Best practice of worldwide product variations regarding planning, conduct and implementation

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List of Abbreviations and Acronyms

ACTD	ASEAN Common technical Document
API	Active Pharmaceutical Ingredient
ASEAN	Association of the Southeast Asian Nations
CC	Change Control
CFR	Code of Federal Regulations
CIS	Commonwealth of independent states
CMC	chemistry, manufacturing and control
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
EP	European Pharmacopeia
EU	European Union
FDA	Food and Drug Administration
GCC	Gulf Cooperation Council
GMP	Good Manufacturing Practice
HPLC	High performance Liquid Chromatography
ICH	International Conference of Harmonization
JP	Japanese Pharmacopeia
MA	Marketing Authorization
MAH	Marketing Authorization Holder
NCA	National Competent Authority
NeeS	non-eCTD electronic Submission
PANDRH	Pan American Network for Drug Regulatory Harmonization
RA	Regulatory Affairs
SADC	Southern African Development Community
SmPC	Summary of Product Characteristics
US	United States
USP-NF	United States Pharmacopeia and National Formulary
USR	Urgent safety restriction
WHO	World Health organisation
xEVMPD	Extended EudraVigilance Medicinal Product Dictionary
XML	Extensible Markup Language

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1 Introduction

The pharmaceutical Industry is a highly regulated environment; in most countries, it is forbidden to sell Medicinal products, unless you have obtained a Marketing Authorization (MA) by the respective National Competent Authority (NCA) to do so.

This obligation is laid down in the respective legislations on Medicinal Products, e.g. Directive 2001/83 [1] and Regulation 726/2004 [2] in the European Union (EU), or the Federal Food, Drug, and Cosmetic Act (the Act) [3] and Title 21 of the Code of Federal Regulations (CFR) [4] in the United States (US).

This requirement, however, is not limited to these countries with a high regulative standard, but is also basis for pharmaceutical legislation in countries all over the world.

The application for Marketing Authorization includes (besides the necessary administrative information), a regulatory dossier summarizing the obtained information on the quality, efficacy and safety of the medicinal product, which is then assessed and approved by the NCA. With this approval, the respective product can be marketed in the country in which the approval has been granted.

1.1 Reasons for changes to the registered information

During the life-cycle of the product, changes to the approved dossier might occur for a variety of reasons. All information included in the dossier is considered part of the Marketing Authorization, and therefore most - if not all - changes made to the approved dossier have to be notified to the Regulatory Authority before the change can be implemented.

A few of the most common reasons for changes to the marketing authorization are listed on the next pages.

1. changes introduced for marketing reasons

Many changes to a product are introduced to allow for a better product placement or to gain advantage over the competition in the market. These include for example

- changes to the information in the Summary of Product Characteristics (SmPC) as the basis for better product placement, e.g. elimination of adverse events or warning statements, or inclusion of additional age groups or indications
- elimination of excipients that require a warning statement on the packaging, or are viewed critically in the public, e.g. colouring agents or preservatives
- changes to the layout of the packaging to make it more appealing or to build the overall brand

2. cost related changes

In an environment of cost savings in the health systems of many countries, the price pressure on pharmaceutical products is steadily increasing. This is especially the case for generic products, but also for many originator products.

Cost savings can be achieved by different measures, such as

- change of manufacturing sites to countries with lower production costs for part or all of the manufacturing process,
- changes to make the manufacturing process more effective, e.g. by achieving higher yields, excluding personnel-intensive production steps, or using less expensive starting materials
- change of sources of Active Pharmaceutical Ingredient (API) or starting materials to more cost-effective suppliers, e.g. from countries with lower production costs like India or China

3. changes due to acquisitions/mergers

If two companies merge, or a company is bought by a different company, several changes might result from this, such as

- changes to the name of the manufacturer or Marketing Authorization Holder (MAH) that is part of the merger
- Change of the product name, if the former company's name is part of the product name, or if the old name does not fit the combined portfolio
- change of address, if the company had to be relocated due to the merger,
- change of production site, e.g. insourcing of the production from external contract manufacturing to manufacturing at a site within the new pharmaceutical group

4. changes requested by authorities

Not all changes are initiated by the MAH; some of them also have to be introduced upon request by the authorities. Requested Changes to the agreed documentation after the initial marketing authorization are normally required due to safety or quality concerns.

This includes for example

- introduction of additional warnings, precautions or restrictions to the indication or patient groups listed in the product information to ensure the safety of the patient,
- introduction of additional testing methods for the product, starting materials or active pharmaceutical ingredient due to newly identified risks, e.g. testing for additional impurities or testing for viruses
- introduction of features against falsification of the product on the packaging, e.g. data matrix codes or tamper-proof features

5. changes due to external influences

Some changes are not planned by the MAH, but have to be introduced due to external factors that require action from the pharmaceutical company, such as

- introduction of a different source of materials due to unavailability from the previous source
- closure of production sites due to safety or Good Manufacturing Practice (GMP) related concerns
- changes to the equipment due to malfunctioning of the one currently in use
- alteration of the product information due to safety signals observed in clinical studies or during post-marketing surveillance

6. changes to keep up with the latest scientific developments

The MAH is required to always keep the dossier up to date, and to consider any scientific developments that may help to improve the safety and quality of the product. This can include for example

- improvements in the sensitivity of methods, to lower the detection limit of possible impurities or to get more reliable results on content measurements
- reduction of product and process related impurities by improvements in the process or better purification methods

1.2 Classification of variations

The changes listed in section 1.1. are just a few examples for changes that have to be notified to the regulatory authorities. Not all changes have the same impact when implemented, so they have to be classified according to the possible effect they might have on the authorized product.

There are different classification guidelines in place in different countries, but in most regions, the classification differentiates between minor and major variations or variations of Type I and type II:

Type I variations are classified to have a relatively minor impact on the medicinal product, and the respective procedures therefore are relatively short and require less documentation. They are mostly rather formally assessed for completeness than undergoing a scientific review.

Type II variations are required for changes that might have a significant impact on quality, safety and/or efficacy of the product. They are therefore assessed more thoroughly and consequently have longer approval timelines.

Changes that have such a profound impact on the product that they can no longer be considered just a variation of the existing product, but will lead to a new medicinal Product, e.g. introduction of a different API, a new registration will be required. Most variation guidelines also provide guidance on when a change will lead to a new marketing authorization application.

This division between minor and major changes and the corresponding adapted assessment follows a risk-based approach – depending on the risk the change poses to the product and as a consequence to the patient, a more or less detailed assessment is required by the authority.

1.2.1 Variation Guideline EU

The variation classification in the EU is regulated in Commission Regulation (EC) No 1234/2008, as amended [4]. The respective conditions, timelines and procedures are further elaborated in the corresponding variation guideline [6].

The regulation differentiates between the following variation classes:

Type IA “do and tell”

This variation type is foreseen for minor changes, mostly of administrative nature, that will have no or little impact the quality, safety or efficacy of the product. They can be directly implemented and have to be notified to the authorities within a year after the change has been made. A subtype is the IA_{IN} variation, which in deviation to this timeline has to be notified immediately after implementation. These changes do not require a full assessment; the procedure only comprises a check for completeness with a validation period of 30 days.

Type II “tell and wait –prior approval”

Changes that might have a significant impact on the quality, safety or efficacy of the product need to be requested via type II variation.

This type of variation requires full assessment by the authorities, and follows a defined timetable including a possible clock-stop in which the applicant is requested to address deficiencies identified by the authority. The normal assessment time (without clock-stop) is 60 days for the RMS, with an overall procedure timeline of 90 days. It might be extended to 90 days (overall timeline 120 days) for more complex changes as defined in annex 5 of the variation regulation (extension of indication), or if several variations have been submitted and are to be assessed together (so called “grouping” according to Article 13d(2)(c) of the Variations Regulation).

If the variation application is provided to address a safety issue, there is also the possibility to shorten the timelines to 30 days, in order to ensure the safety relevant information is implemented as soon as possible.

If a very serious safety issue has been identified (by either the MAH or the authority), the variation regulation also foresees the possibility to use the procedure of an Urgent safety restriction (USR). This procedure, as laid down in the respective SOP [6] allows for a review period for the change of only 24h – if no objections arise by the respective authorities, the change may be implemented within a timeframe agreed upfront with the authority. Afterwards, the change has to be submitted via a "normal" variation procedure within 15 days. This allows for a quick reaction by the MAH to mitigate the identified risks to the patient.

