processed as a Type IB variation;

– The '2nd step' inclusion of an updated/amended PMF/VAMF would be processed as a Type IA (hence under the abovementioned "Do and Tell" procedure, see Section 3).

This mechanism would preserve the involvement of all Member States in the assessment of the PMF/VAMF, through the 1st step and the operation of the EMEA network. It would also preserve the competence of Member States as regards the finished products and the corresponding marketing authorisation dossiers, without increasing the regulatory workload of the PMF/VAMF mechanism.

7.4. Coordination Group for Mutual Recognition and Decentralised Procedures (CMD)

For products authorised under mutual recognition, the current Variations Regulations lay down the possibility for a concerned Member State, where it is not in agreement with the assessment of the reference Member State, to initiate an arbitration procedure[13]. However, the introduction of the Coordination Group for Mutual Recognition and Decentralised Procedures (CMD, human and veterinary)[14] in the 'Pharma Review' and the related procedures for addressing disagreements between Member States are at present not reflected in the Variations Regulations. It is therefore proposed to introduce the appropriate references.

7.5. Monographs and Certificates of suitability

At present, changes that affect existing certificates of suitability to monographs of the European Pharmacopoeia are handled through a Type IA variation. With the current Type IA procedure, this may appear disproportionate where those changes are of purely administrative nature, such as:

– Change of the certificate due to a new version of the European Pharmacopeia (*e.g.* next edition), without any technical change;

– Renewal of the certificate (a certificate is valid five years, renewable once; it is then valid for an unlimited period, provided it is kept up to date by the holder) while its content remains unchanged;

– Administrative changes applied for by the holder of the certificate (*e.g.* change of name of the holder etc.).

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[13] Article 35(2) of Directive 2001/83/EC and Article 39(2) of Directive 2001/82/EC.

[14] Article 27 of Directive 2001/83/EC and Article 31 of Directive 2001/82/EC.

With the proposed "Do and Tell" mechanism (See Section 3), all these changes would no longer trigger single variations, but would be grouped and reported through the annual reporting system.

7.6. Clarification of deadlines

Currently, there is no explicit deadline for national competent authorities to update or amend the marketing authorisation following approval of a given variation[15]. In certain cases, this can lead to delays and discrepancies that may jeopardize the actual implementation of the change by economic operators.

For this reason, it is proposed to introduce a fixed deadline for national competent authorities to update/amend the marketing authorisation following approval of a variation (*e.g.* one month).

7.7. 'Sweep' mechanism to update centralised authorisations

According to the Variations Regulations, centralised marketing authorisations are to be updated in respect of Type I variations every six months by the Commission[16]. Within the Commission, a system of 'sweep' decisions has been introduced, whereby updates related to Type I variations are made either through the 6-months update or at the occasion of a Commission Decision for the concerned product (*e.g.* Type II variation, transfer of the marketing authorisation, renewal etc.), whichever is the earliest. This system is quicker and decreases the number of decisions.

In order to bring further flexibility, it is therefore proposed to formally introduce this 'sweep' mechanism in the Variations Regulations, and to increase the periodicity of the update from 6 months to one year.

[15] Articles 4(5), 5(7) and 6(10) of Regulation (EC) No 1084/2003.

[16] Articles 4(5) and 5(7) of Regulation (EC) No 1085/2003.

8. ANNEXES

8.1. Variations conditions: Type IB to Type IA ?

Variation #	Current classification	Proposal	Rationale
12(b) Change in the specification of an active substance or a starting material / /reagent used in the manuf. of the active substance	Type IB (addition of a new test parameter to the specification)	Type IA	Addition of a new test parameter which is not the result of unexpected events arising during manufacture can only improve quality.
19(b) Change in the specification of an excipient	Type IB (addition of a new test parameter to the specification)	Type IA	Same as 12(b).
24 Change in synthesis or recovery of a non-pharmacopoeial excipent (when described in the dossier)	Type IB	Type IA	The specifications are not adversely affected; no change in qualitative and quantitative impurity profile or in physico-chemical properties.
25(a) Change of specification(s) of a former non-European pharmacopoeial substance to comply with European Pharmacopoeia or with the national pharmacopoeia of a Member State	Type IB	Type IA	This is a switch to comply with European or national, established standards.
26(b) Change in the specifications of the immediate packaging of the finished product	Type IB (addition of a new test parameter)	Type IA	Same as 12(b).
30(b) Replacement or addition of a supplier of packaging components or devices	Type IB	Type IA	The qualitative and quantitative composition of the packaging components /device remains the same and the specifications and quality control method are at least equivalent.
31(b) Change to in-process tests or limits applied during the manufacture of the product	Type IB (addition of new tests and limits)	Type IA	Addition of new tests and limits which is not the result of unexpected events arising during manufacture can only improve quality.
33 Minor change in the manufacture of the finished product.	Type IB	Type IA	The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
37(b) Change in the specifications	Type IB (addition of a new	Type IA	Same as 12(b).

of the finished product	test parameter)		

8.2. Variations conditions for biologicals: cases for reclassification ?

Variation #	Current classification for biologicals	Proposal	Rationale
8 Change in batch release arrangements and quality control testing of the finished product	8(a): Type II 8(b)1: Type IA 8(b)2: Type II	8(a): Type IB 8(b)1 unchanged (Type IA) 8(b)2: Type IB	Successful method transfer is a condition (condition 4) to be met anyway.
12 Change in the specification of an active substance or a starting material /intermediate /reagent used in the manuf. of the active substance	12(b)1: Type II (addition of a new test parameter to the specification of an active substance)	12(b)1: Type IA	No justification for a Type II where more stringent requirements (*i.e.* addition of a new test parameter) are introduced.
13 Change in test procedure for active substance or starting material/ intermediate / reagent used in the manuf. of the active substance	Type II	13(a): Type IA 13(b): Type IB	No justification to have different requirements in the case of biological substances. Other conditions would anyway apply.
17 Change in the re-test period of the active substance	17(a): Type II	17(a): Type IB	No justification to have different requirements in the case of biological substances.
19 Change in specification of an excipient	19(b): Type II (addition of a new test parameter to the specification)	19(b): Type IA	Same as 12.
20 Change in test procedure for an excipient	20(b): Type IB 20(c): Type II	20(b): Type IA 20(c): Type IB	Same as 13.
37 Change in the specification of the finished product	37(b): Type II (addition of a new test parameter)	37(b): Type IA	Same as 12.
38 Change in test procedure of the finished product	38(b): Type IB 38(c): Type II	38(b): Type IA 38(c): Type IB	Same as 13.
42 Change in storage conditions of the finished product or the diluted/ reconstituted product	42(b): Type II	42(b): Type IB	Same as 13.

Appendix 3

EFPIA/EBE/EVM RESPONSE TO
EUROPEAN COMMISSION CONSULTATION PAPER ON
REVISION OF VARIATIONS REGULATIONS
Final–20th December 2006

Executive Summary

EFPIA/EVM/EBE very much welcome the inclusion of the revision to the existing Variation Regulations as part of the Commission's 'Better Regulation' initiative. We believe that its stated aims of reducing the administrative burden and simplifying the existing regulations will stimulate the introduction of changes beneficial to the patient while making a significant contribution to the overall goal of enhancing the competitiveness of the European economy.

For EFPIA/EVM/EBE, representing the research based pharmaceutical industry, the key goals are:

- Simplify and clarify regulatory procedures for post-authorisation changes
- Ensure the continued protection of public health
- Reduce the number of regulatory events associated with post-approval changes and the associated regulatory burden
- Facilitate innovation and continual improvement
- Enable clarity and predictability of regulatory requirements
- Enable predictability of variations procedure timelines, in order that beneficial changes can be introduced in a timely manner
- Support the competitiveness of the Pharmaceutical Industry in Europe.

We are delighted with the EC's current proposals, as they support a number of these goals, namely by:

- Recognition of ICH developments
- Proposal of 'Do and Tell'
- Single evaluation of common changes
- Common principles for biologics and small molecules
- Predictable timelines for implementation of a change by the MAH.

Key Item 1 Application to National Authorisations

EFPIA/EVM/EBE 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. The new Regulations must also define timelines for Member States for the issuance of their approvals where these are required.

Key Item 2 ICH Developments

EFPIA/EVM/EBE strongly supports including the benefits of the adoption of the recent ICH guidelines (Q8/9/10) into the revised regulations. These benefits must include a reduction in

post-authorisation submissions and a reduced intensity of regulatory oversight for companies adopting ICH Q8/9/10.

Key Item 3 Do and Tell Procedure
We strongly support the introduction of a 'Do and Tell' procedure.

EFPIA/EVM/EBE proposes two categories of change: minor changes (immediate notification or annual notification) and major changes requiring pre-approval.
Our proposal is that two lists be created: one of minor changes considered to require immediate notification and the second to contain those changes deemed to be major changes. For all other changes an assessment should be conducted by the MAH in order to ensure appropriate categorisation of changes. We propose that a Commission guideline be developed to address this assessment and facilitate a harmonised approach.

