Challenges and Considerations in Developing a Regulatory Compliance Department in a Medium-sized German Pharmaceutical Company

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List of Abbreviations

AMG	Arzneimittelgesetz
AMWHV	Arzneimittel- und Wirkstoffherstellungsverordnung
APEC	Asia-Pacific Economic Cooperation
API	Active Pharmaceutical Ingredient
ASEAN	Association of Southeast Asian Nations
BAH	Bundesverband der Arzneimittel-Hersteller e.V.
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte, Germany
BPI	Bundesverband der Pharmazeutischen Industrie e.V.
CC	Change control
CMC	Chemistry, Manufacturing and Controls
CTD	Common Technical Document
DGRA	Deutsche Gesellschaft für Regulatorische Angelegenheiten
DIA	Drug Information Association
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
GMP	Good Manufacturing Practice
HQC	Head of Quality Control
HP	Head of Production
HRA	Head of Regulatory Affairs
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers Association
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PANDRH	Pan-American Network for Drug Regulatory Harmonization
PIL	Product Information Leaflet
PQR	Product Quality Review

QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RAPS	Regulatory Affairs Professionals Society
RegCom	Regulatory Compliance
RegA	Regulatory Affairs
RI	Regulatory Intelligence
RING	Regulatory Intelligence Network Group
RSS	Really Simple Syndication
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TOPRA	The Organization for Professionals in Regulatory Affairs

1 Introduction

1.1 What is regulatory compliance?

1.1.1 Definition of regulatory compliance

The term *compliance* generally indicates the state of conforming to a rule, such as a law or a policy. However, *regulatory compliance*, within the scope of this thesis, refers to conformity with a marketing authorisation (MA) and current legal requirements and laws.

The registered documentation of a medicinal product approved by a competent authority is the regulatory basis for marketing the product. The documentation includes, amongst other information, a detailed composition of the product, an exact specification for the release, and information about analytical tests. Manufacturing of a pharmaceutical product must be carried out in accordance with these documents, which are kept by the regulatory authority of the country concerned. Any discrepancy between the registered documents and the manufacture of a distinct product leads to regulatory non-compliance.

1.1.2 Legal and regulatory background

In the European Union (EU), a medicinal product may not be placed on the market without a MA issued by one of the competent EU authorities [1].

The grant of a national MA allows the marketing authorisation holder (MAH) to place the product on the relevant market. However, along with the grant of the MA, the holder also is obliged to comply with relevant regulations. In Germany, for example, these are the German Drug Law (AMG) [2] and the Arzneimittel- und Wirkstoffherstellungsverordnung (AMWHV – ordinance on the production of pharmaceuticals and active pharmaceutical ingredients) [3].

According to the AMWHV, Part I of the EU GMP guidelines applies to medicinal products, for the interpretation of the principles of GMP. It says that medic-

inal products must be manufactured, tested and released in accordance with GMP requirements. The introduction of the EU GMP guidelines, Part 1, Chapter 1 [4] points out the link between GMP and regulatory compliance:

> *The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation* [emphasis added] *or Clinical Trial Authorisation, as appropriate and do not place patients at risk due to inadequate safety, quality or efficacy.*

The relevant competent authority must be notified by a variation of any amendment to the registered dossier after authorisation. In the EU, variations are regulated in the Commission Regulation (EU) No. 1234/2008, as amended [5] (European variation regulation). This regulation applies to MAs granted through national, mutual recognition, decentralised, as well as centralised procedures.

1.2 Case setting

1.2.1 Developing a Regulatory Compliance Department in a medium-sized pharmaceutical company

In Germany, there are many small- and medium-sized companies operating in the pharmaceutical industry. These enterprises have different needs and challenges than large companies, with different ways of, and approaches to, working and frequently limited financial and personnel resources. Nevertheless, they must comply with all the relevant regulations and laws in the same manner and to the same extent as “Big Pharma.” Regulatory compliance is not negotiable and smaller companies must find methods to handle the challenges that attend constant shifts and changes in the regulatory environment.

This master thesis provides some considerations and suggestions for the management of regulatory compliance and the development of a Regulatory Compliance (RegCom) Department. It looks at two major components: achieving and maintaining regulatory compliance. Additionally, the thesis examines

different departments and key personnel involved in regulatory compliance as well as regulatory intelligence aspects.

The example of a fictive medium-sized pharmaceutical company in Germany will demonstrate what to consider when planning the development of a RegCom Department, and what practices ensure regulatory compliance with German and EU registration dossiers.

1.2.2 Description of the company

This fictive pharmaceutical company is a family-owned, owner-managed company based in Germany, and a specialist in the manufacture of chemically-defined active pharmaceutical ingredients (APIs) and drug products. For convenience, the company is called *Example Pharma*. With some 300 employees, it is a medium-sized company. It focuses on the manufacturing of APIs and finished drug products, in contract for customers as well as for its own business by using own production facilities. The company has the following main departments: Quality Assurance (QA Department), Quality Control (QC Department), Regulatory Affairs (RegA Department), Pharmacovigilance and manufacturing facilities for APIs and for finished drug products. Management, administration, and productions facilities are at a single location in Germany – there are no affiliates.

Company-owned products are only marketed in Germany and a few European countries. Products manufactured for customers, on the other hand, are distributed worldwide.

1.2.3 Why establish a Regulatory Compliance Department?

In recent years, regulatory compliance in pharmaceutical companies has become increasingly important. The management of *Example Pharma* recognized that regulatory compliance is a future trend and that avoiding non-compliance can be essential for economic survival, especially for small, independent companies. Therefore, they decided to establish a RegCom Department, in order to develop a systematic approach to ensuring regulatory compliance.

1.2.4 How was regulatory compliance ensured in the past?

In the past, *Example Pharma* implemented no systematic approach or strategy for ensuring regulatory compliance. In general, small- and medium-sized companies with a manageable portfolio of medicinal products do not have strong pressure to professionalise regulatory compliance efforts. As a result, regulatory compliance has been ensured through occasional single actions and each department has developed its own compliance agenda. In contrast, large pharmaceutical companies, with large product portfolios and various affiliates, have many more products and data, which results in the absolute necessity for structured processes to ensure regulatory compliance.

2 The Regulatory Compliance Department

2.1 Challenges of a Regulatory Compliance Department

The ultimate goals of a RegCom Department can be summarized in three tasks:

1. Achieving or re-establishing regulatory compliance
   Checking all registered documents against the instruction documents currently in use in the manufacturing unit. In case of non-compliance, arranging remedy of non-compliance.

2. Maintaining regulatory compliance
   Ensuring that all changes that might affect the safety, quality or effectiveness of a product or a process are assessed and implemented in a proper and controlled manner.

3. Ensuring compliance with all relevant laws and directives
   Monitoring regulatory developments, as well as gathering and analysing publicly available regulatory information. Communicating this information within the company.

Over the past years, the regulatory environment worldwide has become increasingly more complex. However, the importance of compliance is often recognized only in crisis situations – generally, when products are released on the market, but do not comply with the requirements of the MA. Unreported product changes are usually the reason for this state of non-compliance. The following sections focus on the challenges and responsibilities of a RegCom Department.