Extension application

Changes as defined in Annex 1 of the Variation Regulation lead to very significant alteration of the product and therefore will be handled as extensions to the original marketing application. The procedure for the assessment for these extension applications follows the same rules as for an original marketing authorization application, both regarding documentation and timelines.

Type IB "tell, wait and do"

Type IB variations are defined by exclusion criteria: Any change not defined as Type IA, Type II or extension application in the variation regulation is automatically classified as Type IB variation (IB by default). These include minor changes, for which, however, an impact on safety, quality or efficacy of the product cannot be completely excluded.

In order to facilitate assessment, however, and to give guidance on the required documentation and conditions for different changes, the variation guideline also includes several changes classified as Type IB variations, based on their risk potential.

Type IB variations require an assessment by the authorities, the review period (following a formal validation period of 7 days) is 30 days. If no request for further information or other communication by the authority is received within this period, the change can be implemented by the MAH.

There are also changes that do not fall under the scope of the variation regulation:

For changes to the Product information that do not affect the SmPC, a separate notification procedure is in place according to Article 61(3) of Directive 2001/83/EC [1].

Some changes are not regulated on a European level, and may therefore be implemented via national procedures, e.g. the Change of MAH.

1.2.2 Variation guideline US

The variation classification in the US, which is laid down in section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) [3] and § 314.70 of the Code of Federal Regulations [8], also follows a clear risk-based approach, and has a similar way of classification to the EU classification – here the changes are divided into minor, moderate and major changes. Guidance on the classification of variations is given in the respective guideline by the Food and Drug Administration (FDA) [9].

Major changes or "*Prior Approval Supplements"*

These changes are the equivalent to the Type II variations in the EU. Major changes might have a significant impact on the product and therefore need approval by the authorities prior to implementation.

As for the original marketing authorization application, there are no fixed timelines for the procedure, but the assessment will vary depending on the change submitted.

Moderate changes or "*Supplements - Changes Being Effected*"

There are two types of Moderate Changes – "Supplements - Changes Being Effected in 30 Days" and "Supplements - Changes Being Effected". These changes are the equivalent of the Type IB variation and the Type IA IN variations in Europe. They both have relatively small impact on the product, and therefore do not need in-depth assessment by the authority.

The changes being effected in 30 days have to be notified to the authority 30 days before planned implementation, the changes being effected can be implemented directly after the notification h been received by the authority.

Minor Changes, ”*annual report*”

Minor changes are thought to have a negligible effect on the product, and therefore can be submitted in an annual report, which summarizes all minor changes that have occurred during the past year. This is the equivalent to the Type IA changes in Europe, which also need to be reported within a year after implementation.

1.2.3 Variation Guidelines worldwide

There are numerous other variation guidelines available for countries all over the world. Many of them are country specific, but there have also been initiatives to harmonize the regulation of drug registration procedures in different regions.

Examples for such harmonized co-operations are the following Organizations:

- Association of the Southeast Asian Nations (ASEAN)
- Gulf Cooperation Council (GCC)
- Pan American Network for Drug Regulatory Harmonization (PANDRH)
- Southern African Development Community (SADC)
- World Health organisation (WHO)

PANDRH and SADC only have harmonized guidelines on the Drug Registration Process [10,11], and leave the regulation of variations to the member states, whereas ASEAN and GCC both have issued harmonized variation guidelines [12,13].

The ASEAN Guideline has its own naming convention, classifying changes as Major Variation (MaV), Minor Variation – Notification (MiV-N), and Minor Variation - Prior Approval (MiV-PA). The classification is similar to the one in the EU regarding classification and documentation to be provided; timelines and detailed procedures are not regulated within the guideline, but are subject to country specific requirements. Biologics are not covered by this guideline.

The GGC guideline directly adopted the variation system laid down in the European Variation Regulation [5], including the division into Type IA, IB and Type II variations, as well as documentation to be provided and conditions to be fulfilled. The timelines, however have been adapted – Type IA variations need to be submitted within 60 days after implementation (instead of 1 year), the review period for type IB variations is 120 instead of 30 days, and for type II variations, no approval timelines are given in the GCC guideline.

The WHO also has issued guidelines on the handling and classification of variations, which can serve as a basis to be adopted by countries that have not yet developed an own variation classification system [14]. It also follows similr classification rules as the EU.

The guidelines issued by the NCA of single countries can often be found on the authorities' website.

Some of the countries have just adapted the EU variation classification in their own legislation, like for example the variation classification in Switzerland [15], which is closely following the guidance in the EU, and is also revised every time the classification in the EU is updated.

Others follow the same basic classification rules, but have some differences in how the different change are classified, e.g. the respective health directive in Peru [16]. In this guidance, changes are classified into only two categories: minor or major changes, subdivided into Administrative Changes, Quality changes, Changes in safety, efficiency and risk management plan, and Changes of Plasma Master Files and vaccine antigens. It also provides a sell-off period for minor changes of one year.

Although often very similar in the classification, there are also many differences in the requirements for implementing changes in different countries, which need to be considered when planning a worldwide variation roll-out.

2 Realizing Worldwide product variations

If a product is marketed worldwide, introducing any change to this product may have a major impact on the product registrations in the respective countries and requires careful planning and coordination before, during and after implementation of this change.

Regulatory Affairs (RA) plays a major role in coordinating the internal and external stakeholders to make sure the implementation of the change is done in compliance with the registered information.

There are differences in the way big and small companies will deal with such a project, but there are also a lot of similarities, as the challenges faced are mostly universal independent of the size of the company.

Big companies will have affiliates in the different countries, which will normally be responsible for the local submissions, whereas smaller companies will more likely rely on a network of partners they are working with. These might range from partners that are equipped with the relevant staff to deal with all aspects of the variation locally, to partners that only are responsible for local distribution of the product.

Therefore, the responsibilities in rolling out a variation might be distributed differently between central and local functions, depending not only on the size of the company, but also on the contractual situation between the Headquarter and the local partners.

The points to be considered, however, are mostly the same for all and can be universally applied independently of the contractual model, only the way of execution will differ from company to company.

2.1 Planning phase

For the planning phase, it is important to first evaluate all parameters of the change in order to ensure the most efficient execution of the variation roll-out.

Lack of planning can result in problems later on during roll-out and implementation, whereas a good planning can reduce the overall workload by avoiding unnecessary duplicate work and can help streamline the overall process.

2.1.1 Determination of the scope of the variation

The first task in planning the worldwide submission of a change is evaluating the exact nature and extent of the project to ensure all aspects have been covered and the required resources can be allocated.

To achieve this, it is necessary to have a closer look at the proposed changes and to answer the following questions:

What exactly needs to be changed?

This sounds like a trivial question, but to evaluate the impact of the change on marketing authorizations in different countries, it is necessary to describe the change as precisely as possible. The better the change has been defined in detail, the easier its regulatory implications can be assessed.

In addition to that, sometimes one change will also trigger other consequential changes, which need to be submitted as well, e.g. a change of manufacturing site leading to slight changes in the manufacturing process or in the used testing methods. These consequential changes might not be apparent right away, but need to be considered in the variation planning. A thorough assessment therefore is needed to make sure all aspects of the proposed change have been accounted for.

Which documentation is affected?

For further planning, it needs to be evaluated which of the internal documents will be affected by the change. All documentation that has been submitted to the authorities and that need to be altered as a consequence of the proposed change is subject to variations to be submitted.

As the submitted documentation will differ from country to country, it is important not only to consider the internal core documentation for the evaluation, but also the additional documentation that might have been submitted to the authorities during the life cycle of the product, like statements on the quality of the product, site master files etc..

Where should the change be submitted?

To evaluate the scope of the variations, it is also important to determine which countries will be affected by the change – is the change to be introduced for all of them, only certain countries or certain regions?

Some changes will need to be implemented for all countries the product is registered in, others might not affect all registrations, or it might be possible to choose the countries it should be implemented.

The more countries are affected, the more complex the planning of the change will become, as requirements will sometimes differ significantly, especially across regions, therefore a more careful planning is needed if a broader scope of countries is affected.

What additional regulatory submissions can/must be considered?

In addition to the change planned, other regulatory activities might be on-going or planned in some countries, such as other variations or renewals. These might be combined with the changes to be submitted, or can alter the planning of the variations.