It should also be noted that the above-mentioned lists should be developed under a process, which makes them amendable through a relatively fast process to ensure the lists reflect current knowledge and new learning from practical application of the process.

EFPIA/EVM/EBE believes that annually notifiable changes are consistent with many of current Type IB list of changes. Our recommendation is that the submission of the reports should be linked to an agreed birth date of the product.

Key Item 4 Single Evaluation of Common Changes
Worksharing is strongly supported. It can only apply to those variations requiring approval and must not be optional on the part of Member States. The Commission goals of 'Better Regulation' can be met only with the full participation of all Member States and their commitment to implement the worksharing decision into their national authorisations.

The proposal for single evaluation of common changes is appreciated but we would emphasise the need to define related and grouped changes as different options (one change impacting many products versus multiple changes to one product).

Key Item 5 Use of the Type IB Procedure by Default
EFPIA/EVM/EBE strongly support that variations should not automatically default to Type II variations. However, we do not agree with the proposal for a "tell/wait/do" procedure. Such a procedure would result in disharmony, complexity, and unpredictability of outcomes.

(Please also refer to previous comments under Key Item 3.)

Other Suggestions
We support the EC suggestion that variations be reclassified <u>where appropriate</u> to be consistent with chemical entities.

Detailed comments to the "Other Suggestions" are given in section 6 below.
However in addition to those specific comments we would like to make the following proposals:

1) <u>Introduction of the concept of a **'Regulatory Agreement'**</u>
We believe that the concept of a **'Regulatory Agreement'** should be introduced, as this will significantly improve the management of post authorisation changes.
The Regulatory Agreement is one which:

- Describes compliance related information, by differentiating between what is 'binding' and what is provided as supportive knowledge

    - Changes to binding information COULD require variation whereas changes to all other supporting detail should be outside the scope of the new Variations Regulations
- Depends on the outcome of 'regulatory flexibility' discussion[1]
- Benefits regulators by clarifying the separation of review and inspection related information.

2) Extension of the Master File concept

We believe the application of the master file concept in the following situations would offer substantial benefits in terms of reducing administrative burden and simplifying procedural aspects:

a) Pharmacovigilance Master File - a detailed description of a Company's pharmacovigilance system is now legally required (as defined by Article 8 of Directive 2001/83/EC as modified by 2004/27/EC.), and consequently even relatively minor changes to this information result in a Type II variation.

b) Excipients and Container/Closure – the extension of the Master File concept to excipients and container/closure could reduce the number of duplicate reviews of the same information, as well as enabling the provision of confidential information to the Competent Authorities.

[1] ICH Q8 guideline on pharmaceutical Development (EMEA/CHMP/167068/2004)

EFPIA/EBE/EVM Detailed Responses to the European Commission Consultation Paper titled: Better Regulation Of Pharmaceuticals: Towards A Simpler, Clearer And More Flexible Framework On Variations, Version: 20 October 2006

Key item 1: Application to National Authorisations

EFPIA/EBE/EVM strongly support the Commission's proposal to harmonise the variation system to include all changes into the scope of the revised Variations Regulation regardless of their route of authorisation.

We support the proposed approach for the application of the future Variations framework to the existing national systems. However, the transitional period should be kept to a minimum. This would benefit all parties, including the authorities who would not have to manage multiple systems at the same time.

The initiation of the Co-Decision procedure to change the legal basis in Directives 2001/83/EC 2001/82/EC and Regulation No 726/2004 must be initiated as soon as possible to potentially allow the implementation of the revised Variation Regulations for all changes at the end of the transitional period. This co-ordination of the Comitology procedure and the Co-Decision procedure should be co-ordinated to the best possible extent. We advocate the decoupling of the Co-Decision procedure handling the Variations topic from other Co-decision procedure regarding any other subject to avoid potential prolongation of the process.

Key item 2: ICH Q8-Q9-Q10

While we agree with the statement that the current regulations represent a rather 'prescriptive' approach, we are disappointed that the Commission has not fully appreciated the intentions of the recent ICH guidelines, nor their full implications. We appreciate that the ICH Q10 guideline is still in its early stages of development. However, the Step 1 version 8 document says: "Flexible regulatory approaches may be achieved when an effective pharmaceutical quality system is in place and demonstrated during inspection. Further flexibility may be realised where product development adheres to the principles of the ICH Q8 and Q9 guidelines."

The current proposals do not address this flexibility in a specific way. The new Variations Regulations must empower Industry to manage its own changes and provide incentives to generate and submit the enhanced product and process understanding that is envisioned in the ICH Q8 guideline. Without this incentive, there is no point continuing the development of ICH guidelines. It is also important to correct an apparent misunderstanding. The ICH Q8 guideline states that movement within an approved Design Space is not a change. Therefore such movements are not subject to any form of regulatory notification or approval.

It should also be acknowledged that the adherence to these ICH guidelines is optional and any reference to them in revised regulations should reinforce this optionality.

EFPIA/EBE/EVM Recommendations

We recommend the new Variation Regulations: -

a) Provide significant and specific incentives for applicants to develop enhanced product and process understanding, to use the principles of Q8, quality risk management (Q9) and to develop effective quality management systems (Q10). These incentives would include self-management of changes to approved Design Spaces, and the more general shift of

changes currently requiring authority pre approval to changes which require only notification. Ways of achieving this could be through comparability protocols and/or through the concept of a Regulatory Agreement.

b) State that the flexibility envisioned in these guidelines can be utilised for drug substances, drug products and their associated analytical procedures for human products and veterinary products irrespective of the submission format.

Rationale

The ICH guideline Q8 defines the concept of Design Space. The guideline explicitly states that working with the Design Space is not considered to be a change and we note the Commission's agreement on this point. Working within a Design Space is conceptually no different from working within any other parameters or ranges already approved in a marketing authorisation - any modifications of processes or products that are contained within the approved Design Space are not required to be captured in a annual report nor do they require any regulatory approval.

We are concerned about the suggestion of a 'robust' design space since this concept has no meaning: either quality is assured or it is not, there are no degrees. Additionally there is a misinterpretation of the concept of 'real-time quality control' that is described in the ICH Q8guideline. While it is true that the later encourages quality being built in, full end product testing may still be required even within an agreed Design Space. An applicant may be able to demonstrate that a reduction of end product testing is appropriate because they have the necessary product and process understanding but this is optional.

It is important that Industry be encouraged to develop adaptive manufacturing processes, that is processes which can be adjusted to accommodate variability in input materials. The concept of Design Space was created to encourage such approaches. For these manufacturing processes, each batch may be processed slightly differently depending on particular attributes of the raw materials in order to minimise the variability of the output. There may even be adjustments during the process. The Commission proposal would result in all these inter and intra-batch changes within the Design Space being notified.

The net result of the proposals would be the complete negation of the flexibility sought and encouraged by ICH and a huge increase in complexity and workload for both Industry and Regulators.

Where a new Design Space is proposed, then we agree that an appropriate variation would need to be submitted. We do not agree that this would need to be evaluated as a line extension. Furthermore, where a change to an existing Design Space is suggested (e.g. extension or contraction) Industry would like to see a much simpler approach to the change, such as through an agreed comparability protocol whereby as long as the amendment was demonstrated to meet pre-approved quality criteria, the applicant would be free to use a notification procedure.

We note that the ICH Q8 guideline is concerned with the information to be supplied in Section P2 of the Common Technical Document (CTD). Future ICH activities may address similar concepts for the active ingredient, and possibly analytical procedures. Until such time as these are available, the proposal could indicate that the Q8 concepts are equally applicable to these as yet unaddressed areas. In addition, a general statement of acceptance for veterinary products would be helpful, adding that this does not require submission in CTD format.

It is assumed that if a Design Space is registered for a biotech product, then all changes within the Design Space would be handled in the same manner as that applied for small molecules.

The Regulatory Agreement

A Regulatory Agreement would summarise the applicant's compliance commitments and post-approval change strategy and this is not a new concept. In Japan the application form distinguishes between those parts of the dossier that need approval prior to a change and those where notification can be accepted. In the USA, the FDA is actively promoting the concept of a Regulatory Agreement and encouraging companies to submit proposals as part of their so-called 'pilot study'. (We recognise that such agreements in the USA are only exploratory at this stage.) Given the current EU situation where the whole dossier represents the applicant's compliance commitments, applicants choosing to share extensive knowledge and detail in their dossier are later potentially burdened with a large number of variations as they optimise their processes. A Regulatory Agreement could form the basis for separating the parts of the dossier which represent ongoing commitments from the enhanced knowledge, thus encouraging a greater sharing. Additionally, the applicant and the authorities could agree a post-approval change management protocol which would not be complicated by the current prescriptive regulations.

Key Item 3: 'Do & Tell'

EFPIA/EBE/EVM welcome and support the introduction of such a concept. It also needs to be clarified via a listing that there would be certain minor changes subject to immediate notification, rather than through annual reporting.