2.1.1 Non-compliance can only occur where changes are made

After its approval, the manufacturing process of a medicinal product represents the current technology standard of manufacturing. At the moment of approval, it is relatively easy to be compliant and to produce the medicinal products according to the details recorded in the MA. However, during its life cycle each drug product will undergo a number of changes. The regulatory authorities must be notified of any amendment, any deletion or any change made to the registered information. Possible areas affected by changes may include: the summary of product characteristics (SmPC), synthesis of the API, manufacturing process, specifications, test procedures, stability tests, and batch size. Examples of regulatory change processes that can result in discrepancies between the manufacturing process and the MA are:

- variations that are not submitted or not submitted correctly;
- renewals that are not submitted;
- post approval commitments that are not fulfilled in due time.

The goal of every company should be to avoid non-compliance. However, non-compliance is often only revealed coincidentally. Reasons may be: insufficient tracking of regulatory processes, frequent changes of personnel in key positions, unclear responsibility, incorrect assessment of a change or simple lack of awareness of correct change control procedures.

If non-compliance occurs, the period of non-compliance should be kept as short as possible and arrangements must be made in order to avoid a repetition.

With regard to variations, renewals, and post approval commitments, small- and medium-sized companies struggle with basically the same challenges and workload as large-sized companies. Differences in the number of products and MAs (large companies have many more products than smaller ones) are usually offset by number of staff.

2.1.2 Reasons for changes to the registered information

There are many reasons why process changes of pharmaceutical products may be necessary. Some examples are listed below:

- advances in science, technology and knowledge;
- experiences as a result of full-scale production;
- changes in the needs of the market product, such as a process scale up;
- improvements in the quality of the medicinal products, such as improved product stability;
- optimization of the manufacturing processes;
- remaining state-of-the-art with manufacturing methods and analytical techniques;
- transfer of product to a new MAH and new manufacturing site;
- reaction to a corrective or preventative action, due to out of specification results or deviations.

Any of these examples can result in the submission of a variation, when an amendment of the approved dossier information becomes necessary. Not submitting a necessary variation leads to non-compliance.

2.1.3 Changes triggered by the agencies and new laws

Further reasons for changing MAs often come from regulatory authorities. Most often there are one of two origins: deficiency letters and new or amended laws, directives, and guidelines. Deficiency letters are always the result of a submission of regulatory information. Changes to laws and regulations are product independent.

The regulatory environment is an evolving one and, in recent years, there are more frequent interactions between the relevant authorities. A trend towards the globalization of pharmaceutical issues can be recognized. Driven by this

development, several initiatives have been established – mostly in regional clusters, aiming to harmonize international regulations and guidelines (e.g. International Conference on Harmonisation (ICH), Association of Southeast Asian Nations (ASEAN) or Pan-American Network for Drug Regulatory Harmonization (PANDRH)). The ICH, for example, understands its work as follows:

ICH's mission is *"To make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration and the maintenance of such registrations*" [6].

These harmonisation processes simplify the regulatory requirements in the long term, but likely lead to a number of changes and variations in the short term. Large-sized, global companies especially benefit from this development. Companies with a focus on just one or two national markets do not have many advantages, but do need to manage the changing regulatory requirements. However, as a contract manufacturer for global-acting customers *Example Pharma* benefits indirectly, too.

2.1.4 Submission of regulatory information: How detailed?

The dossier information submitted to a regulatory authority is legally binding after approval and this information cannot be changed by the MAH without agreement by the authority. For the submission of regulatory information, in general, the registration dossier should contain the minimum required information demanded by regulatory authorities. Every change and every variation includes the risk for non-compliance. This is the reason why it is crucial to carefully check the content of each dossier before submission, in order to decide which information is absolutely necessary for the regulatory authority.

If the dossier contains very detailed information, even a minor change can trigger a variation procedure. A well-known example is the detailed description of an analytical instrument including the exact product name and name of the manufacturer. The exchange of the old instrument for an identical new one after a few years of use is often not possible, as the manufacturer does not

produce it anymore. Comparable new instruments have different names or a different manufacturer, which results in the need to submit a variation.

As a general rule to consider, amendments to documents or details which are not part of the registered information do not trigger a variation.

2.2 Role of a Regulatory Compliance Department within the company

The activities of a RegCom Department depend on each company's structure and organisation. One thing that all companies – large- and small-sized – have in common is that, due to the nature of regulatory compliance, there are always overlaps between the RegCom Department and other technical departments. This is one primary reason that open communication and clear responsibilities are the basis for successful compliance work.

2.2.1 Communication with, and coordination of, internal and external stakeholders

Effective internal communication of all relevant information, including changes in manufacturing and testing of a product, as well as changes coming from the RegA Department to all involved parties within the company is a pre-requisite to regulatory compliance. It is not only the responsibility of the RegCom Department to ensure that all necessary information is shared, but its communication skills and the ability to serve as a communication link between the involved departments are key factors that contribute to a successful assurance of compliance.

Moreover, the short spatial distance between internal departments that can be found in small companies is a considerable advantage over large companies. Possible inquiries and misunderstandings can quickly be clarified. In order to take full advantage of this, standard operating procedures (SOPs) and work-flows discussed with all parties involved are highly advisable. Following this approach, small- and medium-sized companies ensure that all involved

stakeholders know what to do, and open communication prevents possible misunderstandings.

As *Example Pharma* also manufactures medicinal products in contract, effective and clear external communication is extremely important as well. External communication with customers aims to provide clarification about valid documentation, with regard to registered information at the authorities, and to the manufacturing instructions used for manufacturing the products. Changes, coming from either the manufacturer or the customer, must be communicated.

2.2.2 Key personnel and departments involved

The maintenance of regulatory compliance requires the participation of many different departments at all levels within a company. A number of individuals and departments in pharmaceutical companies have a major influence on regulatory compliance. Figure 1 depicts the internal departments that the RegCom Department interacts with, in order to ensure regulatory compliance

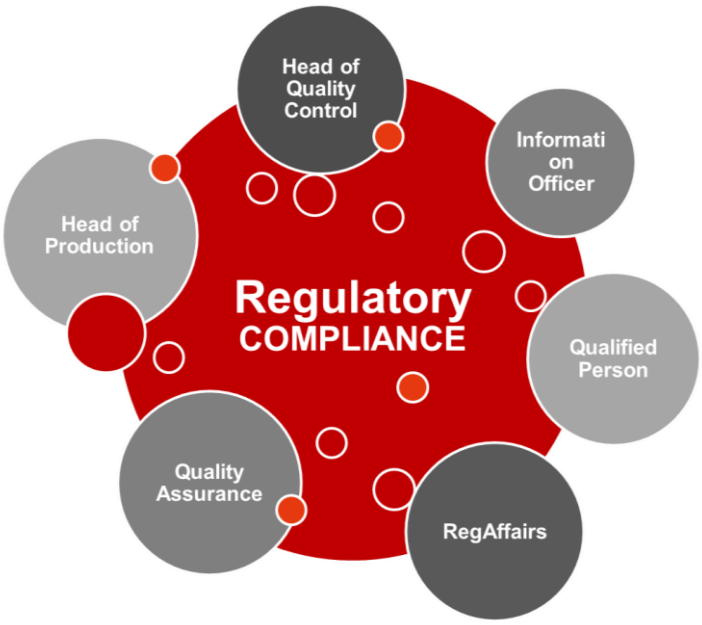

Fig. 1: Internal departments that the RegCom Department interacts with, in order to ensure regulatory compliance.