Some countries do not allow for submission during an on-going regulatory procedure, so it is important to assess any running or upcoming submissions in order to avoid delays in the roll-out. Some changes might also be combined – for example different changes to the manufacturing process, the product specification or the Product Information might be combined in one submission, so that the respective documents only have to be updated once for this country.

In any case, the regulatory status should be assessed upfront in order to avoid interference with the planned variation submission.

Should only the planned change be submitted, or additional changes to update the registration to the most recent status be included?

Updating the registrations over the world opens opportunities to not only include the planned changes, but to get the dossier up to the most recent status.

This is highly desirable from the point of view of the headquarter, as different registration status lead to higher complexity and therefore higher workload for the Regulatory Affairs and Quality Assurance department regarding tracking, but also for the technical departments regarding testing and manufacturing.

Adding several additional changes per country, however, contributes significantly to the complexity of the variation planning, and might severely delay the implementation of the change.

It is therefore important to decide whether additional changes can be submitted together with the planned variations, or if it is more advisable to restrict the submissions to the original scope.

If only a few countries are affected, it might be a good opportunity to align the registration status in all of them, but if a complex change needs to be submitted in many countries, it will either make the planned submission unmanageable, if it is submitted within a reasonable timeframe, or it will stretch the submission roll-out over a long time period, thus making implementation very difficult.

If for example the manufacturing process for the product needs to be adapted, and it is not feasible to run the old and the new process in parallel for a very long time, it is more important to get the change approved as soon as possible, rather than have a harmonized dossier status for all countries. In this case, it is better to restrict the roll-out to the planned change, and disregard all other differences.

2.1.2 Evaluation of the current status

Knowing the current status of the MA in a given country is the basis for any future changes. In order to change an MA, it is essential to know the content of the dossier as a starting point for filing future changes.

The current status of products which have been submitted recently is often easy to evaluate, but the longer the product has been on the market, and the more MAs have been obtained, the harder it will be to get a clear picture of the whole regulatory status.

Most likely, the dossiers have diverted over time, and the current status is something that needs to be evaluated and confirmed country by country.

In some countries, the documents that are affected by the change might not even be registered, as they were not required by the local legislation to be submitted. In others, in order to get to the expected result it might be necessary to introduce further changes that have not been submitted in this country before.

Once the scope of the variation has been defined, the affected documentation will be determined. The status of this documentation in the different countries is the minimum information that should be collected and included in the planning. For the proper planning, it is important to know how many different versions of the same document are registered worldwide. These are the basis for the compilation of the variation documentation.

Sometimes it might not be possible to evaluate the current status, as no record on the submitted information is available, e.g. if the registration has been purchased and transferred from a different MAH, or if no records have been kept when submitting the original MA. In this case, it should be discussed with the local partner and/ or the local authority if it is possible to submit the most recent version of the documentation available. As the authorities are also interested in having a state-of-the-art dossier registered, this will be an acceptable solution in most cases.

2.1.3 Evaluation of the requirements

Regulatory requirements in different countries are not identical, but might differ significantly, so that the documentation that is considered sufficient for a certain variation in one country, might not lead to approval of the same change in another country.

For the EU countries, the requirements are laid out in the respective variation guideline [6], as for the US in the corresponding guideline from the FDA [9]. For many other countries, similar guidelines can be found on the websites of the Health authority. Many countries and regions have adopted similar requirements as for the ICH countries (see also section 1.2.3).

A lot of additional requirements, however, might need to be considered especially for so-called “Rest of the world” (RoW) Countries. These concern additional administrative documents as well as special requirements on the format and content of the documentation to be presented.

Certificates

RoW Countries can be categorized in two different classes – countries that have a fully functional regulatory authority that is able to perform a full assessment on Marketing Authorization Applications (A), and countries that rely (at least partly) on the assessment in a reference country with high regulatory standards (B).

Countries falling under category B will need proof that the authority in the reference country has performed is assessment first before granting approval. This can be achieved by submitting a Certificate of Pharmaceutical Product (CPP). It is document stating the regulatory status in the originating country, which normally follows the format proposed by the WHO. In addition to the CPP, sometimes also a copy of the original registration certificate in the country of origin is needed.

Another common request is for the manufacturing license and the GMP certificate of the manufacturing company to be provided, and/or the proof of establishment.

A letter of authorization or a power of attorney is also very often required for the local representative to be able to communicate with the authorities.

If these documents are needed for several countries, it can save some time to order the certificates all at once, and not to wait for the individual planned submission dates in the respective countries. It needs to be considered, however, that they might have a limited time of validity, so they should not be ordered too far in advance, as they then would expire before the submission time and would need to be re-ordered.

In addition to these official certificates, some statements issued by the company itself might also be needed, e.g. stating the absence of allergens, explaining differences in product names in the reference country and the country of submission, justifications for not performing bioequivalence studies or similar.

Original Signatures

Many Countries require key documents to be signed by the responsible person, e.g. the Qualified Person, the Managing Director, the Head of Manufacturing, etc. and expect to receive the original wet paper copies of the signed documents. This should be figured in the time planning, as not every responsible person will be available at all times for signing the documents.

Legalisation

For many of the documents, the signatures also need to be legalized by one or more official bodies, sometimes additionally by the embassy of the receiving country. The first step is the notarization of the signature. For countries that are part of the Apostille Convention, the documents might also be certified by an Apostille. These procedures can take up a lot of time and should therefore also be figured in at an early stage of the planning in order to avoid delays later on.

Translations

Although submissions in English are common nowadays, many countries still require at least part of the documentation to be submitted in the local language. This is relatively easy if the documents do not have to bear the original signature, but are accepted in the form of translated copies.

If the document needs to be issued by the responsible person at headquarter or at the manufacturer, this is more difficult, e.g. for certificates of analysis issued in the respective language. The responsible person will not readily sign a document that he or she cannot read and understand. In this case, it is advisable to issue bilingual certificates in order to avoid problems in getting the required signatures.

Raw data

The regulatory dossier should contain as little information as possible, but as much as needed for the assessor to be able to evaluate the Marketing Authorization. Any data submitted will be subject to variations when changed; It is therefore common not to include any raw data or other details in the submission. This is common practice and acceptable in the EU, but some RoW countries still require all raw data to be submitted to support the change, like HPLC Chromatograms, executed batch records and similar. As these data often contain confidential information, it is important to make sure they are only submitted when strictly necessary and are only used for the planned submission.

Reference to local Pharmacopoeias

There are several standard Pharmacopoeias that are used as reference - the United States Pharmacopeia and National Formulary (USP-NF), the European Pharmacopeia (EP) being the ones most commonly used.

Besides these, however, there are a lot of local Compendia, that are either only applicable to one country, or are referenced in a certain region. Examples for these are the Japanese Pharmacopeia, the Chinese Pharmacopeia, and the Russian Pharmacopeia.

This needs to be kept in mind when referencing to a monograph of the EP or the USP-NF – some countries might not accept this reference at all, while other may only require a copy of the relevant monograph.

Samples and reference standards

A lot of authorities perform their own quality testing of the altered product when a change is proposed, so samples of the “new” product with the proposed changes implemented are required. The amount may range from as few as two or three samples for visual inspection to the amount of samples it takes to perform the complete release testing three times. Often the layout of the product has to match the product that is intended to be marketed after the change. As most likely no production of the new product has taken place at the time the change is submitted, the samples normally cannot be taken from the normal production run, but need to be provided via an alternative route. As the will not be in conformance with the current approved status, special provisions will also be needed for release of the samples.

Although guidelines request analytical methods to reflect the scientific „state-of-the-art“-knowledge, they also need to be robust enough to be used in laboratories with lower technical standards as used by these authorities. It is therefore important to have alternative testing methods in place, if the release testing is performed by sophisticated testing methods that cannot easily be reproduced in a laboratory run by local authorities.

Before the samples can be imported to the country, mostly an import permit is required, or they will not receive customs clearance. Import permits have a limited validity, so they cannot be ordered far in advance. This is also a time limiting step and should also be included in the overall time plan.

These are just a few of the requirements that will be encountered in worldwide variations. Many of these requirements change over time, and it is hard to keep track on all of them for all countries.

It is therefore very important to get confirmation on these requirements, either directly from a partner or affiliate in the country, or a consultant providing this service, if the local partner is not able to do so.

2.1.4 Planning of resources

Once the scope of the variation is defined, it needs to be decided whether it is possible to cover the workload with internal resources, or if recruitment of additional external resources needs to be considered. Both approaches have advantages and disadvantages.