The scope of the 'do & tell' procedure should explicitly allow for immediate notification of labelling (including SmPC) changes which are simply the implementation of previously agreed changes with no further scientific assessment being required and the update of annexes to the MA dossier in line with the most current QRD template.

Key item 4: Single Evaluation of Common Changes

EFPIA/EVM/EBE strongly support the proposed single evaluation of common changes, as this may be one of the most efficient ways to prevent unnecessary duplication of work and has the potential to limit much of the current administrative burden involved with variations. The worksharing procedure can only apply to those variations requiring approval and must not be optional on the part of Member States. The Commission goals of Better Regulation can be met only with the full participation of all Member States and their commitment to the worksharing decision.

The question as to whether this concept will prove to be effective depends on the details of the procedure. At a minimum, the following should be addressed:

1. **Participation Confirmation**

The use of the worksharing procedure should remain optional for the MAH.

The need for prior confirmation by Member States per variation to participate has the potential to make the procedure unworkable. Not only will this step have a negative impact on the timelines, it also provides uncertainty due to the possibility for Member States to opt out of this procedure.

EFPIA/EBE/EVM believes that this confirmation should not be needed on a case-by-case basis. With the assumption that mutual understanding and trust between National Competent Authorities is the basis for the worksharing procedure participation should not be optional for National Authorities. Objections during the worksharing procedure must be based only on potential serious risk to public health grounds.

We acknowledge there are legal obstacles to the mandatory national implementation of the outcomes of the worksharing procedure. However we encourage the Commission to explore ways of using the Co-Decision procedure to enable this significant advantage.

2. **Minor versus Major Variations**

The Commission Paper proposes that the worksharing procedure would apply to both current Type IB as well as to Type II variations.

However, changes in the current Type I category (minor variations) have a minimal potential to have an adverse effect on the Quality, Safety and Efficacy of the approved product and are considered in the EFPIA/EBE/EVM proposal as either immediate notification or annually reportable. Therefore we are of the opinion that such changes should be reported in the annual report, which by definition excludes them from the worksharing procedure. Thus the worksharing procedure would only be applicable for major variations (requiring prior assessment).

3. **Approval and update /amendment of the MA**

The right of Member States not to agree with the assessment should be expressed before the assessment is finalized, and not afterwards. When the assessment has been finalized and the outcome is favorable the MAH should have no further uncertainties about the approval in the other Member States.

Implementation of changes which have no impact on Product Information (e.g., Chemical Manufacturing & Control changes) should be allowed immediately after a positive outcome of the assessment of the variation.

Implementation of changes which have an impact on product information should be allowed if, after a positive outcome of the assessment and that the MAH has not received any objections on the translations, within 10 days following the submission of the translations.

4. **"Related" vs "Group"/"Bulk" variations.**

The Commission's proposal addresses "group" or "bulk" variations: i.e. where the same change affects several different products. In addition to such changes, EFPIA/EVM/EBE propose that a category of "related" variations be included in the future Variations Regulations, allowing submission of a single variation application for multiple, non-consequential changes to the SmPC and other labelling components, or to a distinct process or procedure in the Quality dossier of a single product.

Key Item 5: Use of Type IB Procedure by Default

The EFPIA/EBE/EVM proposal does not include a "tell/wait/do" procedure although we do agree an automatic default to a Type II variation is not appropriate.

We propose to introduce only two categories of changes:

- A **minor change** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or efficacy or the risk-benefit profile of the medicinal product.
- A **major change** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a medicinal product as these factors may relate to the safety or efficacy or risk-benefit profile of the medicinal product.

Our proposal is that two lists be created: one of minor changes considered to require immediate notification and the second to contain those changes deemed to be major changes. For all other changes an assessment should be conducted by the MAH in order to ensure appropriate classification. We propose a Commission guideline be developed to address this assessment and facilitate a harmonised approach.

The timing of notification of a minor change may have to be considered in certain cases. Therefore, we propose to further define notifications into immediate notification and annual notification.

It should also be noted that the above-mentioned lists should be develop under a process which make them amendable through a relatively fast process to ensure the lists reflect current knowledge and new learning from practical application of the process.

We have provided in Annex to this paper a diagram outlining how our proposed system would work. We believe that this proposal would achieve the objective of simplification and would be a major contribution to the Commission's goal of 'Better Regulation'.

Other suggestions

7.1. Variations conditions: Type IB to Type IA

The Commission proposals provide a sound basis for further discussion on re-categorisation of changes.

7.2 Variations Conditions for Biologicals

Whilst as a general principle we would prefer to see that biological/biotechnological medicinal products are treated in the similar way as chemical entities, we recognise that a number of changes for which annual notification is appropriate for chemical entities will become major changes for biological/biotechnological medicinal products. There should be a single list for major changes but some entries may only apply to biological/biotechnological medicinal products.

The EC proposal to revisit the current classification for biologics is welcome but more variations in addition to the EC proposal should be removed from the de facto Type II. EVM/EBE will provide at a later stage a proposed list of changes which shall be excluded from Type II.

7.3 Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF)

EVM supports the Commission's proposal to streamline the 2nd step of the VAMF procedure.

7.4 Coordination Group for Mutual Recognition and Decentralised Procedures (CMD)

The suggestion to introduce the appropriate references to the CMD in the Variations Regulations is welcome, and requires no further comments.

7.5 Monographs and Certificates of Suitability

The proposal to handle administrative changes for existing Certificates of the European Pharmacopoeia (CEP) via the 'do and tell' principle is welcome, because this will clearly lower the current administrative burden.

However there are additional problems with the current CEP procedures that need to be addressed:

1. New versions of a CEP based on technical changes are issued by EDQM after scientific assessment of the change. Therefore the submission of new versions of certificates based on technical changes should be considered administrative and should qualify for "do and tell" as well.

2. Currently in case of changes in the specifications or impurity profile of the active substance the submission of the corresponding new version of the CEP is automatically a current Type II variation. This is excessive if the change is an obvious improvement e.g. in the case of a narrower specification or the deletion of an impurity or residual solvent, and these changes should be annually reportable changes.

3. It is recognised that changes in the active substance can work out differently for different final products, but for most changes this is not the case. Communication between EDQM and national health authorities should be improved in order to allow EDQM assessors to state in general if the change in the active substance has the potential to negatively influence certain types of pharmaceutical formulations, in order to avoid multiple assessments of the technical details of new CEPs.

4. The timelines for assessment of CEP related submissions and the issue of CEPs remain of concern. The procedure should be such that similar timelines as for variations via the decentralised procedure can be met.

7.6. Clarification of Deadlines

EFPIA/EVM/EBE strongly supports the introduction of a fixed deadline for national competent authorities to update/amend the marketing authorisation following the approval of a variation. Since the updating/amendment of the marketing authorisation is mostly of administrative nature, we propose a maximum period of 15 days for this exercise.

For labelling changes, the submission of final translations would occur 5 days after finalisation of the assessment. Competent Authorities would have another 5 days to notify justified revision requests to the translated texts. If they did not react within this period the translated text would be considered approved.

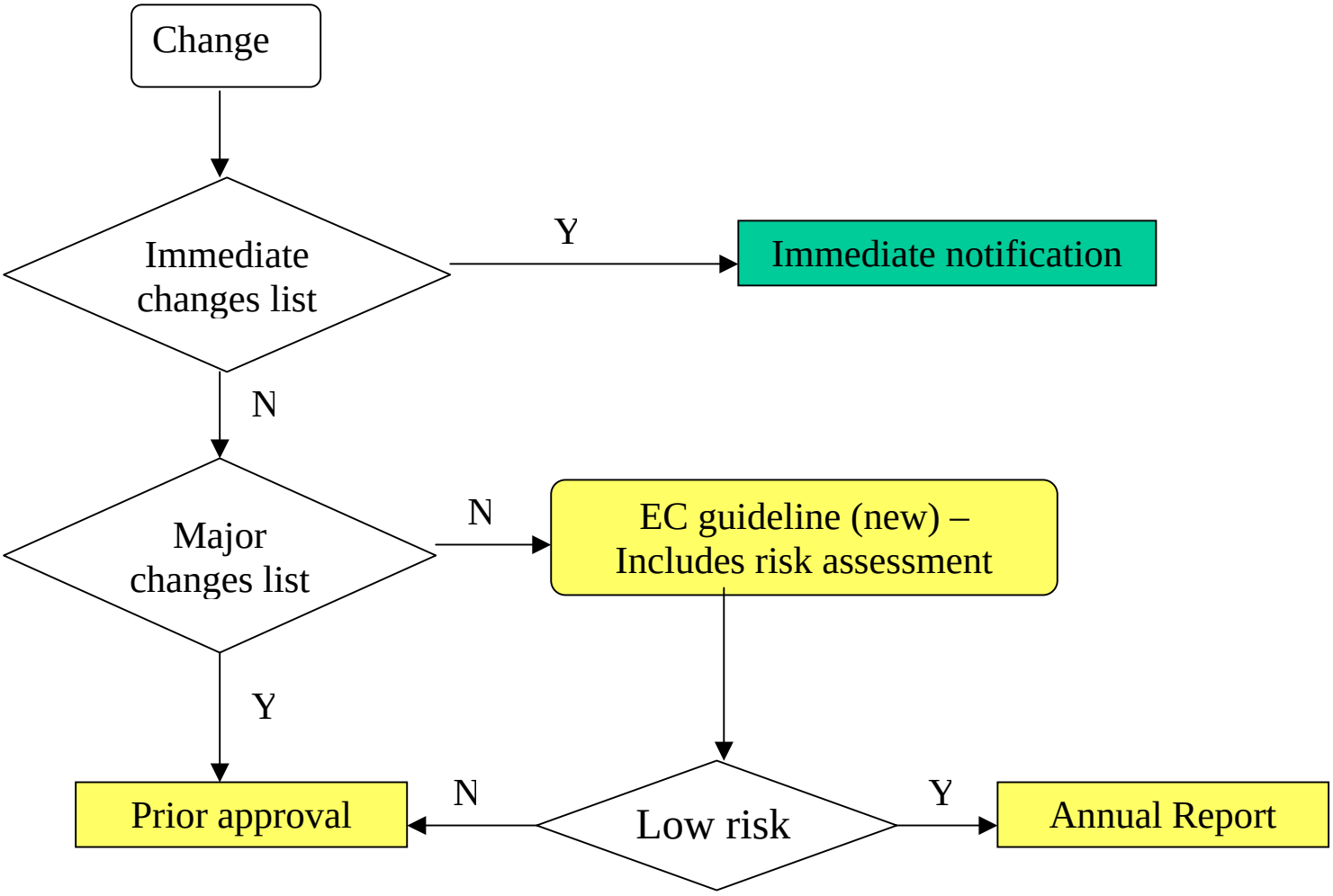
It must be explicitly stated that for notifications, an update of the marketing authorisation is not warranted to occur before implementation of the change.