The following sections describe their relevant roles and responsibilities.

2.2.2.1 Qualified Person

A key figure in the quality system in each pharmaceutical company in the EU is the Qualified Person (QP). The legal basis for the qualified person is defined in the European Directive 2001/83/EC, in EU GMP guidelines Chapter 2 (Personnel) and in Annex 16 (Certification by a Qualified Person and Batch Release). The QP holds a unique position of importance and is personally responsible for ensuring the quality of all drug products produced for the European market [3]. No produced batch can be released for sale or supply prior to certification by the QP [7]. Each MAH must have, permanently and continuously available, the services of at least one QP [1].

With regard to regulatory compliance, the QP holds a critical position in the company. The duties are described in Article 51 of Directive 2001/83 [1]. Accordingly, the QP is amongst others responsible for ensuring "*in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization* [emphasis added]".

In April 2016 the revised Annex 16 to the EU GMP guidelines came into effect [7]. This annex underlines the duties of the QP with regard to regulatory compliance, too: "the *QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State where certification takes place, in accordance with the requirements of the marketing authorisation (MA)* [emphasis added] *and with Good Manufacturing Practice (GMP)*".

Looking at the legal responsibilities of the QP, it is apparent that the position is a close ally of the RegCom Department in ensuring regulatory compliance. A specific point of contact between the QP and the RegCom Department is the assessment of compliance gaps by the QP discovered during compliance dossier checks performed by the RegCom Department (see also section 2.3.1).

In the present example of a company manufacturing medicinal products in contract, as well as products for its own business, it is important to differentiate between these two possibilities in regard to the responsibilities and duties of the QP. In case of contract manufacturing, most often the contract giver is the MAH. The QP usually has no direct access to the current registered dossier information, such as release specifications and descriptions of the manufacturing process. Therefore, it is of the highest importance that an agreement details the obligations of both parties. According to the EU GMP guidelines, Chapter 7 – Outsourced Activities "*Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality Management System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility"* [8].

In the case of the company manufacturing products for its own business, the QP must pay attention to compliance between manufacturing instructions and registered information. In order to fulfil its responsibilities, the QP has to rely on a functioning quality system within the company.

2.2.2.2 Head of Production

Another important player with regard to regulatory compliance efforts is the "Leiter der Herstellung" according to §12 of AMWHV [3]. The corresponding function in the EU GMP guidelines is the "Head of Production". The general duties and responsibilities of the Head of Production, according to the EU GMP guidelines Chapter 1 [4] include the following:

- to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- to approve the instructions relating to production operations and to ensure their strict implementation;

- to ensure that the production records are evaluated and signed by an authorized person;
- to ensure that the appropriate validations are done.

This list of duties shows that the Head of Production is responsible for all productions steps, with the exception of the final batch release. The fulfilment of most of these responsibilities requires knowledge of the registered documentation of the dossier deposited at the regulatory authority. By signing the corresponding manufacturing protocols, he confirms the compliance of production with the MA.

2.2.2.3 Informationsbeauftragter / Information Officer

Another key person with regard to regulatory compliance, in any pharmaceutical company that places medicinal products on the German market, is the information officer, according to §74a AMG [2]. The provisions of the AMG on the information officer are based on Article 98 of Directive 2001/83 / EC [1]. Information officers are responsible for a number of activities. On the one hand they are responsible for all medicinal information about marketed pharmaceuticals, with a special focus on advertising materials and materials for field representatives. On the other hand, they ensure that the labelling, package leaflets and SmPC comply with the content of the registered MA. That means that the information officers have their own interest in ensuring compliance. Therefore, they should be involved as an important part of the internal approval process for variations concerning SmPC, PIL and labelling. In this regard, it is to be noted that the German information officer is only responsible for products on the German market. For any other European country where products are marketed, a separate information officer is required.

2.2.2.4 Regulatory Affairs Department

The RegA Department is a key department in any pharmaceutical company and central to maintaining regulatory compliance. Activities RegA is involved in comprise the entire spectrum of product development, manufacturing,

registration, post-marketing activities, as well as lifecycle management. Internally, the RegA Department often facilitates project teams and is a close partner to the RegCom Department due to its textual overlaps with regard to regulatory information and processes. Externally, the RegA Department acts as a link between the company and regulatory health authorities.

In connection with the variation and change management, the RegA Department is responsible for the regulatory classification of changes or variations and for the preparation of the relevant documents – and, subsequently, for their submission. After approval, it is the responsibility of the RegA Department to provide this information to all relevant departments, in order to implement the change (e.g. in a manufacturing process).

Using a regulatory database comprising information on all ongoing regulatory processes, it is possible for the RegCom Department to track variations and monitor the maintenance of regulatory compliance. Depending on a company´s structure and organization, the RegCom Department may also be directly involved in variation management by being responsible for maintaining the regulatory databases and for communication within the company.

2.2.2.5 Quality Assurance Department

The QA Department is responsible for a wide range of activities, in order to ensure that medicinal products are produced and controlled with the quality required for their intended use [9]. Within the Pharmaceutical Quality System, the QA Department ensures compliance to relevant standards (e.g. the GMP).

With regard to regulatory compliance, there are two important points of contact between the QA Department and the RegCom Department. The first responsibility of the QA Department is the change control (CC) management. It guarantees that all changes are evaluated and implemented appropriately in a systematic approach. The CC procedure enables the RegCom Department to monitor and track the status of changes within the whole company what makes an important contribution to the maintenance of regulatory compliance (see also section 2.3.2).

The second point of contact with regard to regulatory compliance is the preparation of the Product Quality Review (PQR) by the QA Department. The PQR is an annual quality report required by the EU GMP guidelines and has to include a review of all MA variations submitted, granted or refused. The regulatory information is provided by the RegA Department. The availability of these data allows a conclusion on the current state of regulatory compliance in the company (see also section 2.4.2).

2.2.2.6 Head of Quality Control

The Quality Control Department is responsible for sampling and testing starting materials, packaging materials, intermediate, bulk, and finished products [4]. The general duties and responsibilities of the Head of Quality Control are described in §14 AMWHV [3] or in the EU GMP guidelines, Chapter 2 – Personnel [10]. Accordingly, amongst other duties, the Head of Quality Control has "*To approve specifications, sampling instructions, test methods and other Quality Control procedures*". Moreover, the tests and methods of medicinal products which are authorized or registered must comply with the MA [4]. In order to fulfil these tasks, the Head of Quality Control is dependent on having current approved information. In return, he provides relevant documentation on methods and specifications to the RegCom Department for the performance of gap analyses.

2.2.2.7 Senior Management

Looking at the responsibility within the company with regard to regulatory compliance, the EU GMP guidelines, Part 1, Chapter 1 [4] state that the attainment of regulatory compliance as part of the quality objective is "*the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company*".