Project realization with internal resources only

A clear advantage of using internal resources is that no additional costs will be generated, as the salaries of the staff involved are fixed costs that need to be paid regardless of the project.

The project members will be well acquainted with the internal workflows, and will ideally have been working on the product in the past and therefore have a good understanding of the whole history of the product.

The involved departments can be coordinated more easily by internal project managers due to the already existing workflows and the established working relationship between the project members. In addition, the whole project can be controlled more closely when it is completely managed in-house.

Depending on the existing workload, however, big projects like a worldwide roll-out can lead to severe resource constraints in RA and other involved departments, as the work needs to be realised in addition to the existing daily work.

The resulting high workload could potentially also have impacts on the progress in other projects, if the same project team members are involved, and if both projects are competing for the same resources. If the timing of the roll-out is based on available resources, and not on the needs of the project, the limited resources might lead to delays in the roll-out and as a consequence in the implementation of the change, thus leading to a longer interim period where both the new and the old status are registered in the different countries. This might be acceptable for changes which can be implemented independently in one country, but not for changes that need to be implemented in different countries all at once.

Project realization with additional external resources

The alternative to realize a project with internal resources only is to involve some external resources the entire project or for part of it. The support from external providers might range from gathering of information to complete project management with only minor input from internal departments.

One of the most apparent advantages is the possibility to free up internal resources. Especially if several projects need to be realized in parallel, it is important to identify internal resource conflicts and to resolve them by hiring external help where needed. This way, the daily business will be less affected, and also bigger projects can be realized even if only very limited resources are available.

An additional advantage is the gathering of know-how in areas which are not covered by internal experts. In most cases, not all potentially needed information (especially on country specific requirements) will be available in-house, and gathering all information on your own will be very cumbersome and time-consuming. It might also be beneficial to get some new angle on the project, as an external expert might offer a different view or alternatives to the proposed strategy.

One big disadvantage is, of course, the additional costs that are needed for hiring external help for the project, which need to be considered in the total project budget. Hours put in by some external source will also be more expensive than hours invested by internal staff. To correctly estimate the overall costs, the scope of the project needs to be fixed at the beginning; otherwise the initial estimates will be exceeded very quickly.

It is also a common misconception that it is possible to completely source projects out to some external vendor. As most projects cannot be managed completely by external resources, in the majority of cases, the project will be handled by a mixture of external and internal resources.

In conclusion, it is important to consider how much preparation would be needed in-house before considering involving an external supplier. If the workload to accomplish this preparation is very high, the project is probably not suited for outsourcing. If it is possible to implement standardized processes for at least part of the project, or additional external know-how is needed for the completion, it might be beneficial to get the support of an external supplier.

In a worldwide variation roll-out of variation, most likely the involvement of external help will be beneficial – many steps can be standardized, and depending on the countries involved, there will also be the need for additional information on the regulations in the different countries or regions. Depending on the scope of the project, however, the form of the external support may vary – you may want to ask a freelancer to work in-house as part of your project team, a consultant to take over part or all of the project coordination, or just rely on an external source for information, e.g. on local regulatory requirements.

Budget and fees

One part of planning the resources is to determine the overall budget needed for realization of the project. This includes not only the amount to be spent on external support, where appropriate, but also the authority fees for the variations to be submitted. These fees form a wide range from being free of charge to several thousand Euros, depending on the country and the change to be implemented. A type II variation, for example, will range from no fee in Luxembourg (already covered by annual fees), or under 100 Euros in Cyprus, to over 9000 Euros in Italy (or even more than twice as much if new clinical data is presented). Some of these fees will not be due upon submission, but will be invoiced by the authority after approval, but they all need to be considered for the overall budget.

2.2 Conducting the roll-out

Once the planning has been completed, the next phase is the compilation of variation documentation and the roll-out to the different countries. If the planning has been done taking all aspects into account, this phase is relatively straightforward, but still very demanding in terms of workload and coordination.

2.2.1 submission timetable

If there are a significant number of countries involved, it will be necessary to split the roll out in different waves. These waves should already be arranged in the planning phase, although the detailed roll-out plan can only be fixed close to the roll-out, when all parameters of the change have been determined.

The timing of submission can be triggered by two different factors: on the one side the planned implementation date in the respective country, and on the other side the existing regulatory requirements, timeline and interdependencies. First, it needs to be decided if there is a priority of countries in which the change needs to be introduced first, e.g. for commercial reasons. When there is a fixed implementation date planned for one or more countries, regulatory submission needs to be planned backwards taking into account the assumed approval timelines. As these timelines are not the same in all countries, it might be necessary to submit at different times to achieve the same approval date.

The implementation date, however, is not the only factor in planning the submissions – there are also different interdependencies between the different countries to be figured in.

For Mutual Recognition Procedures (MRP) and Decentralized Procedures (DCP) in Europe, it is not possible to plan submission in the countries independently – as they are combined in a common procedure, these countries will have to be submitted together and will also receive approval at the same time (although the length of the national phase after approval might differ). This is also the case for the Centralized Procedure (CP), as with this procedure only one MA is valid for the whole of the European Union, and the approval will therefore be issued for all EU countries at once.

If more than one variation has to be submitted to implement the proposed change in one given country, it should also be considered how these different variations can be harmonized in terms of approval timelines.

The variations may fall into different variation categories with different procedural timelines, e.g. a type II change combined with one or several type IA or IB variations. In order to have all of them approved at the same time, they have to be combined in one procedure.

The variation system in Europe offers special procedures to combine several changes to one MA (grouping), or combine one change or a group of changes across several different MAs of one MAH (worksharing).

This way, it is possible to have one approval date for all changes submitted for one MA or several MAs - also for different procedure types like national Procedures, MRP and DCP. This is specific for the EU, but similar procedures are also available in other regions.

For many of the RoW Countries, prior approval in a reference country is needed for the change to be submitted. They can therefore never be included in the first wave, but will have to be submitted in a later phase.

In the countries of the former Soviet Union, the Commonwealth of independent states (CIS) countries, in many cases it is still beneficial to have the approval in Russia available at time of submission. Although no formal recognition procedure is in place, it helps in many cases if the change is approved there, as other authorities in the region still rely on the assessment by the Russian Authority.

Another trigger might be other regulatory procedures such as renewal procedures: sometimes it might be easier to introduce changes with renewal procedures, as these require the submission of an updated dossier. An already running renewal, however, might preclude the submission of any changes as long as the assessment has not been finalized. In that case, changes should be submitted either before or after the renewal procedure.

In any case, the timetable for submission should allow for some flexibility, as despite careful planning there will always be some last minute changes that need to be considered.

2.2.2 Compilation of submission documentation

Each country needs its own individual variation package for submission to the local authority. This can either be compiled centrally in the Headquarter, or can be delegated to affiliates or partners. There are several ways, however, how the compilation of documentation can be streamlined so that the workload can be minimized.

2.2.2.1 Structure and format of the variation dossier

There are different ways a dossier can be structured, depending on the countries the submission is planned for. This should be considered when compiling the variation dossier.

There are country specific formats and requirements, but there have been several initiatives to harmonize the format of the dossier in order to reduce the complexity for parallel submissions in different countries.

Common technical Document (CTD)

One of the most common formats is the Common Technical Document (CTD) dossier structure that has been agreed in the countries of the International Conference of Harmonization (ICH). Many other countries outside of the ICH region have also adapted this structure or at least accept submissions that are structured according to this format.

The CTD structure contains 5 sections. As the size of the sections is not equally distributed, the CTD structure is often depicted as a pyramid (see Figure 1 - Structure of Common technical document (CTD)).