7.7. "Sweep" mechanism to update centralised authorisations

EFPIA/EVM/EBE supports the extension period of "sweep" updates for Commission Decisions from 6 months to one year. In addition, we strongly encourage other competent authorities to introduce such a mechanism for updating their national authorisations.

However, we would like to point out that the Commission should investigate the potential impact on regulatory activity with international markets.

Annex Illustrations of Procedures with Various Categories of Changes



Appendix 4

a. Type I Notifications for minor changes

i. Type IA: Immediate Notifications

Principles & Definition

Immediate Notifications are required for specific changes that impact the ability of a Competent Authority to fulfil its legal obligations with respect to effective supervision of the Industry and the need to be kept current for patient safety or sourcing issues. These types of changes are mainly amendments to the administrative information included in the EU application form and examples are listed below.

Such changes do not require validation , assessment or approval, however Industry would require immediate acknowledgement of receipt from the Competent Authorities. Conditions for acceptable classification of these changes should be substantially the same as the current Regulations

In addition, changes in the product information (SPC, PIL, Label) that have been previously assessed by the competent authority through procedures other than variations, should also be treated as "immediate notifications".

For example, changes made at the request of competent authorities (e.g. product information changes following the assessment of a PSUR or renewal application; implementation of class labelling statements from new or revised core SPCs or Article 31 referral procedures), where the MAH fully complies with the request and submits no further data, do not require further scientific evaluation. In addition, changes to product quality which result in changes to product information (e.g. shelf life extension) belong to this category.

EFPIA believes that changes that have already been discussed and agreed with authorities do not need to be re-evaluated.

Procedure & Timelines

The notification would be sent simultaneously with the implementation of the change or with the target date for implementation. The agency immediately acknowledges the

receipt of the notification.

A letter and replacement pages for the MA dossier or Application form should be provided as documentation.

The system of periodic updates to the Decision by the European Commission following Type IA and IB variations, currently applicable to centrally authorised products, is a process which should be applied for the updating of marketing authorisation particulars following immediate notifications for all procedures (i.e. MR/DCP, Centralised and National). It should be made clear in the legislation that these changes can be implemented before the Decision or national authorisation is revised and the updated product information is published by the EMEA/National Competent Authority.

ANNEX I: Type IA Immediate Notifications

Examples of Proposals for Administrative Changes requiring Immediate Notification
Note that these apply equally to all types of product, including Biotech.

- **Change in the name and/or address of the MAH (formerly 1)**
- **Change in the name of the medicinal product (formerly 2)**
- **Change in the name of the active substance (formerly 3)**
- **Change in the name and/or address of a manufacturer of the finished product (formerly 5)**
- **Change in ATC Code (formerly 6)**
- **Replacement or addition of a manufacturing site for primary or secondary packaging for all types of pharmaceutical forms, where the site does not require verification of GMP status (formerly 7a, 7b).** ***Note The replacement or addition of a manufacturing site for all other manufacturing operations except batch release (formerly 7c) should be considered as an annually reportable change***
- **Change to batch release arrangements and quality control testing of the finished product when it concerns the replacement or addition of a manufacturer responsible for batch release (formerly 8b). *Note The replacement or addition of a site for batch control/testing (formerly 8a) should be considered as an annually reportable change***
- **Replacement or addition of manufacturer of the active substance where no EP Certificate is available (formerly 14b).** ***Note The change in site of the already***

approved manufacturer - replacement or addition - (formerly 14a) should be considered as an annually reportable change.

Note : Proposal is to differentiate active substance (AS) changes from reagents (R)/starting material (SM)/intermediates (I)

Changes to R/SM/I =Annual report

AS 14a = Annual report

AS 14 b =Immediate notification

All other changes = Annual report

- **Change in the name and/or address of a manufacturer of the active Substance (formerly 4,) including :**

  Submission of a European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance from a manufacturer (replacement or addition) that was not previously named in the submission (formerly 15 in part).
- **Submission of a new or updated European Pharmacopoeia TSE certificate of suitability for an substance sourced from a TSE relevant species from a new manufacturer (replacement or addition) for a Substance in a veterinary medicinal product for use in animal species susceptible to TSE (formerly 15 16, 21 22)**
- **Replacement of an excipient with a comparable excipient if the change leads to a change in the SPC (formerly 18)**
- **Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used) if specifically mentioned in the SPC (formerly 28)**
- **Change in the qualitative and/or quantitative composition of the immediate packaging material for all pharmaceutical forms if specifically mentioned in the SPC and if the new material is at least equivalent to the approved one (formerly 29)**

  Comment: Including sterile, biological and biotech products
- **Change in the colouring system or the flavouring system currently used in the finished product IF specifically mentioned in the SPC (formerly 34)**
- **Change in coating weight of tablets or change in weight of capsule shells if it is mentioned in the SPC (formely 35)**
- **Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules (formerly 39)**
- **Change of dimensions of tablets, capsules, suppositories or pessaries if specifically**

mentioned in the SPC (formerly 40)

Change in pack size of the finished product outside the range of the currently approved pack sizes (formerly 41a)2). ***Note If the change is mentioned in the SPC or is within the range of the currently approved pack sizes (formerly 41a(1)) it should be considered as annually reportable.*** *Comment: Including parenteral products*

- **Change in the fill weight/fill volume of multidose products where the posology is not affected (formerly 41b but embracing all multidose products – including parenteral products formerly Type II)**
- **Change in the shelf-life or of the storage conditions of the finished product when the change is not the result of unexpected events arising during manufacture or because of stability concerns (formerly 42)**
- **Addition or deletion of a measuring/administration device not being an integrated part of the primary packaging if specifically mentioned in the SPC and patient leaflet (formerly 43)**
- **Change in the summary of product characteristics of an essentially similar product following a Commission Decision for a referral for an original medicinal product in accordance with Article 30 of Directive 2001/83/EC or Article 34 of Directive 2001/82/EC (for Mutual Recognition Procedure only, Regulation 1084/2003)**
- **Change in the summary of product characteristics, labelling and package leaflet/insert as a consequence of a final opinion in the context of a referral procedure in accordance with Articles 31 and 32 of Directive 2001/83/EC or Articles 35 and 36 of Directive 2001/82/EC (for Centralised Procedure only, Regulation 1085/2003)**
- **Deletion of: a pharmaceutical form, a strength, or a pack-size(s (formerly 47)**
- **Change in name of the Qualified Person responsible for Pharmacovigilance nominated in the detailed description of a Company's Pharmacovigilance system.**
- **Changes to the SPC already assessed and approved by other Competent Authorities (eg change to ATC code following adoption by WHO; change in name of product following agreement from EMEA Invented Name Review Group.**

<u>Notes to the examples.</u>

EFPIA envisages that examples would not be included in the Regulations to simplify maintenance of the list.

Many of these examples simultaneously affect many Marketing Authorisations; therefore simplification of the administration should be facilitated. (See related and grouped changes).

Appendix 5

List of Type II variations related to Quality changes

We would propose that the list of Type II major variations is developed as a separate Commission guideline to allow flexibility and easier adaptation, once experience is gained with the new variation system, rather than including as an Annex to the revised Variation Regulation.