According to Annex 16 to the EU Guidelines for GMP [7] the "*ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorisation holder (MAH)*".

Both statements clearly place the senior management in a position of responsibility.

That means that effective regulatory compliance needs the proactive support of the senior management. In a first place, a corporate compliance policy can help establish a compliance culture within the whole company.

In public, large pharmaceutical companies are often under greater observation than smaller competitors. This may be one reason why these companies are often ahead of smaller ones, with regard to company policies. The global policy of AstraZeneca regarding quality and regulatory compliance is a good example of such a serious company policy. According to the introduction of this policy, ”*the development, product licencing, manufacture, and distribution of active pharmaceutical ingredients, medicinal products and devices by the Company must be conducted in compliance with relevant International Codes and Standards, regulations for Good Laboratory Practice /General Laboratory Standard, Good Clinical Practice, Good Manufacturing/Distribution Practice and AstraZeneca Good Regulatory Practice. Local regulatory requirements, as well as the requirements of the countries to which products or data are supplied, must be satisfied”* [11].

Senior management may also influence efforts on regulatory compliance by ensuring that:

- the organisational units have sufficient suitably trained staff;
- suitable and sufficient equipment and facilities are present ;
- training programmes are in place in order to ensure understanding of the Quality Management System including an effective CC System.

This overview of responsibilities shows that the management must provide the infrastructure that ensures the successful establishment of a RegCom Department and compliance culture at the company. The top management must show leadership. This applies to large-, as well as to small- and medium-sized companies.

2.3 Getting There and Staying There - Achieving and Maintaining Regulatory Compliance

In practice, regulatory compliance actually means two distinct things – achieving compliance and maintaining it. Ideally, all authorisation documents have been carefully archived, maintained and regularly updated to reflect the current status and knowledge. That would mean that one is compliant and just has to continue that way in order to stay compliant. However, in reality the situation is often very different. For many reasons, it cannot be assumed that all registered information reflects the current status at all time. In the present case, *Example Pharma* aims to establish a RegCom Department. So far, regulatory compliance was just a small part of the RegA Department's daily business. Therefore, the first step for the RegCom Department is to achieve compliance by comparing all registered dossiers and documents with the current manufacturing documents, in order to make a gap analysis. The second step – ideally in parallel – is the development and implementation of a structured system, with the ultimate goal of staying compliant in the future.

2.3.1 How can regulatory compliance be achieved?

2.3.1.1 Regulatory oversight and checking registered information

As mentioned above, the starting point for achieving regulatory compliance is regulatory oversight. That means a comprehensive overview of all documents currently registered with regulatory authorities. In a second step, these documents, or registration dossiers, must be checked against the manufacturing instructions currently in use in the manufacturing units of the company.

2.3.1.2 Review of registered dossiers and the current production documentation

Depending on the size of a company or, rather, on the number of drug products and registration dossiers, the aim of getting an overview of all registered information and checking it against manufacturing protocols can cost a considerable amount of time and resources. This work can easily

exceed the personnel resources of smaller companies. In such a case priorities have to be set together with the QP and the senior management. Of course, quality, safety and efficacy of medicines are the top priority at any time, and regulatory compliance by itself is not negotiable; however, there is a set of core documents in each registration dossier that almost entirely reflects these requirements. Checking only the set of documents in Table 1, containing key parameters such as release specification and batch formula, can – in exceptional cases – make possible a rapid overview for an initial risk assessment.

Tab. 1: Priority documents for a compliance check.

3.2.S – Drug Substance	**3.2.P – Drug Product**
3.2.S.2.2 – Description of Manufacturing Process and Process Controls	3.2.P.1 – Description and Composition of the Drug Product
3.2.S.2.3 – Control of Materials	3.2.P.3.2 – Batch Formula
3.2.S.2.4 – Control of Critical Steps and Intermediates	3.2.P.3.3 – Description of Manufacturing Process and Process Controls
3.2.S.4.1 – Specification	3.2.P.3.4 – Control of Critical steps and intermediates (IPC)
3.2.S.4.2 – Analytical Procedures	3.2.P.4 – Control of Excipients
3.2.S.6 – Container Closure System	3.2.P.5.1 – Specifications
3.2.S.7 – Stability	3.2.P.5.2 – Analytical Procedures
	3.2.P.7 – Container Closure System
	3.2.P.8 – Stability

Registration dossiers of medicinal products already on the market for a long time require special attention. The probability of non-compliance increases with the age of the dossier.

Figure 2 shows a workflow describing the steps of a compliance check. The RegCom Department performs the check to identify gaps in compliance and the corresponding report includes and describes possible discrepancies.