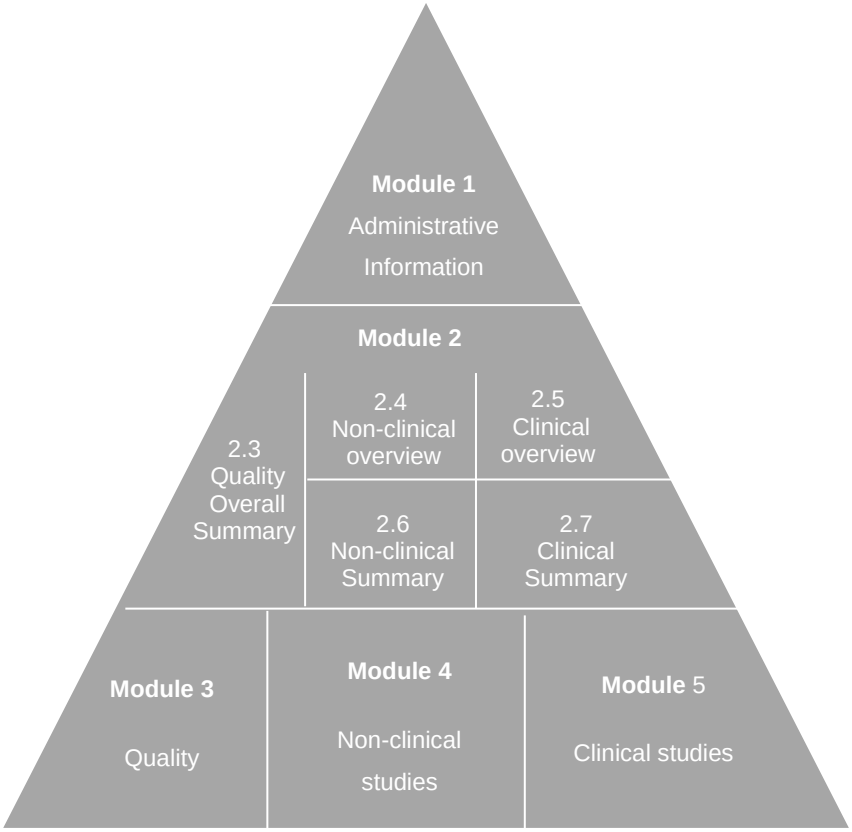

FIGURE 1 - STRUCTURE OF COMMON TECHNICAL DOCUMENT (CTD)

Section 5 contains the clinical data reports that are part of the submission, including all detailed information – it is therefore in general the most extensive part of the dossier.

Section 4 is the non-clinical counterpart to section 5 – it contains all the reports from non-clinical studies that have been performed to support the respective application.

Section 3 is the quality part of the dossier – it contains all information on the chemistry, manufacturing and control (CMC), i.e. all information regarding the pharmaceutical quality of the drug substance and the drug product itself.

Section 2 contains the overviews and summaries for Modules 3, 4 and 5 – here the information is presented in condensed form in order to facilitate the review of the dossier for the assessor at the authority. The clinical and non-clinical summaries only sum up the content of module 4 and 5 without analysing the

content, whereas in the quality, clinical and non-clinical overviews, an evaluation of the content is given by the respective experts of the applicant.

Module 1 contains the administrative information. As this part is not harmonized, but has to be compiled according to country-specific (or region specific) requirements, it is not as such part of the CTD structure.

ASEAN Common technical Document (ACTD)

The Association of Southeast Asian Nations (ASEAN) has adapted the CTD structure to form its own harmonized dossier structure (see Figure 2 - Content and Structure of ACTD).

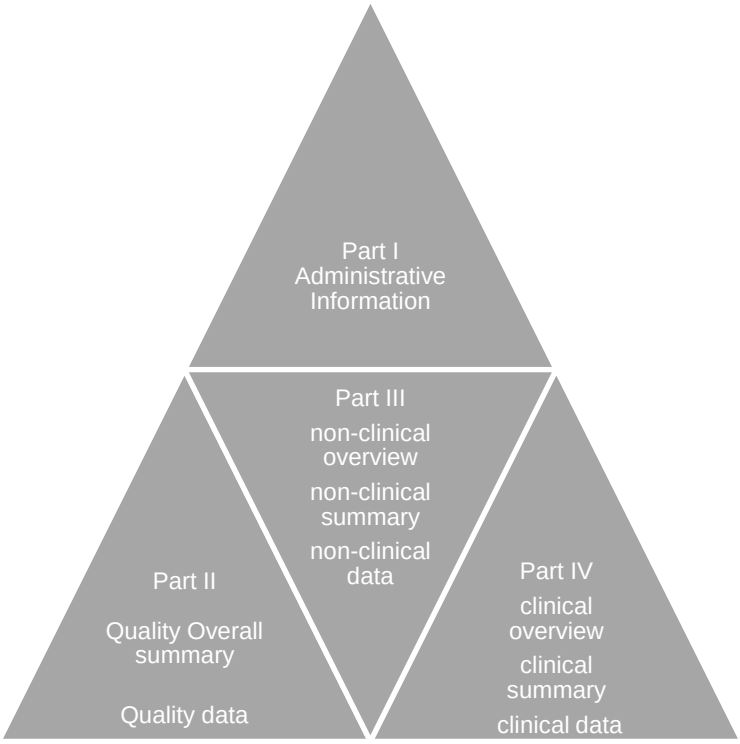

FIGURE 2 - CONTENT AND STRUCTURE OF ACTD

It is very similar in the content of the dossier, but follows a slightly different overall structure - Instead of the 5 sections of the CTD, there are only 4 parts to the ACTD.

Part I contains the administrative Information and corresponds to section 1 of the CTD. It is partly harmonized across the region, but also includes country specific information like the counterpart of the CTD.

As in the CTD structure, there are parts for the quality, non-clinical and clinical information. Instead of including the overviews, summaries and complete data in a separate section, in the ACTD these are included in the respective parts containing the full information – Part II contains the quality overall summary and quality data, Part III contains the non-clinical overview, - summary and –reports, as part IV does for the respective clinical information.

Normative document

In Russia (and several countries in the CIS region), another dossier structure is used – the normative document.

The initial application for the marketing authorization in Russia contains the same elements submitted with the CTD and the ACTD structure (administrative, quality, non-clinical and clinical information), but it is structured in a different way, as the application procedure is separated in different stages, and also includes the additional requirement for the finished product to be tested by the State Institute.

All information that is needed to perform this testing is included in the normative document:

- The drug product specification including specification parameters, testing methods and limits
- the composition of the drug;
- testing methods for drug substance and excipients
- description of the primary and secondary packaging
- the proposed labelling
- storage conditions and the shelf life of the drug.

A signed version of this Normative document, as well as the Patient Information Leaflet (which is directed both at the patient and the physician, as there is no separate SmPC registered in Russia), and a mock-up of the registered packaging is part of the registered information, and changes to this document need to be submitted as variation and are subject to approval by the authority.

Once the regions/countries are defined, it is possible to decide on the basic format of the variation package – is a variation dossier in CTD structure acceptable in all countries, or do you need to have other structures as well?

If CTD is in general acceptable, the variation dossier can already be compiled in the CTD structure - the structure helps to assign the documents to the respective sections.

If several different dossier structures will be required, it is however advisable to apply a generic naming/numbering of dossier sections in order to facilitate adaptations to local requirements. The dossier still can follow the basic CTD structure, but by keeping it more generic, it can be more easily converted to a different structure without the need to rewrite sections.

Adaptation can either be done in the Headquarters or by the local representative, depending on the company structure, and depending on the need for original signatures on the documents.

2.2.2.2 Electronic vs paper submission

Many countries, especially in the ICH region, today require electronic submission of variations. It is therefore advisable to already compile the variation documentation in a compatible electronic format.

There are two common formats for electronic submissions – electronic Common technical Document (eCTD) and non-eCTD electronic Submission (Nees).

The eCTD, as the name suggests, is the further development of the CTD structure in an electronic format. It adds a naming convention for the electronic files for the different sections, as well as an XML backbone to the basic structure of the CTD. It can be viewed either using specific eCTD programs, or using a simple internet browser.

The XML backbone contains the overall structure of the submission and allows for navigation within the structure, as well as the possibility to assign attributes and Metadata to the submitted documents, also allowing for a life-cycle of the dossier.

The submission is done in sequences; any changes made to the dossier can be assigned to different attributes, allowing for the reviewer to see if they have been exchanged, amended, deleted or newly added. Each submission sequence only contains the new information submitted, but if all sequences are combined, they allow for a consolidated view of the dossier information.

The non-eCTD electronic Submission (NeeS) format is very similar to the eCTD, but lacks the XML backbone. It can be compiled using the same software as for eCTD, but can also be compiled by saving single electronic files in a suitable file structure. Due to the lack of the XML backbone, this format is less comfortable to review than the eCTD, and it always only contains the altered information. Besides the advantage of not needing specific software for compilation, there is little advantage using this format. If the respective eCTD software is available, it is therefore preferable to use the eCTD structure.