The purpose of the guideline is to help both Reviewers and Industry to conduct appropriate risk assessments that enable them to classify changes that require prior approval and distinguish them from those that do not. It is not envisaged that this will become an exhaustive list of Type II changes.

Quality Related Changes

Any changes that are carried out according to a process, conditions or parameters that are part of the approved dossier (including the design space) do not require prior approval unless the MAH becomes aware of unexpected consequences, where these should be notified.

Major changes (those having significant potential to impact quality, safety or efficacy) should be classified as such, through a risk assessment in comparison with this list and prior-approval sought through a Type II approval process.

The 60 days procedure would be the default procedure for these Quality changes.

Below are examples of Quality related changes, which would require the submission of a type II variation unless a notification procedure has been proposed and approved (e.g. via a regulatory agreement):

- Major change in manufacturing process for active substance (e.g. change to critical quality attribute (CQA), critical process parameter (CPP), change of synthetic route)
- Major change in manufacturing process for finished product (e.g. change to CQA, CPP, change to principles of manufacturing technology, change in qualitative composition)
- Change in specification of active substance involving a widening or addition of an acceptance criterion
- Change in specification of finished product involving a widening or addition of an acceptance criterion
- Revision to or replacement of an analytical technique and/or procedure (e.g. change to the technology used - HPLC to GLC, UV to NIR) where the method performance criteria of the original method are not met

- Change to less protective primary packaging materials where there are associated changes in storage conditions and/or shelf life

- Change to elements of the agreed change control strategy as defined in the regulatory agreement

- Establishment of a regulatory agreement where none was previously submitted and approved with the marketing authorisation

- Change in the qualitative formulation of a finished product

- Replacement or addition of a manufacturing site for part or all of the manufacturing process for the active substance (post introduction of the active substance starting material)

- Replacement or addition of a manufacturing site for part or all of the manufacturing process for the finished product, where the site requires verification of GMP status

Specific Type II changes for biological medicinal products

- Change in manufacturer and/or supplier of the active substance

- Replacement or alteration to the cell bank system when this is not in conformity with the Marketing Authorisation dossier. ~~where not pre-agreed through a comparability protocol in the marketing authorisation~~

- ~~Introduction or replacement of a new active substance stating material~~

- Introduction or replacement of an excipient of biological origin or an adjuvant (in vaccines)

- Change in biological analytical test procedure or specification of an active substance or finished product

- Change in batch size of active substance or finished product, involving more than a 10 fold increase or decrease

- Significant change in manufacturing process (active ingredient or finished product)

Regulatory Changes

Generally, most MAH initiated changes to the product information should be handled through a major variation procedure with a 60 days review timeline.

The following types of changes are proposed to follow an extended 90 day or reduced 30 day timeframe:

- Changes to, or addition, of therapeutic indications, adding a new strength, a new pharmaceutical form or a new route of administration alone or as a consequence of a new indication.

  Proposed review timelines: 90 days instead of the extension application required in the current system.

- Changes made at the request of competent authorities (e.g. product information changes following the assessment of a PSUR or renewal application; implementation of class labelling statements from new or revised core SPCs or Article 31 referral procedures), where the MAH does not comply fully with the request and/or submits further data.

  Proposed review timelines: 30 days.

- Changes to product information following an Urgent Safety Restriction

  Proposed review timelines: 30 days.

- Changes to the safety-related information in the SPC (sections 4.3-4.9), initiated by the MAH

  Proposed review timelines: 30 days.

Appendix 6

Bundesverband der Arzneimittel-Hersteller e.V.
B.A.H

Anmerkungen des BAH

zum Consultation Paper der Europäischen Kommission

vom 20.10.2006

"Better regulation of pharmaceuticals: Towards a simpler, clearer and more flexible framework on variations"

Vorbemerkung

Der BAH begrüßt das Vorhaben der Europäischen Kommission, das Variations-System zu überarbeiten und dabei die Erfahrungen der Behörden und der Antragsteller seit dem Jahr 1995 zu berücksichtigen. Das bisherige System hat sich als insgesamt aufwendig und in weiten Teilen bürokratisch, unflexibel und schwerfällig erwiesen, was dazu geführt hat, dass sowohl Behörden als auch Antragsteller unverhältnismäßig belastet wurden bzw. werden. Der BAH sieht den entscheidenden Grund dafür im Grundkonzept des derzeitigen Variations-Systems. Es hat sich als schwerfällig und unflexibel erwiesen, und Verbesserungen sollten konsequenterweise auf dieser Ebene ansetzen.

Die Europäische Kommission hat in ihrem Consultation Papier vom Oktober 2006 die Verbesserungsansätze zusammengefasst, die derzeit diskutiert werden. Obwohl viele von ihnen sinnvoll und begründet scheinen, werden sie doch nicht zu einer entscheidenden Verbesserung der derzeitigen Situation führen. Aus Sicht des BAH wird es nicht ausreichen, oberflächliche Korrekturen wie die derzeit angedachten vorzunehmen, ohne das Prinzip des Variations-Systems grundsätzlich zu hinterfragen. Der BAH unterstützt die Bestrebungen, das Änderungssystem einfacher, klarer und flexibler zu gestalten, hält dieses Ziel aber nur für erreichbar, wenn die Grundzüge des Verfahrens in die Umgestaltung einbezogen werden.

Das deutsche Änderungssystem als Modell für Europa

Das Änderungssystem gemäß § 29 AMG stellt ein klares, unbürokratisches und „schlankes" System dar. Damit hebt es sich positiv vom derzeitigen Variations-System und von vielen anderen nationalen Änderungssystemen ab. Es zeichnet sich

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gegenüber dem europäischen Variationssystem insbesondere dadurch aus, dass

- anstelle der geringfügigen Änderungen die größeren Änderungen definiert und abschließend gelistet werden,
- einfache Änderungen in einer „tell and do procedure" abgewickelt werden, größere Änderungen über eine „tell, wait and do procedure".

Bisher sind keine Defizite im Hinblick auf die Arzneimittelsicherheit bekannt geworden. Der BAH hält das deutsche System insgesamt für zukunftstauglich und für ein geeignetes Modell für ein europäisches Änderungssystem.

Typ 1B-Verfahren „by default"

Um zukünftig zu vermeiden, dass auch unproblematische Änderungen im Rahmen eines Typ II-Änderungsverfahrens abgewickelt werden, wird gemäß Consultation Paper vorgeschlagen, diese Fälle zukünftig grundsätzlich als Typ IB-Änderungen einzustufen; die zuständige Behörde soll ermächtigt werden, in begründeten Fällen die Umstufung in eine Typ II-Änderung vorzunehmen. Der BAH sieht in einer solchen Lösung keinen Fortschritt. Sie trägt zwar der grundsätzlichen Kritik Rechnung, dass nicht alle Änderungen, die nicht als Typ I-Änderungen eingestuft sind, automatisch ein umfangreiches Genehmigungsverfahren erfordern. Eine solche Regelung würde aber dazu führen, dass letzten Endes in jedem Einzelfall entschieden wird, ob es sich tatsächlich um eine Typ IB-Änderung oder doch eher um eine Änderung vom Typ II handelt. Die derzeit zwar unbefriedigenden, aber zumindest eindeutigen Kriterien, nach denen der jeweilige Änderungstyp bestimmbar ist, würden von einer Regelung abgelöst, die die Handhabung des bestehenden Systems nicht vereinfacht, sondern weitere Unsicherheiten bringt und insgesamt das Verfahren zusätzlich kompliziert. Für den Antragsteller muss auch zukünftig anhand eindeutiger Kriterien ersichtlich sein, welchem Änderungstyp die von ihm angestrebten Modifizierungen seiner Zulassungen zuzuordnen sind. Die angedachten Veränderungen stehen dem Bemühen um eine klare und rechtssichere Regelung entgegen und sind aus diesem Grund abzulehnen.

Bereits am Beispiel der Überlegungen, die nicht gelisteten Änderungen zukünftig als Typ IB-Änderungen anstelle von derzeit Typ II-Änderungen einzustufen, wird deutlich, dass die Imbalancen des bestehenden Systems grundsätzlich anzugehen und nicht dadurch zu beheben sind, dass die unerwünschten Auswirkungen davon abgeschwächt werden.

Ausweitung des europäischen Variations-Systems auf eigenständige nationale Zulassungen

Eine Harmonisierung von Verfahren ist grundsätzlich ein erstrebenswertes Ziel, wenn dies der Vereinfachung und der Entlastung der damit befassten Personen bzw. Institutionen dient. Von verschiedenen Seiten wurde angeregt, den Geltungsbereich des zukünftigen Variations-Systems auch auf eigenständige nationale Zulassungen auszuweiten. Im Hinblick auf Zulassungen, die nach dem deutschen Arzneimittel-

gesetz zugelassen worden sind, wäre eine solche Vereinheitlichung nur dann attraktiv, wenn ein europäisches Änderungssystem geschaffen wird, das zumindest ebenso unbürokratisch und anwenderfreundlich gestaltet ist wie dasjenige nach dem deutschen Arzneimittelrecht. Anderenfalls würden gerade diejenigen Zulassungsinhaber, die überwiegend oder ausschließlich auf dem deutschen Arzneimittelmarkt vertreten sind, in nicht vertretbarem Maß benachteiligt.