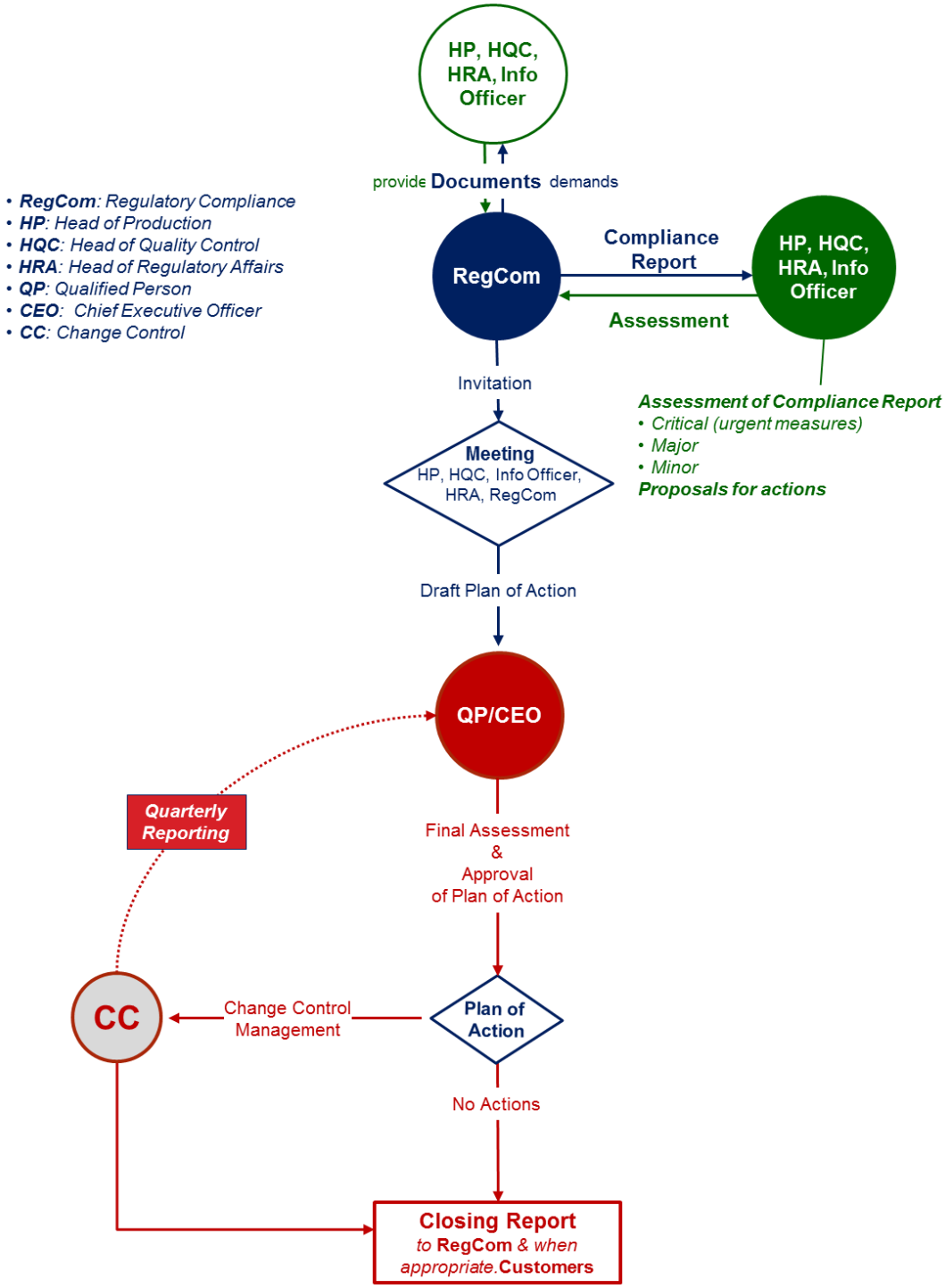

Fig.2: Workflow describing the process steps of compliance checks.

The report is then presented to the respective responsible persons (e.g. Head of Regulatory Affairs, Head of Quality Control, Head of Production, et cetera) for assessment. In addition, suggestions for remediation are made by these persons. Final evaluation of the discrepancies between registered information or manufacturing documents and proposed activities should be performed by the QP and the senior management.

2.3.1.3 Identifying and remediating compliance gaps

When checking registration dossiers for regulatory compliance, in order to make a comprehensible gap analysis, it is important to use a systematic approach. QP and senior management prioritise the products to be checked and the RegCom Department performs the compliance checks. An exemplary compliance sheet for a systematic compliance check can be found in Annex 1. The check form contains the general data of the product (name, strength, MAH, MA date, et cetera), as well as information about the manufacturing documents against which the check is performed. The main part consists of the individual sections of the dossier, structured according to the CTD format. If affected, the Head of Quality Control, the Head of Production, and the Head of Regulatory Affairs, as well as the information officer, should assess the findings of the compliance check and suggest activities for remediating compliance gaps. A representative of the senior management and the QP make the final assessment. Actions agreed upon for the remedy of non-compliant portions of the dossier or manufacturing documents will be handled in CC procedures.

2.3.2 Maintaining regulatory compliance

Maintaining regulatory compliance is a company-wide, ongoing process of managing changes to products. Even small changes can have a large influence on regulatory compliance, if these changes are not controlled and assessed properly. Therefore, the key element of managing changes is an effective CC management system by which all changes are evaluated.

2.3.2.1 Change control management

Introduction of changes that affect the manufacturing process and controls of the drug product or the active substances is a fundamental part of a product´s lifecycle. In order to ensure regulatory compliance, it is essential that an effective and comprehensive CC system, spanning all involved departments, is in place. According to Annex 15 of the EU GMP guidelines, a "change control system" is defined 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 that would ensure and document that the system is maintained in a validated state*" [12].

In this way, the CC procedure is a formal process for the assessment of all intended changes to a product or a system. Many quality-related changes affect several areas in parallel (e.g., regulatory requirements, GMP requirements and quality control). The CC system ensures that all relevant departments can evaluate and assess every change. As a result, implementation takes place in a controlled and coordinated manner and drug products are released in compliance with the relevant MA.

In general, short distances between departments in small- and medium-sized companies can be an advantage for an effective CC system. However, in order to benefit from these short distances, there must be SOPs in place, defining the whole process in detail, and an awareness of these procedures and documents. Because so many stakeholders are involved in the process of change management, the SOPs need to clearly state the roles and responsibilities of each, ranging from the manufacturing unit, QC Department, and QA Department to RegA Department, Pharmacovigilance Department and the RegCom Department.

2.3.2.1.1 Change control procedure

Figure 3 demonstrates the following process steps of a CC procedure.

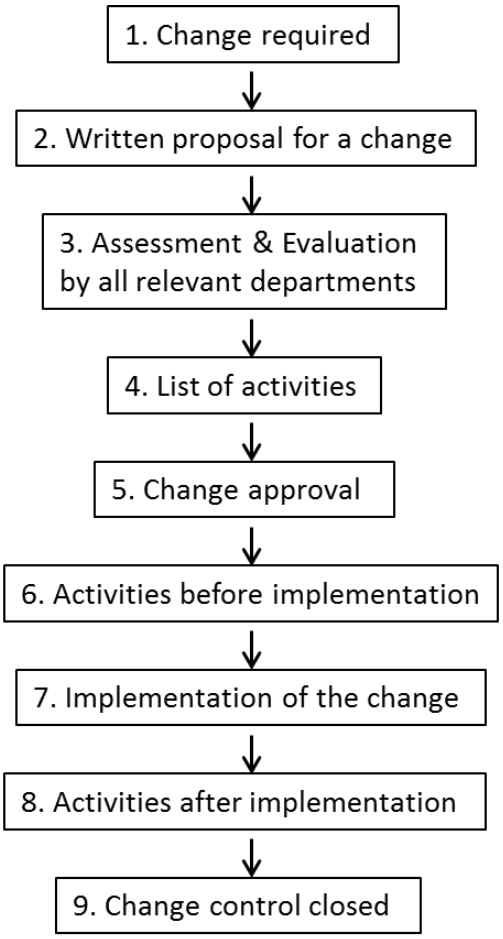

Fig.3: Flowchart describing the process steps of a CC procedure.

Step 1: A change is required in a technical department.

Step 2: The department where the change should be implemented writes a change proposal. This proposal contains a detailed description of the change, the possible influence on the product or the production process, and a justification.

Step 3: The different stakeholders perform an assessment and evaluation of the change, with regard to the potential impact on the current valid status.

Step 4: Based on previous assessment, activities and actions are defined that need to be carried out before and after the implementation of the change. The consequences of implementing the change must be described in detail, in order to enable a fact-based decision for or against the implementation of the change.

Step 5: A decision must be reached, whether or not to implement the change.

Step 6: Relevant parties will initiate activities to be carried out before implementation.

Step 7: After all these activities are completed, the change will be implemented.

Step 8: Afterwards, all activities to be carried out after implementation will be initiated.

Step 9: The CC procedure will be closed after confirmation that all activities have been completed.

In general, the QA Department is responsible for the company-wide CC procedure, rather than the RegCom Department. However, this procedure enables the RegCom Department to track and monitor the current status of changes in the whole company. Moreover, all affected departments are involved in the implementation process, which also contributes to regulatory compliance. Depending on a company´s structure, regulatory assessment of CCs can either be performed by the RegA Department or the RegCom Department.

2.3.2.2 Tools and databases

There are many commercial regulatory (compliance) management software solutions. Small companies in particular should analyse their precise needs. There is an extensive range of functions and costs.