Not all countries, however, accept electronic submissions. Although it becomes more and more common also in the countries outside the ICH region to accept or even request electronic submissions, it needs to be considered in a worldwide roll-out that there will also be countries that still require a full paper-based submission, e.g. if it is required for all pages of the documentation to be signed by the responsible representative of the company, like the Qualified Person or the Head of Quality Control.

For the countries requiring paper based submissions, it needs to be decided whether a complete paper copy of the required variation package will be sent to the respective country, or if the package can be printed there, and only documents required in original are sent as wet paper copy. Some offices do not have the means of printing the material themselves, so they will rely on the documents to be sent to them as paper copies. If there are local adaptations to be made, e.g. translations of the documentation, or if extensive documentation is needed, it makes more sense to submit an electronic copy to the partner. This can be achieved by sending a CD or DVD with the content, or via electronic gateways like exchange platforms or suitable ftp server.

2.2.2.3 Individual variation packages vs. Modular compilation

As the current regulatory status in the countries where the change should be introduced most likely will be different, the variation documentation needs to reflect this diversity.

One way to deal with the situation is to compile a unique variation package for every registration in every country. The advantage is that all specific requirements can be individually addressed. However, this will also lead to a lot of additional work, as all documentation needs to be compiled separately for each submission, regardless of possible similarities between the documentation in the different countries affected.

If relatively few countries are affected by the change, this can be an effective way to handle the submissions, especially if the change is planned to be combined with other regulatory procedures such as renewals or other variations.

If a significant number of registrations need to be adapted, the workload soon will become hard to handle, and therefore it would be better to divide the documentation in different modular sections, which are dealt with separately.

If two countries have the same information registered in one section, the same generic documentation can be used for both of them. This approach is, however, only useful if there are enough similarities in the documentation registered in the different countries, and if no complete dossier update is planned to be submitted. The granularity of the modular sections should be determined based on the differences between registrations – the more countries a modular section can be used for, the lower the overall workload for compilation will become.

The downside of this approach is that a lot more planning and care needs to be applied in order to ensure that the correct information is submitted in the respective country. For this, a planning table showing the registered information in different sections, and the corresponding updated sections can help to ensure that the correct information in the respective country is used, and to

compile the correct variation package. This can be done using a simple excel spread sheet.

An example for such a planning table is provided in Annex 2.

2.2.3 Coordination – internal stakeholders

Depending on the variation submitted, there are different departments involved in the preparation of the documents to be submitted – an overview of examples of the departments that may be required to give input is given in Figure 3 - internal departments involved in compilation of variation documentation.

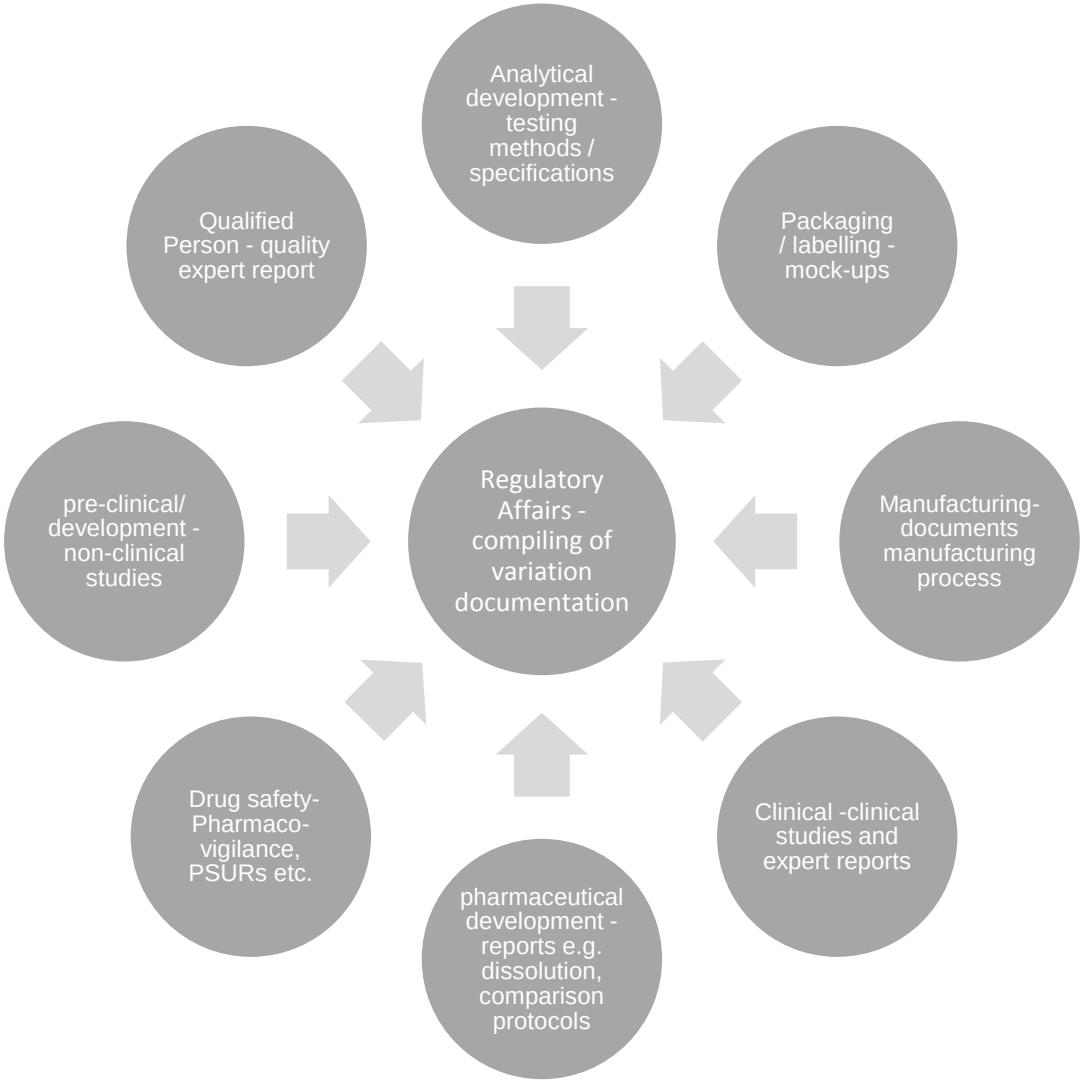

FIGURE 3 - INTERNAL DEPARTMENTS INVOLVED IN COMPILATION OF VARIATION DOCUMENTATION

These departments need to be informed upfront on what documentation will be needed for the submission of the change. Depending on the workload associated with compiling these documents, it is important to include enough time for preparation in the overall time planning. If the documents also need to be implemented in the quality system before submission, this also should be figured in.

The compilation of the respective documentation, however, is not the only activity that needs to be considered in this phase.

In order to smoothly transition from the old to the new registered status, it is also important to involve the commercial and supply chain functions. Stock levels should be surveyed and if necessary adapted in line with the submission timetable. In some countries, it is not possible to import further goods during the evaluation period of the variation, or after the variation has been approved, making it necessary to build some bridging stock in the respective countries in order to avoid stock out. In other countries, it might be necessary to reduce the stock levels in order to be able to implement the change within a reasonable timeframe.

In order to ensure optimal exchange between the different stakeholders involved, it is advisable to establish regular project team meetings (or to get the topic on the agenda of existing meetings, where already established structures exist). The frequency of the meetings might vary in the different project phases, but they should be held on a regular basis, independent on whether any problems are encountered or not. This ensures for a transparent communication at all times and helps to avoid problems caused by a different state of knowledge.

2.2.4 Coordination – external Stakeholders

The partners and/or affiliates also need to be informed upfront of the final planned timing of the variation, and need to give feedback if this planned submission timetable is feasible. The requirements that have been gathered in the planning phase should be confirmed once more by the local partner before the final submission package is compiled.

Once the variation package is submitted to the partner, confirmation should be given on the final submission date. During the evaluation phase, it is important to keep in touch to get any updates on the running procedure. Not all local representatives will pro-actively give feedback, so getting in contact with them on a regular basis will ensure the best possible information flow. This way, it can also be assured that additional requests from the partner or the respective local authority reach you in a timely manner.

The exchange with external stakeholders can mostly be done via email, but it will also help to have regular exchange via telephone conferences to ensure the project is properly managed.

In order to keep track on the different on-going procedures, it is advisable to use some kind of tracking tool. If the regulatory database used in the company has the capability of tracking the submissions, it is best to use this function.