Dass die Änderungsverfahren, die eigenständige nationale Zulassungen betreffen, nach wie vor erhebliche Bedeutung haben, wird durch folgende Zahlen belegt:

Im Jahr 2004 gingen rund 37.000 Änderungsanträge bzw. -anzeigen beim BfArM ein. Davon stellten die Änderungen nach § 29 AMG mit 63 % oder ca. 23.000 Verfahren den größten Anteil dar. Die Zahl der Änderungsverfahren für Zulassungen aus dem gegenseitigen Anerkennungsverfahren belief sich auf ca. 10.000, d. h. 27 %.

Für international agierende Unternehmen könnten europaweit harmonisierte Änderungssysteme interessant sein. Um jedoch zu erreichen, dass gleiche Zulassungen, unabhängig von ihrem Zulassungsstatus, nach dem gleichen Verfahren und mit dem gleichen Ergebnis geändert werden können, ist es nicht erforderlich, den Geltungsbereich der Variations-Verordnungen auszuweiten. Vielmehr besteht bereits jetzt die Möglichkeit, über ein Artikel 30-Verfahren zu harmonisierten SPCs zu kommen und die Vorteile einer Harmonisierung zu nutzen.

Die Abwicklung von Änderungen bestehender Zulassungen und die Harmonisierung von Zulassungen sind voneinander unabhängige und deshalb zu trennende Bereiche. Eine Vermischung der beiden Aspekte ist daher abzulehnen. Darüber hinaus ist es nicht akzeptabel, dass auf diese Weise die Eigenständigkeit der nationalen Zulassungen untergraben würde.

"Design space"

Die ICH-Guideline Q8 verfolgt den Ansatz, Zulassungen mit einem "design space" im Bereich pharmazeutische Entwicklung zu versehen, d. h. bei einzelnen Parametern eine definierte Spanne anstelle eines fixen Wertes anzugeben. Dies hätte den Vorteil, dass bei einer Modifizierung des Arzneimittels innerhalb dieser Spanne auf ein Änderungsverfahren verzichtet werden kann.

Eine der Überlegungen zur Vereinfachung des Variations-Systems, die aus dem Consultation Paper hervorgeht, greift die Idee eines "design space" auf, d. h. Verzicht auf Änderungsanzeigen bzw. -verfahren in den oben genannten Fällen und die Möglichkeit der Einrichtung eines "design space" per Änderungsverfahren. Der BAH befürwortet diesen Ansatz ausdrücklich. Er erhöht die Flexibilität des derzeitigen Systems und vermeidet zahlreiche Änderungsverfahren, ohne dabei die Sicherheit der Arzneimittel zu gefährden.

Fazit

Der BAH sieht in der anstehenden Revision des Variations-Verfahrens die Chance, elementare Schwächen des Systems auszuräumen. Aus Sicht des Verbands kann das formulierte Ziel, nämlich ein vereinfachtes, klares und flexibleres Regelwerk für die Änderung von Zulassungen zu schaffen, nur erreicht werden, wenn nicht nur einzelne Schwachstellen, sondern in erster Linie die Prinzipien des derzeitigen Verfahrens auf den Prüfstand gebracht und einer grundsätzlichen Prüfung unterzogen werden. Das deutsche Änderungssystem zeichnet sich durch einfache, klare und ausreichend flexible Regelungen aus, es könnte daher als Modell für ein europäisches Variations-System dienen.

Die anstehende Revision des Variations-Systems dient dazu, vorhandene Schwächen auszuräumen und den Verfahrensablauf zu optimieren. Um allein dieses Ziel zu erreichen, sind erhebliche Anstrengungen erforderlich. Der BAH plädiert dafür, die Aktivitäten auf dieses prioritäre Ziel zu konzentrieren und nicht weitere sachfremde Überlegungen anzuschließen. So sind weder das aktuelle Revisionsverfahren noch die Variations-Verordnung als solche dazu geeignet, Zulassungen mit unterschiedlichem Status zu harmonisieren, indem die eigenständigen nationalen Zulassungen in den Geltungsbereich der Verordnungen einbezogen werden.

22.01.2007 / Sch

Appendix 7

AESGP
Association Européenne des Spécialités Pharmaceutiques Grand Public
Association of the European Self-Medication Industry
Europäischer Verband der Arzneimittel-Hersteller

AESGP Response to the European Commission's Consultation Paper (of 20 October 2006) on Better Regulation of Pharmaceuticals Towards a simpler, clearer and more flexible framework on variations

AESGP represents the manufacturers of non-prescription medicines in Europe.

The European Commission's initiative to amend the current legal provisions on variations can considerably improve the competitiveness of medicines manufacturers in Europe without compromising public health. It is a major contribution to the 'Better Regulation' initiative of the European Commission and fully in line with the so-called Lisbon strategy. It is also consistent with some national initiatives aiming to simplify minor product changes in particular for non-prescription medicines.

AESGP would like to focus its comments on some key issues addressed in the consultation paper. We would like to refrain from commenting on further details as we believe that, at this point in time, it is important to get the overall orientation right.

Application to national authorisations

Most non-prescription medicines were approved at national level, and this route continues to play an important role in our sector. Indeed, there are considerable differences in the way variations are handled by the EU Member States, obliging our member companies to invest considerable resources.

Before considering a harmonisation of the national requirements in relation to variations, it is critical to get the principles right first. From an AESGP perspective, a number of countries in the European Union have established an approach which defines major (Type II) variations only. Variations not covered by the listing/categorising of major variations are automatically considered as minor (Type I) variations. Some countries, such as for example Germany and Austria, have been using this system satisfactorily for nearly 30 years, both from the point of view of the regulatory authorities and from that of pharmaceutical companies. No public health concerns have been reported. The system is efficient and simple and could provide a model for the revision of the Variation Regulations.

The United Kingdom more recently started the development of a more pragmatic system for handling variations of non-prescription medicines in the framework of BROMI (Better Regulation for Over the counter Medicines Initiative), which is in line with the above-mentioned systems.

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From an AESGP point of view, it is a prerequisite to agree on such an approach before discussing details of a harmonised system for variations in the centralised, mutual recognition/decentralised and national procedures.

From a "Tell and Do" to a "Do and Tell" Procedure

Currently, Type IA variations in the centralised and mutual recognition/decentralised procedures require the marketing authorisation holder to notify the competent authority. The latter then acknowledges receipt of the notification within 14 days and updates the relevant authorisation. Changes can be implemented only after acknowledgement of the notification is received ("Tell and Do" procedure). This system in practice often does not work well, and the Commission's proposal to replace such a system by a simple 'Do and Tell' procedure is therefore greatly appreciated. This will allow implementation of the change first and notification of the concerned competent authorities afterwards.

However, such a system should be applicable to all variations not necessitating pre-assessment given that it has already successfully been implemented in some Member States.
AESGP supports the suggestion to group the necessary notifications in the form of an annual report. Variations which for administrative purposes need to be notified to the Competent Authorities without delay could be notified via email.

ICH Q8-Q9-Q10

The large majority of non-prescription medicines are well-known medicinal products which have been on the market for a long time. While AESGP in principle appreciates the introduction of the 'design space concept', this is for the moment not viewed as particularly relevant to our sector.
Therefore, we would appreciate that the use of the ICH guidelines remains fully optional for the applicant.