As it is not uncommon for the approved details of a product to differ from country to country, the basis should be a regulatory database that contains the detailed regulatory status and product information for each submitted product

for all countries. The value of such a powerful tool crucially depends on the accurate maintenance of the data. Decisions based on outdated or incorrect data can lead to serious consequences for the concerned product. Designing and implementing appropriate SOPs and checklists can help achieve uniformity of performance of maintenance, and reliability of the data as well as data integrity.

2.3.2.2.1 Tracking, tracking, tracking

The continually evolving regulatory environment results in an ongoing and increasing number of changes and variations. Tracking of regulatory procedures and the current regulatory status of all products is the foundation of regulatory compliance. In order to track the various ongoing procedures, it is highly advisable to use a tracking tool. Regulatory databases often have the function of tracking submissions, which should be used in this case. Comprehensive tracking of all relevant regulatory procedures reduces the probability of non-compliance.

If one is working without a regulatory database, or does not have an integrated tracking function, there are also several stand-alone solutions. Depending on the size of the company and the number of regulatory activities and submissions per year, there are different possibilities to track activities. The easiest and cheapest way to handle and track a small number of submissions is to use a simple self-made Excel spreadsheet. Another common solution in small- and medium-sized companies is a company-specific, self-developed database. However, keeping such a system current is comparatively complex and can exceed the personnel resources of smaller companies in the long term. Therefore, commercial software tracking solutions should also be considered – especially when tracking more than a few submissions per year. There are a large variety of commercial tracking tools available. Examples are: drugTrack (Lorenz LifeSciences), ViewPoint (Octagon), MPDmanager (EXTEDO) or Regulatory Tracker (CSC).

2.3.2.3 Regulatory intelligence – gathering and analysing regulatory information

A definition of the term regulatory intelligence (RI), proposed by two Regulatory Intelligence Network Groups (RINGs) in association with the Drug Information Association (DIA), says:

"*Regulatory intelligence is the act of processing targeted information and data from multiple sources, analysing the data in its relevant context and generating a meaningful output – e.g. outlining risks and opportunities – to the regulatory strategy. The process is driven by business needs and linked to decisions and actions"* [13].

In order to ensure regulatory compliance, it is of great importance to have current knowledge of all relevant regulatory requirements in the regions of interest. Knowing these requirements enables the company to identify the regulatory requirements necessary to stay compliant. Thus, RI is one prerequisite for the ability to ensure regulatory compliance and is increasingly important for regulatory compliance. However, RI activities often depend on each company´s structure and size. Originator companies, with strong research and development activities across different therapeutic areas on a global level, have different needs concerning RI than smaller companies, with a manageable portfolio of medicinal products. In general, large pharmaceutical companies have an RI team scanning and routinely checking the global regulatory environment (e.g. reviewing homepages of relevant health authorities, looking for emerging regulatory trends and using software systems and commercial databases). As relevant information and topics come from diverse sources, gathering them is a time-consuming process. For smaller companies without the financial resources for a dedicated RI team, it should be one basic part of a regulatory affairs professional`s job to keep abreast of the latest requirements from authorities. There are a number of ways to access this information, which is often distributed in newsletters and bulletins or directly by email:

- Membership in a pharmaceutical industry organisation such as the Bundesverband der Arzneimittel-Hersteller e.V. (BAH), the Bundesverband der Pharmazeutischen Industrie e.V. (BPI) or the “International Federation of Pharmaceutical Manufacturers” (IFPMA). Such associations represent the interests of large and small companies. The BAH, for example, regularly provides information about relevant regulatory and legislative procedures at the national and European level and offers scientific and practical advice [14].

- Membership in a regulatory affairs professional association such as the German Society for Regulatory Affairs (DGRA), The Organization for Professionals in Regulatory Affairs (TOPRA), Mid-European Society for Reg. Affairs (MEGRA) or Regulatory Affairs Professionals Society (RAPS). The DGRA, for example, aims to promote and provide training, standardization, cooperation, information, news and the exchange of ideas within the field of regulatory affairs [15].

- Commercial services that provide up to date regulatory affairs information on regulations, guidelines, et cetera – often enhanced with information on interpretation and applicability. Examples of service providers are: ERA Consulting (European Regulatory Intelligence) or European Drug Regulatory Affairs Consulting (EUDRAC).

- The usage of a comprehensive commercial database of regulatory information. Well-known examples are “Thomson Reuter Cortellis Regulatory Intelligence” or TARIUS. They also combine subject areas and offer intelligence reports and summaries.

- Newsletters and so-called RSS (Really Simple Syndication) Feeds, directly from the homepages of the diverse regulatory authorities. RSS Feeds immediately provides notification when new or modified documents on a specified subject are published on the authority´s

homepage. Regular newsletters also share such news. Most of the European authorities offer this kind of service, for free. The BfArM, for example, even has a Twitter account for publishing news [16]. In this way, gathering RI information can be partly automated. Particularly noteworthy is the news bulletin for small- and medium-sized enterprises of the EMA. The "*newsletter for micro-, small- and medium-sized enterprises (SMEs), published four times a year, provides key updates to SMEs on the European regulatory environment*" [17].

- Some new approaches also provide information on the changing regulatory environment. Many regulatory-related groups or web blogs can be found on social media and networking sites. They are often lead by regulatory professionals and most of these sites have a discussion forum enabling the exchange of intelligence and advice on regulatory matters. A good example of a regulatory oriented blog is "*Eye on FDA"* [18].

To determine which of these options is the best, or most suitable, a medium-sized company should take into account that RI is not a one-time action, but a process that lasts as long as the company sells products. Financial expenses should not be overlooked. As most pharmaceutical companies are already members of at least one pharmaceutical industry organisation, the regulatory information from this side should build the foundation. The membership in a professional regulatory affairs association is also more or less mandatory and not cost-intensive. Checking and assessing regulatory news and information from these sources on a regular basis, in combination with information from the homepages of the relevant authorities, it is possible to stay current with a minimum expenditure of time and effort. It is also worth reviewing the possibilities that social media sites provide with regard to RI.

And last but not least, if regulatory information for distinct countries and regulatory authorities is required, the services of consultants can be taken into account.

2.4 How to measure regulatory compliance?

Most companies – larger and smaller ones, as well – prefer measurable outcomes. There are a number of possible methods to evaluate the performance of regulatory compliance activities.

2.4.1 Periodic compliance report to management

The basis for the assessment of efforts to achieve and maintain regulatory compliance should be a periodic report to the organization's CEO. This report should include the outcome of compliance checks performed, as well as any actions taken to remediate compliance gaps.

2.4.2 Information for PQRs

In 2006, Chapter 1 of the EU GMP guidelines introduced the so-called Product Quality Review (PQR) [4]. Accordingly, this kind of quality review should include *"A review of Marketing Authorisation variations submitted/ granted/refused, including those for third country (export only) dossiers"*.

In this way, the PQR and the annual filing of regulatory data can be an important tool to check and control the quality of regulatory compliance in a company. The regulatory information is provided by RegA. Rapid and uncomplicated data communication indicates a good working compliance system.