If not, a simple excel spreadsheet will also suffice to make sure all submissions are properly followed up. An example of tracking list is given in Annex 3. With this simple tool, it is possible to keep track on all ongoing procedures without missing single submissions when receiving no feedback. It can also be used to gain a quick overview when informing internal stakeholders on the status of the submissions.

2.3 Implementation phase

Once the variation has been approved in one country, the next phase of the change starts – the implementation into the quality system, and in the production process. In this phase, as in the steps before, many different departments are involved, and ensuring a proper information flow both internally and externally is vitally important in order to ensure regulatory compliance.

In addition to the coordination of other departments, one of the duties of RA in this phase is to update the internal regulatory database. As these entries are basis for regulatory compliance checks, they should be kept up to date and need to be revised within a reasonable timeframe.

For European countries, it is now also mandatory to update the respective entry in the Extended EudraVigilance Medicinal Product Dictionary (xEVMPD), the EMA Pharmacovigilance database within a period of 30 days. This legal requirement is based on Article 57(2) of Regulation (EC) No 726/2004 [2].

2.3.1 Change control

Volume 4 of "The rules governing medicinal products in the European Union" [17] contains guidance for the interpretation of the principles and guidelines of good manufacturing practices. The guideline defines Change Control as "*A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.*"

Every pharmaceutical company has to have a Change Control (CC) procedure in place to ensure changes are implemented in compliance with the rules of GMP. As the CC procedure is part of the quality system that is mandatory for companies working within a GMP environment, the responsibility for this procedure lies with the quality department.

The RA department is normally only one of the stakeholders giving input on the planned change. At least part of the information gathered during the planning phase is already needed to assess the regulatory impact for the CC procedure.

CCs go through different phases: First, the change is assessed for its potential to impact the validated status. In this phase, also the impact on the registered status is evaluated.

Then, different measures are defined that need to be carried out before the change can be implemented, and others that need to be carried out after implementation of the change.

Afterwards, a decision is made on whether the change should be implemented or not. If not, the change request will be closed; if yes, the measures before implementation will be initiated.

When all these actions are carried out, the change can be implemented, and all measured defined after implementation can be carried out. The CC procedure can only be closed when all defined actions have been completed.

If the overall costs exceed a certain amount, it might be possible that the whole project will not be realized at all, e.g. if the change was planned to achieve some savings that will be consumed by the costs for implementing this change.

Any change requiring a worldwide variation roll-out will have a significant impact on the validated status and will therefore start with the initiation of a CC procedure. Although normally not triggered by the RA department, the CC is an important tool to track and communicate the status of the proposed change, and input should be given at an early stage to the process owner of the CC and it should be agreed how to best deal with the change.

When the change affects more than one country, it needs to be decided whether it can be tracked in only one CC procedure, or if it should be split into several CC procedures.

One CC has the advantage that the change can be more easily followed up and coordinated, but this way it will not be possible for the change to be implemented in only part of the countries, and the procedure can only be closed once the variations in all of the affected countries have been approved.

Singe CCs per country facilitate a more detailed tracking, and allow for single CCs to be closed in a timely manner, but that approach increases the overall workload and makes it harder to keep track of all the open actions.

2.3.2 Timing of implementation

To decide on the best way to coordinate the timing of implementation, it is important to decide whether the change can be implemented separately for individual countries or if the change has first to be approved in all of the countries it has been submitted in. There may also be some scenarios in between, where just a sufficient number of countries need to be adapted for a change to be implemented.

If a change can be implemented individually country by country, it is relatively easy to determine the best timing. Once the approval is received, the implementation is normally triggered by the next planned production run, the available stock levels, and the sell-off period for the old goods in the respective country. For marketing driven changes, the implementation needs to be coordinated with the respective communication to the customer.

Some countries will allow for sell-off of all the old stock that has been imported, but will not allow for another import of the old goods. Some others have fixed timeframes of six month or one year, in which the old stock has to be exhausted. In others, no specific timeframe is mentioned in the legislation, and therefore the decision lies with the pharmaceutical company.

Timing of implementation also depends on the type of change made to the product – if it is a change that is made to improve the safety of the product, the change will be implemented much quicker than if there are only administrative changes to be implemented.

It becomes more complicated if the change cannot be implemented independently, but need to be coordinated for part or all of the countries.

In the roll-out phase, the stock levels should already have been monitored. If coordinated properly, no excessive stock of the old material should be in the warehouses. Nevertheless, the stock levels will not be the same in all countries in which the change should be introduced. A common fixed implementation date therefore will lead to the old goods that cannot be sold any more to be destroyed, which might have a significant financial impact on the project.

In addition to that, it will also not be possible to gain approval in all countries at the same time. It is therefore important to plan for a transition period, in which the old and the new status can be kept in parallel.

If, for example, there are significant changes to the manufacturing process, it might be possible to implement both the old and the new process in parallel. It does, however, not make sense to start producing according to the new process until enough countries are converted so that minimum order quantities are reached and a production run commercially makes sense.

The reverse is the case when most of the countries have received approval – in this phase, running the old process is not commercially viable any more, and most of the goods are produced according to the new process. This needs to be included in the production planning, so that enough goods are kept in stock for the last countries to receive the approval.

The timing of implementation can, however, become a major problem, if the change is classified as Type IA variation in the EU, and therefore needs to be implemented before submission, whereas for other countries it can only be implemented after approval in the reference country, and a CPP is needed as proof for the approval.

In this case, it needs to be discussed with the local partner or the authorities on how to handle the issue.

One possibility is to issue a statement that the change has already been implemented in the quality system of the marketing authorization holder, signed by the Qualified Person, and to submit the approval by the authorities at a later stage.

If in some countries the variation procedure takes longer than expected, and therefore the implementation of the change is delayed longer than acceptable, it needs to be discussed how this will be dealt with within the company. Depending on the change, it might be possible to inform the authorities on the implementation of the change, and asking for permission to already market goods in the new making. If this is not possible, it is important to discuss internally how the delay can be dealt with, e.g. by producing once more according to the old status.

2.3.3 Coordination and Information flow

As in the planning and the roll-out phase, communication with all is involved stakeholders is key to ensure the change is implemented in a timely fashion, and that regulatory compliance is ensured.

The envisaged way and timing of implementation should be communicated as early as possible, and any changes to this plan needs to be conveyed pro-actively.

Many departments are involved in the implementation of changes, and therefore depend on the feedback by Regulatory Affairs on the approval in a given country – examples re given in Figure 4 - internal departments to be informed on the approval of variations.

The approval of the variation, however, is not the end of the procedure – only when all the changed documents have been implemented, the old goods have been sold off, and the new goods have been produced and have been shipped to the country, the whole process has been finalized.