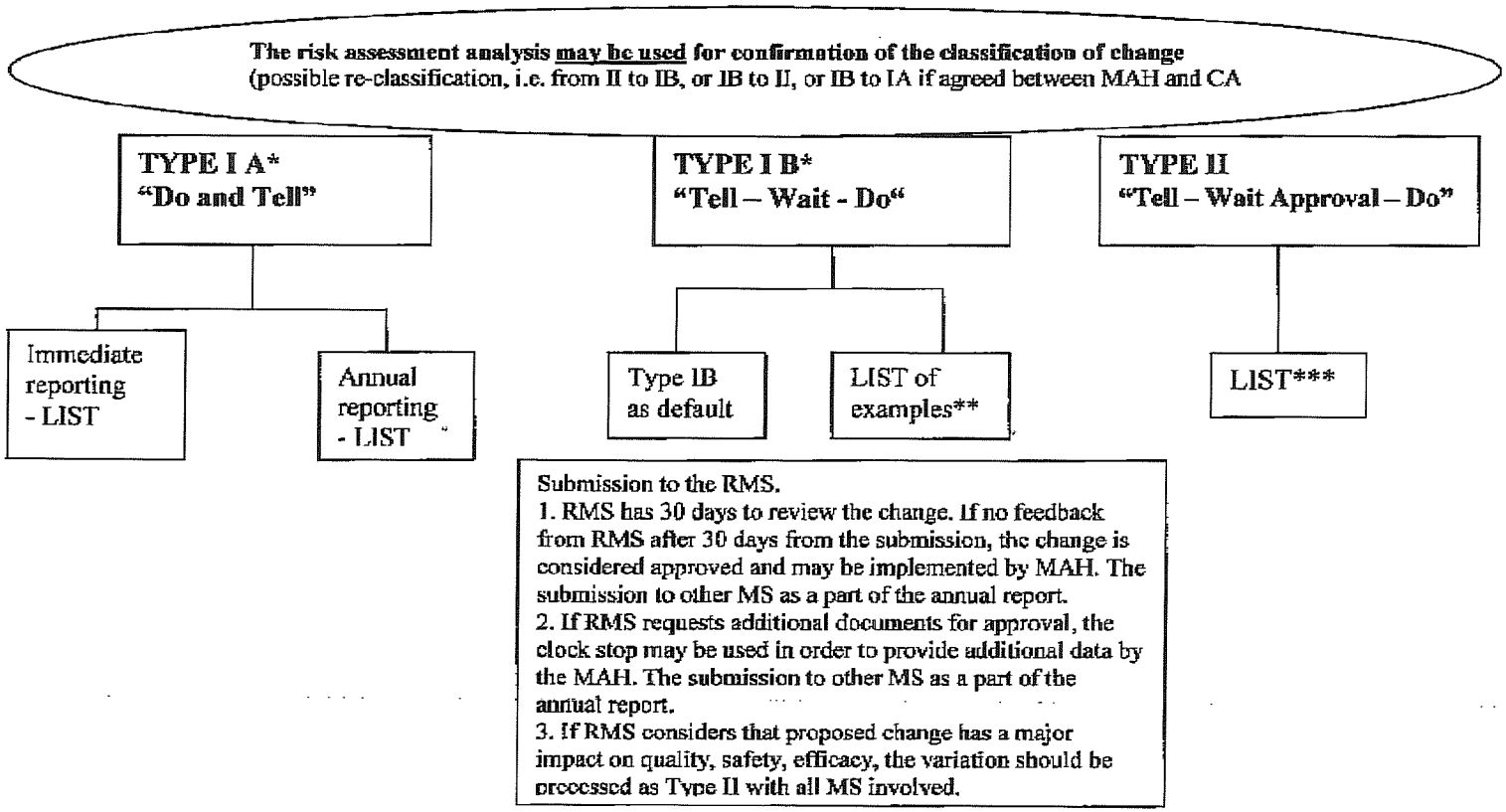
Single Evaluation of common changes

We support the notion of a work sharing between national competent authorities for the assessment of a major change affecting several marketing authorisations. We would however suggest that this procedure be optional for marketing authorisation holder but that competent authorities should be prepared to accept such an approach.

In conclusion, we would recommend that simplified systems which have demonstrated over the years their efficiency and contribution to the protection of public health should serve as a model for the revision of the Variations' Regulations. Once this step is achieved, harmonisation can take place across all procedures.

Brussels, 19 December 2006

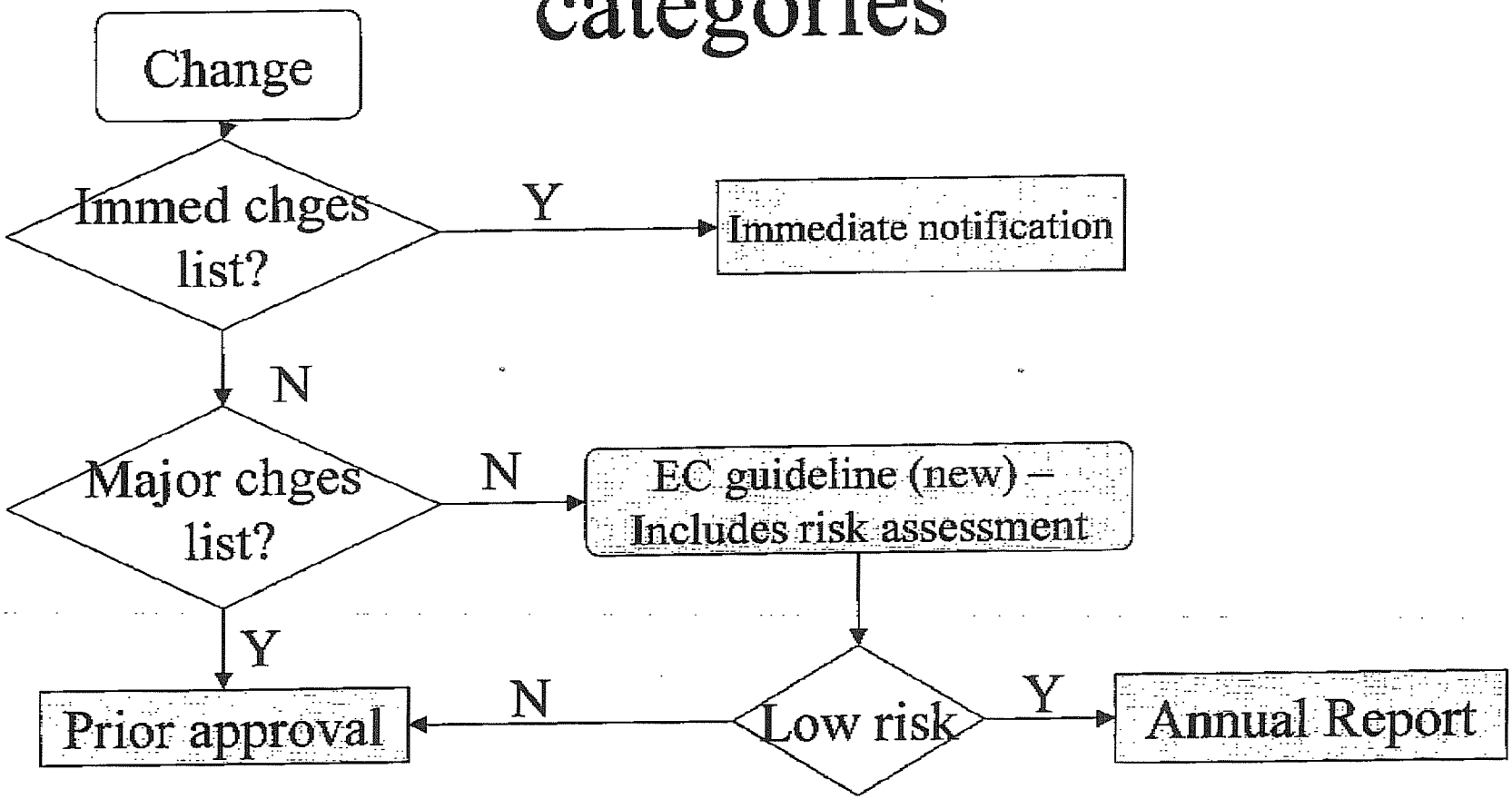
EGA Proposal for Variations system



* Certain variations currently classified as IB should be changed to IA
** Certain categories of the current IB (not planned to be removed to IA), but not so significant to be treated as type II
*** Current list of category II should be revised, as certain variations currently classified as II should be changed to IB

The same principle should apply to all types of medicinal products (including biologicals as well)

EFPIA/EBE/EVM proposal on categories



Appropriateness of company decisions would be through inspections and/or limited checks of annual reports

Appendix 8

APIC Active Pharmaceutical Ingredients Committee

Position Paper
on
Variation Regulations

APIC Position on Change Authorisation Procedures
EC Regulations nr 1084/2003 and nr 1085/2003
relating to the manufacture of APIs

CONTENTS

1. EXECUTIVE SUMMARY

1.1 Introduction

The Active Pharmaceutical Ingredients Committee (APIC) welcomes the opportunity offered by the authorities to involve the industry in the update of the European Variation Regulations. APIC recognises the importance of this initiative as the current Variation system is no longer adequate.

Change is vital in order to enable innovation and continual improvement of pharmaceutical products and manufacturing processes. The manufacture of APIs is no exception to this. Change is the most important tool for industry to create sustainable growth and to remain competitive in continuously changing circumstances. Drivers for change include:

- Improvement of the quality of the API and hence the Medicinal Product
- Introduction of new and/or improved technologies
- Further upgrading of the chemical industry in optimal harmony with the environment
- Use of new scientific knowledge
- Rapidly emerging API manufacturers in the developing world

For many API manufacturers, making a change under the current system is virtually impossible. The 37-page document prepared in February 2005 entitled "Additional Rationale and Examples for ICH Q10 – Quality Systems for Continuous Improvement" illustrates the alarming extent to which changes are being blocked because of the current Regulations (see Appendix).

The current system implies that the authorities have full control over the approval and implementation of changes. However, the lack of workability of this system is in fact resulting in widespread non-compliance in many areas (see Appendix). Therefore, APIC, along with other industry parties, wishes to collaborate with the authorities to create an efficient and effective system for the future that is beneficial to the patient, the authorities and the API industry.