When MAHs and manufacturers are not identical, but different companies, responsibilities with regard to regulatory information in PQRs must be clearly shared via a responsible demarcation agreement. This is also underlined in the requirement that "*The manufacturer and, where different, marketing authorisation holder should evaluate the results of the review*" [4].

2.4.3 Internal self-inspections

Internal self-inspections on a regular basis also measure regulatory compliance. Like self-inspections for GMP, they play an important role in regulatory compliance. The introduction of a schedule of regulatory compliance inspections can help in both supervising the company´s adherence to the

current MAs and proposing necessary improvements. The self-inspection can be conducted as either a product-related or a systemic inspection. A product-related inspection generally includes the examination of product-specific documentation against the related batch documentation, while the systemic approach examines the different processes developed to ensure compliance. Both approaches are useful and can be performed in small as well as large companies without great financial output.

The final audit report should include all gaps identified between the registered information and the manufacturing documents, as well as any gap in the requirements laid down in the different legislations.

2.5 How is regulatory compliance likely to evolve in the future?

Looking at the company's efforts, maintaining regulatory compliance today is a resource intensive process that tries to avoid or minimize non-compliance by optimizing resources, training involved staff and retrospective analyses of data. Trends with an impact on regulatory compliance are most often also trends in regulatory affairs. That is why the perspective on the future of regulatory compliance focuses on regulatory affairs, too.

Over the last years, the number and complexity of regulatory requirements has increased enormously. It can be assumed that this trend will continue in the near future. Keeping up with these developments is a challenge common to all pharmaceutical companies and their RegCom Departments.

An opposite trend in regulatory affairs is the harmonisation of international regulations and guidelines – by the ICH, for example. This development has the potential to reduce the complexity of regulatory requirements, with benefits for regulatory compliance tasks in the long term. Currently, a new ICH guideline is under development (ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management), which is intended to facilitate the management of post-approval Chemistry, Manufacturing and Controls

(CMC) for currently-marketed chemical, biotechnological and biological products [19].

According to the corresponding concept paper endorsed in 2014, two major topics that will be addressed are:

- the regulatory dossier;
- post-approval change management plans and protocols.

With regard to the regulatory dossier, the aim is to reduce the appropriate level of detail and information necessary for regulatory assessment and inspection, in order to create a more enabling post-approval change management system. Furthermore, the concept paper states that "*the concept of a post-approval management plan that can be used to proactively identify post-approval changes and the mechanism to submit and assess these changes by regulatory authorities (Assessors and Inspectors)*" should be introduced [19]. The new ICH Q12 guideline will lead to greater flexibility in post-approval lifecycle management, with the possible result that more CMC changes can be submitted as "do and tell" variations. CMC changes will be more transparent, leading to a more efficient change management.

Another current trend not only in the pharmaceutical industry, but across all industries, is "big data". Precise predictions are difficult; however, it is imaginable that "big data" will have an impact on RI issues by speeding up the collection and analyses of relevant information. Small- and medium-sized companies, as well as big companies, will benefit from this development.

One increasing trend in the pharmaceutical industry that will not apply to regulatory compliance is the trend towards outsourcing. Regulatory compliance is one of the few exceptions in this area. It is hardly possible, or even reasonable, to outsource regulatory compliance actions. In order to ensure compliance, not only the RegCom Department is responsible; a company-wide culture of compliance is required, and many more departments, such as the RegA Department, QA Department, or Quality Control, bear responsibility.

Above all, these trends, and new and updated regulations, ensure that regulatory compliance will continue to be a never-ending journey.

3 Conclusion

Regulatory compliance indicates the conformity of the manufacturing instructions with the details deposited in the MA. After approval by a regulatory authority, the manufacturing process of a medicinal product represents the current technological standard of manufacturing. It is quite easy to be compliant and produce the medicinal products according to the MA at the moment of approval. However, during its life cycle, each drug product undergoes a number of changes. The regulatory authorities must be notified of any amendment to the registered information, any deletion and any change made to the dossier. Small- and medium-sized companies must find methods to handle the challenges that accompany constant shifts and changes in the regulatory environment. When establishing a RegCom Department, many aspects and responsibilities have to be considered.

Regulatory compliance actually refers to two major responsibilities: achieving compliance and maintaining it. The RegCom Department plays a central role in achieving and maintaining regulatory compliance; however, it is not able to ensure regulatory compliance alone by itself – a culture of compliance within a company is also needed. Many stakeholders carry responsibility: the QP, the senior management, RegA Department, Quality Control, QA Department and the information officer.

In order to achieve regulatory compliance, the first step for a newly established RegCom Department is to get a comprehensive overview of all documents currently registered at regulatory authorities, followed by a gap analysis in combination with a compliance check against the manufacturing instructions. In a subsequent step, discrepancies must be remediated.

In order to maintain regulatory compliance, an effective CC system and clear understanding of responsibilities in each department is key to success. Additionally, continuous tracking of all regulatory procedures – ideally through

suitable compliance management software solutions – should ensure compliance.

A further aspect of maintaining regulatory compliance is the need for current knowledge about all relevant regulatory requirements in the regions of interest. Regulatory intelligence is a pre-requisite for the ability to ensure regulatory compliance. Usually, relevant information and topics come from diverse sources and gathering them is a time consuming process, especially for small- and medium-sized companies. However, using usually freely available information from websites of regulatory authorities and pharmaceutical industry organisations, as well as regulatory affairs professional associations, it becomes possible to stay current with a minimum expenditure of time and effort.

In general, the activities of the RegCom Department depend on a company's structure and organization, and there may be some differences in the way large and small companies deal with compliance challenges; however, there are also similarities. Small- and medium-sized companies may have less financial and human resources, but this often correlates with a smaller number of products and effort. In the end, these companies can assure regulatory compliance equally well, with sufficient effort in terms of finance and personnel, when developing and implementing a systematic approach.

4 References

1) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, as amended

2) Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz – AMG) - Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005, as amended

3) Verordnung über die Anwendung der Guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft (AMWHV), as amended

4) Eudralex - EC, The Rules Governing Medicinal Product in the European Union Volume 4 - Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use – Chapter 1, 2013

5) Commission Regulation (EC) No 1234/2008 of 24 November 2008, as amended

6) www.ich.org/about/mission.html

7) Annex 16 to the EU Guide to Good Manufacturing Practice: Certification by a Qualified Person and Batch Release, 2016

8) Eudralex - EC, The Rules Governing Medicinal Product in the European Union Volume 4 - Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use – Chapter 7, 2013

9) Eudralex - EC, The Rules Governing Medicinal Product in the European Union Volume 4 - Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use – Introduction, 2011

10) Eudralex - EC, The Rules Governing Medicinal Product in the European Union Volume 4 - Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use – Chapter 2, 2014

11) http://docplayer.net/12830351-Astrazeneca-global-policy-quality-and-regulatory-compliance.html

12) Annex 15 to the EU Guide to Good Manufacturing Practice: Qualification and Validation, 2015

13) Regulatory Intelligence Working Group, Regulatory Intelligence, 2010

14) www.bah-bonn.de/about-us/

15) www.dgra.de/english/dgra/purpose_and_aims.php

16) www.bfarm.de/DE/Servicefunktionen/Twitter/_node.html

17) www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000331.jsp#section2

18) www.eyeonfda.com

19) Final Concept Paper ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. 28 July 2014.