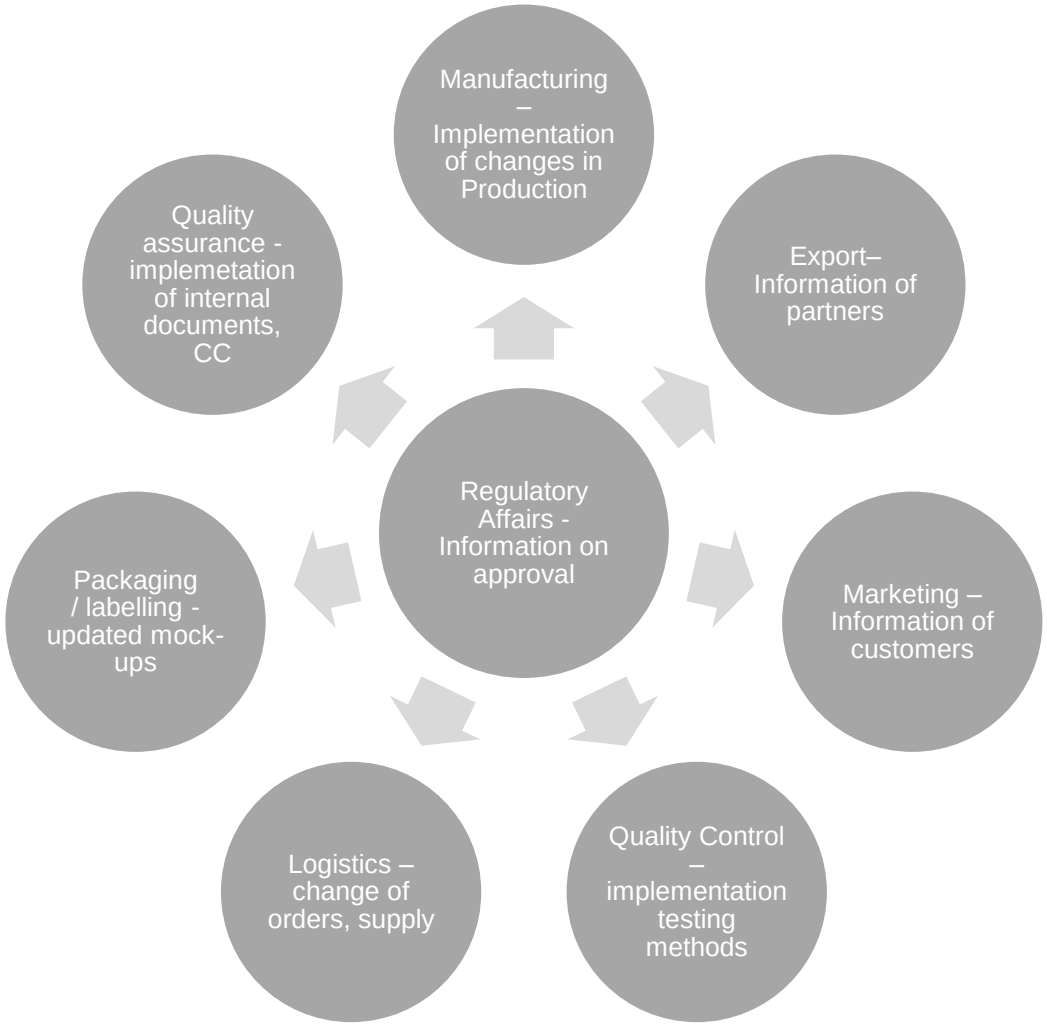

FIGURE 4 - INTERNAL DEPARTMENTS TO BE INFORMED ON THE APPROVAL OF VARIATIONS

Although RA is the central department in coordinating the project, at this point the responsibility does not primarily lie with the RA department any more, but is the responsibility of the respective departments. The main responsibility of RA ends with the timely communication of the approval.

If, however, problems arise with implementation, and the authorities need to be contacted to e.g. extend the transition period, in which the old goods can be sold off, RA once more is responsible for leading these discussions.

3 Conclusion

Any change that needs to be rolled out on a worldwide level needs good preparation, thorough planning and close coordination throughout the process, from the first planning to the implementation of the change in the last country.

Regulatory Affairs plays a central role in such a roll-out, but a lot of other stakeholders need to be involved during the process, which need to be closely coordinated. For this, a clear and constant communication is key to successful management of the project.

Any work invested in the planning phase will pay off later when it will save much of the workload by achieving synergies in the compilation and roll-out of the change.

Proper planning also facilitates the implementation of the change, and if a good overview on the on-going procedures is available, it will also be easier to follow-up with the local representatives.

All careful planning, however, cannot prevent unexpected problems to occur. It is therefore important to also figure in some buffer for issues that may delay the process, and allow for certain flexibility in the process. The better the whole project is managed, the easier unforeseen challenges can be dealt with.

If all elements of the change have been taken into account for the planning, and the different limitation have been considered, it is possible to achieve a roll-out of worldwide variations with available resources, and to implement the change in a reasonable timeframe without violating regulatory compliance.

4 Summary

The pharmaceutical Industry is a highly regulated environment; in most countries, it is forbidden to sell Medicinal products unless you have obtained a Marketing Authorization by the respective National Competent Authority (NCA). This requirement is not limited to countries with a high regulatory standard, but is basis for pharmaceutical legislation in countries all over the world.

The application for Marketing Authorization includes (besides the necessary administrative information), a regulatory dossier summarizing the obtained information on the quality, efficacy and safety of the medicinal product, which is then assessed and approved by the NCA. Changes made to this dossier have to be notified to the authority via variation application.

Therefore, any change made to a product that is marketed worldwide will have an impact on the registrations in all affected countries. Submission of such a change requires careful planning and coordination before, during and after implementation of this change. Regulatory Affairs plays a major role in coordinating the internal and external stakeholders to make sure the implementation of the change is done in compliance with the registered information and legal obligations.

The objective of this Master Thesis is to identify the challenges a worldwide roll-out of variations brings with it during the phases of planning, roll-out and implementation, and to propose strategies and tools on how to deal with them.

5 References

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Annexes

Annex 1 - Questionnaire for submission of a variation

Background

We are planning to submit a change for _____ (insert product) and are currently evaluating the regulatory requirements for submitting the respective variation(s) in your country. Details of the change can be found in the enclosed Change Control Form.

In order to be able to check the feasibility and to be able to work out a detailed roll-out plan, we would therefore require your local expertise and would like to ask you to fill out this questionnaire.

Please send back the filled-out form no later than_____(insert date) to _____(insert HQ contact and return address and/or email address).

Administrative Information

	Partner/Affiliate: please fill out.
Country	
Partner/Affiliate	
contact person	
e-mail	
telephone number	
address	

Product Information

	Partner/Affiliate: please fill out.
Product name	
Registration number	
Date of first authorization	
Date of next renewal	

Questions

	Partner/Affiliate: please fill out.
Is the proposed change of regulatory relevance/ does it need to be addressed at your national competent authority?	☐ YES ☐ NO
If yes, what type of change is it? (Please attach the relevant legislation, If available)	☐ Notification ☐ Type IA variation ☐ Type IB variation ☐ Type II variation ☐ New registration/line extension ☐ Other (please specify) _____ _____
Do we need to await approval for the type of change? If yes: How long does it generally take for your authority to approve this type of change in month?	☐ YES ☐ NO _____ months
Do we have to consider another regulatory activity, e.g. a renewal application? If yes, when will the other application take place?	☐ YES ☐ NO _____ (DD/MM/YYYY)
What is the amount of fees to be paid (please include currency)?	_____
Do they need to be paid in advance/ do you need to provide a proof of payment in the submission package?	☐ YES ☐ NO
If yes, please include payment details	_____ _____ _____
What documentation is needed for the change? Please attach List	
Is a variation dossier in CTD format acceptable?	☐ YES ☐ NO
If not, what is the specific format of the dossier? (Please specify)	_____ _____
Can the variation dossier be provided in electronic format or do you need paper copies? How many copies are required?	☐ Electronic format ☐ Paper format ☐ both _____copies

Annex 1 - Questionnaire for submission of a variation

	Partner/Affiliate: please fill out.
Which of the following certificates are needed for submission? Please also indicate if they need to be signed and/or notarized CPP Product Licence from reference country Manufacturing licence GMP Certificate Proof of establishment Letter of Authorization Power of Attorney any other certificate (please specify) _____ _____	required / signed / notarized ☐
Are any specific declarations or statements needed? Please specify	_____ _____ _____
Does the variation dossier need to be translated into your local language? If yes, which Language?	☐ YES ☐ NO _____
Does the dossier need to be signed by the responsible person? If yes, please specify by whom	☐ YES ☐ NO _____ _____
Do you need mock ups to be submitted?	☐ YES ☐ NO
Are samples required? If yes, please specify amount	☐ YES ☐ NO ☐ ___ Drug Substance samples ☐ ___ Drug Product samples ☐ ___ Reference substance ☐ ___ Others (please specify) _____ _____
Do you need an import permit to import the samples? Is a pro forma invoice required?	☐ YES ☐ NO ☐ YES ☐ NO

Please also provide any additional information that might be useful for the planned change

Annex 2 – Compilation matrix

Country	Trade Name	MA number	MA Holder	planned Parallel submissions	approved Dossier Information	Documentation Section 1	Documentation Section 2	Documentation section 3

Annex 3 – Tracking table

Country	Region	Product Name	Registration Number	Submission Scheme	Planned roll-out date	dispatch to local Partner	submission date	approval date	Comments

Regions:

Asia/Pac (Asia/Pacific)

CIS/RU (Commonwealth of Independent States/Russia)

EEA (European Economic Area)

LATAM (Latin and Central America),

ME/AF (Middle East/ Africa),

RoW (Rest of the world – not assigned to other regions)

US (United States of America)

Submission scheme:

Single variations

Grouped variations

Complete Dossier update

Combined submission with renewal

Other (specify in comments)

Eidesstattliche Versicherung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Dr. Maike Melullis