1.2 Key Expectations

It is imperative that, instead of blocking progress, the revised Variation Regulations allow industry to improve while continuing to protect patient safety. APIC's main expectations are as follows:

- The new system should put the responsibility for managing change into the hands of industry on the basis of demonstrated knowledge of process and product. In doing so, significant harmonisation with the rapid developments taking place regarding the "Pharmaceutical GMP for the 21st Century – a Risk-Based Approach" Program will be achieved.

- The new system should be supported by a verification system through inspections by the authorities.

- The new system should allow the optional replacement of existing regulatory information in the dossier with an evaluation in accordance with ICH Q8, Q9 and Q10 when supported by a Regulatory Agreement between manufacturer(s) and authorities.

These proposals are described in more detail in section 2.

1.3 Suggestions for Interim Improvements

APIC appreciates that such a system will take time and effort to establish. APIC would therefore like to put forward suggestions as to how the current system could be improved in the interim. Please note that these proposals represent APIC's "minimum option" and are seen as a temporary fix to allow time to implement the preferred system outlined above.

- Exclusion of the majority of API changes from the requirement to submit by the MA holder. Changes involving the API should be submitted by the API manufacturer. Only changes with a significant potential to adversely impact the safety / efficacy of the Medicinal Product should require a supplementary submission by the MA holder.

- For APIs, a distinction should be made between changes impacting on the API itself and changes impacting on intermediates / starting materials / raw materials.

- Replacement of the current Type I Variations list with a limited list of major Type II Variations. In addition, it should be possible to incorporate multiple changes within one submission.

- Establishment of a fast track approval system for changes with clear quality, environmental or safety benefits.

- Creation of a single EU (or ideally World Wide…) change authorisation system that is accepted by the whole of the EU to ensure that a change is assessed in the same way by all EU authorities.

- In the absence of a single system, establishment of common, enforceable approval times between the different authorisation systems (National, MRP, Decentralised, Centralised).

- Introduction of an annual payment per MAA instead of a payment per Variation to avoid the blocking of progress in the API industry by the MA holder.

These proposals are described in more detail in section 3.

2. THE PREFERRED SYSTEM

The responsibility for managing change should be put into the hands of industry, supported by a measuring system to verify reliability through inspections.

- Variations currently constitute a huge burden for industry in terms of time, effort, cost and workability. For this reason, changes, in particular those proposed by the dedicated API industry, are often blocked by MA holders (see Appendix for examples).
  For the MA holders, the filing of Variations in different countries, for different formulations, via different procedures with different approval times, means that full approval for implementation may only be obtained after several or even many years. Under these difficult circumstances, it's easy to understand why MA holders are often reluctant to support changes proposed by their API suppliers.

The dedicated API industry is closely related to and interacts intensively with the Medicinal Product industry (MA holders). APIC strongly recommends the adoption of a regulatory approach that will put much of the responsibility for change implementation into the hands of these industries. APIC's view is that co-operation at the interface between API manufacturer and API user should be the primary means of handling and managing change.

APIC also considers it necessary to move away from developing lists of minor/major changes and instead to move towards an assessment system based on performance (a "trust and verify" system). This system should allow companies to demonstrate their knowledge of the product and the manufacturing process, and the good performance of their established cGMP systems, including change management, in line with the principles laid down in ICH Q8, Q9 and Q10. This requires the upgrading of the current inspection system to incorporate these aspects as key elements and to develop a concrete performance scale. Take, for example, changes in suppliers of raw materials and starting materials. These changes should be covered solely by the GMP system of the company. Verification by the authorities should focus on performance assessment and inspection of that company.

The risk-based characteristics of such an approach would fit perfectly within the new "21st Century paradigm".

- APIC fully supports the intention of the EU Commission to build the new Variations system upon the principles of ICH Q8, Q9 and Q10. The inclusion of already marketed products (in addition to New Chemical Entities) within the scope of a system based on these guidelines should be an option. It should, for example, be possible to use either retrospective data, or to generate new data, to update the product knowledge information in existing dossiers. This replacement of existing regulatory information with an evaluation in accordance with ICH Q8, Q9 and Q10 could be supported by a Regulatory Agreement between manufacturer(s) and authorities. For API manufacturers, it is envisaged that the Regulatory Agreement would define the components of the submission that would be changed only through a variation. It could also be extended to summarise the company's proposals for management of post-approval changes.

3. MINIMUM OPTION

Principles to be adopted in order to "fix" the current, malfunctioning system.

Should the EU conclude that the adoption of a system as outlined above would not (yet) be feasible – a conclusion that APIC would regret – then it is APIC's view that at least the following principles should be adopted in order to move as quickly as possible from an inefficient system to a system that provides significant relief for both the authorities and the industry in at least some of the situations involving changes to API manufacture.

- A practical option to resolve the blocking of progress, that would still provide for extensive authority oversight, would be to create a system for approval of APIs that includes its own approval procedures for changes to processes, specifications, analytical methods etc. Under this system, it is envisaged that the majority of changes would be submitted by the API manufacturer and would not require a supplementary submission by the MA holder. This would especially apply to changes that do not have a significant potential to adversely impact the safety / efficacy of the Medicinal Product.

In order for such a system to function properly, a strong relationship / partnership between the API manufacturer and the MA holder is paramount in order to assess the impact of the API change on the Medicinal Product. This should be enforced through inspection by the authorities.

A system similar to this has, to a certain extent, already been in place in the EU and has proved to work well. We refer to the CEP system as it was operated before the introduction of the revised Variation Regulations in 2003. Under this system, minor changes did not result in a variation to the MA which meant that the system was effectively functioning as an API-dedicated approval system. It is APIC's view that changes to CEPs are amongst the most plausible examples of changes that should not require a supplementary submission by the MA holder.

Note

Until 1997, a successful, dedicated API approval system was also in place in the USA – the so-called "Abbreviated Antibiotics Drug Applications for bulk" system ("bulk AADAs"). Its deletion in 1997 was an unintended "side-effect" of the adoption of the FDA Modernization Act that removed the special status of antibiotic APIs versus other APIs.

- For APIs, a distinction should be made between changes impacting on the API itself and changes impacting on intermediates / starting materials / raw materials when it can be scientifically demonstrated that such changes have no impact on the quality of the API. In the current EU system, changes concerning raw materials, starting materials and intermediates are often classified in the same categories as similar ones applying to the API itself. It would be reasonable practice to classify such changes into categories that allow for easier and quicker assessment and approval.

- The current list of Type I Variations creates an enormous administrative burden both for the authorities and the industry and may even preclude a scientific assessment of the fundamental nature of a change. For example, currently, if not all the conditions required by the Regulations are fulfilled, the change must be submitted as a Type II Variation, even if a good, scientific reason exists why a particular condition is not valid. Another example would be the submission of changes that are interrelated because they form part of one project. These cannot be included in a single submission but must be submitted as individual Type I Variations. This prevents the presentation of the overall scope of the project to the authorities. In addition, changes not listed as Type I are automatically and often unscientifically classed as Type II.

  To address this, APIC proposes the replacement of the current Type I Variations list with a limited list of major Type II Variations. Also, it should be possible to include interrelated changes within one submission. This will significantly increase the focus on the essence of the change and, importantly, reduce the workload for both industry and the authorities. This will create a situation in which "non-Type II" Variations really will cover all non-major changes and will, of course, include all administrative changes. We propose that non-Type II changes are notified through biennial reporting.

- A fast track approval system for changes with clear quality, environmental or safety benefits should be established in order to promote the implementation of such improvements.

- The various national systems should be replaced by a single EU (or ideally World Wide…) change authorisation system that is accepted by the whole of the EU. This would ensure that a change is assessed in the same way by all EU authorities. Currently, there is a lack of consistency – situations frequently arise in which a variation is classified as Type I by EU Member State X but as Type II by Member State Y.

- In the absence of a single system, the establishment of common and visible approval times between the different authorisation systems (National, MRP, Decentralised, Centralised) would be an important step forward. These approval times should be legally binding.

- Under the current system, due to the high costs involved, MA holders can refuse to co-operate in the submission of API changes, even when the changes concerned have a positive impact on the Medicinal Product. Removing the Variation fees and replacing them with a single annual payment per MAA would remove this barrier.

4. GENERAL CONCLUSION

APIC recommends a change control system that allows the Medicinal Product industry and the API industry to fulfil their responsibility to the patient. It should be GMP-based, supported by a verification system through inspections by the authorities, to guarantee equal performance of all manufacturers. Such a system should focus on the scientific evaluation and risk assessment of the change, reduce the administrative burden for both authorities and industry and ensure fast approval of changes beneficial to the patient, environment and competitiveness of the industry.

5. APPENDIX

Document on the need for revision of the current – often unworkable – Variations Regulations, submitted to the EU authorities in May 2005 by the unified EU pharma-related industry:

"FINAL DRAFT
RATIONALE AND EXA

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.