Annex 1

Annex 1

COMPLIANCE REPORT

I. Regulatory information

Product:
Strength:
Dosage form:
API:
API manufacturer:
Finished product manufacturer:
Country*:*
MA number:
MA date:
MA Holder:
Approved Pack sizes:
Co-Distributer:
Regulatory status of the product (e.g. Pending authorisation, approval):
RMP (y/n):
Dossier form (eCTD / NTA / NeeS):
Contact person for future communication (name, email, telephone number):

II. Circulation list

HP / HQC / IB / QPPV / HRA	Documents screened, assessed and, if necessary, actions proposed	
	Date	**Signature**
Head of Production (HP)		
Head of Quality Control (HQC)		
Head of Regulatory Affairs (HRA)		
QPPV		
Information Officer (IO)		

III. Information on Module 3

DRUG SUBSTANCE

Ref. CTD		compliant
3.2.S.2.2	***Description of Manufacturing Process and Process Controls***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	

Ref. CTD		compliant
	☐ Critical ☐ Major ☐ Minor ☒ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.S.2.2	***Description of Manufacturing Process and Process Controls (Flowchart)***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	

Ref. CTD		compliant
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.S.2.3	***Control of Materials***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	

Ref. CTD		compliant
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.S.2.4	***Controls of Critical Steps and Intermediates (IPC)***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.S.4.1	***Specification***	**Y ☐ N ☐**
RegCom	Documents checked:	

Ref. CTD		compliant
	Remarks:	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.S.4.2	***Analytical Procedures***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	

Ref. CTD		compliant
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.S.6.	***Container Closure System***	**Y ☒ N ☐**
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	

Ref. CTD		compliant
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.S.7.1	***Stability Summary and Conclusions***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.S.7.2	***Post-approval Stability Protocol and Stability Commitment***	**Y ☐ N ☐**

Ref. CTD		compliant
RegCom	Documents checked: --	
	Remarks:	

Stability data on API		
No. of batches:		
Batch size:	Batch No	Batch size:
Commercial batch size:		
Storage conditions.		
Data available for 25°C/60%	☐ 0 ☐ 3 ☐ 6 ☐ 9 ☐ 12 ☐ 18 ☐ 24 ☐ 36 ☐ 48 ☐ 60	
Data available for 30°C/65%	☐ 0 ☐ 3 ☐ 6 ☐ 9 ☐ 12 ☐ 18 ☐ 24 ☐ 36 ☐ 48	
Data available for 40°C/75%	☐ 0 ☐ 3 ☐ 6	
Primary packaging material:		

HP	*Assessment:*
	☐ Critical ☐ Major ☐ Minor ☐ no deviation
	Actions (Proposal):
HRA	*Assessment:*
	☐ Critical ☐ Major ☐ Minor ☐ no deviation
	Actions (Proposal):
QP /	*Final Assessment:*

Sen.Management	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation
	Actions:

DRUG PRODUCT

Ref. CTD		compliant
3.2.P.1	***Description and Composition of the Drug Product***	**Y ☐ N ☒**
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.3.2	***Batch Formula***	**Y ☐ N ☒**

Ref. CTD		compliant
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.3.3	***Description of Manufacturing Process and Process Controls***	**Y ☐ N ☒**
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	

Ref. CTD		compliant
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.3.3	***Description of Manufacturing Process and Process Controls (Flowchart)***	**Y ☐ N ☒**
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	

Ref. CTD		compliant
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.3.4	***Controls of Critical steps and intermediates (IPC)***	**Y ☐ N ☒**
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.4.	***Control Excipients***	**Y ☐ N ☒**

Ref. CTD		compliant
RegCom	Documents checked:	
	Remarks:	
HP	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.5.1	***Specifications***	**Y ☐ N ☒**
RegCom	Documents checked:	

Ref. CTD		compliant
	Remarks:	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.5.2	***Analytical Procedures***	**Y ☐ N ☒**
RegCom	Documents checked:	
	Remarks:	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	

Ref. CTD		compliant
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.7	***Container Closure System (Primary Packaging)***	**Y ☒ N ☐**
RegCom	Documents checked:	
	Remarks:	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP /	*Final Assessment:*	

Ref. CTD		compliant
Sen.Management		
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.8.1	***Stability Summary and Conclusion***	**Y ☐ N ☒**
RegCom	Documents checked:	
	Remarks:	

Ref. CTD		compliant

Stability data on finished product:

No. of batches:	
Batch size (stability):	
Commercial batch size:	
Storage conditions.	☒ 25°C/60% ☐ 30°C/65% ☒ 40°C/75%
Data available for 25°C/60%	☐0 ☐3 ☐6 ☐9 ☐12 ☐ 18 ☐ 24 ☐ 36 ☐ 48 ☒ 60
Data available for 30°C/65%	☐0 ☐3 ☒6 ☐9 ☐12 ☐ 18 ☐ 24 ☐ 36 ☐ 48 (inverted)
Data available for 40°C/75%	☐0 ☐3 ☒6
Primary packaging material:	
Proposed shelf life:	

Bulk- stability data:

Are bulk-stability data available: yes ☐ no ☐

Storage conditions: °C, % RH

Duration: months

Stability after first opening:

Are such stability data available: yes ☐ no ☐

Storage conditions: 25 °C / 60 % RH

Duration: months

Ref. CTD		compliant
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
	Date: Signature:	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
3.2.P.8.2	***Post-approval Stability Protocol and Stability Commitment***	**Y ☐ N ☐**
RegCom	Documents checked: ---	
	Remarks:	
HQC	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	

Annex 1

Ref. CTD		compliant
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (Proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	

IV. Texts

Ref. CTD		compliant
1.3.1	***SmPC***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
1.3.1	***PIL***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	

Ref. CTD		compliant
	Actions (proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
1.3.1	***LABIP***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	
1.3.1	***LABOP***	**Y ☐ N ☐**
RegCom	Documents checked:	
	Remarks:	

Ref. CTD		compliant
HRA	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions (proposal):	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	

V. Pharmacovigilance		
Ref. CTD		compliant.
	PSUR	**Y ☐ N ☐**
RegCom	Checked documents.:	
	Remarks:	
QPPV	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	

V. Pharmacovigilance		
Ref. CTD		compliant.
	DSUR	**Y ☐ N ☐**
RegCom	Checked documents.:	
	Remarks:	
QPPV	*Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
QP / Sen.Management	*Final Assessment:*	
	☐ Critical ☐ Major ☐ Minor ☐ no deviation	
	Actions:	

VI. Summarized Actions		
Ref. CTD	Issue	Actions

VII. Compliance Report			
Remarks:			
RegCom	Prepared:	Date:	Signature:
	Checked:	Date:	Signature:

VIII. Report on compliance check and actions		
Approved QP:	Date:	Signature:
Approved Sen. Management:	Date:	Signature:

IX. Closure of Compliance Check		
RegCom	Date:	Signature:.

Eidesstattliche Versicherung

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

Ort, Datum	Dr. Christian Strube