



EUROPEAN INDUSTRIAL PHARMACISTS GROUP

Guide to Good Regulatory Practice

Acknowledgments:

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List of abbreviations

CTAs : Clinical Trial Application

CTD: Common Technical Document

eCTDs :electronic Common Technical Document

GRP: Good Regulatory Practice

INDs: Investigational New Drug application

MA: Marketing Authorisation

PIL: Product Information Leaflet

PIM-activities: Product Information Management activities

PSURs: Periodic Safety Update Reports

QA: Quality Assurance

QC: Quality Control

QP: Qualified Person

QPPV: Qualified Person for Pharmacovigilance

RAD: Regulatory Affairs Department

RSD: Regulatory Strategy Document

SPC: Summary of Product Characteristics

TQM: Total Quality Management

GUIDE TO GOOD REGULATORY PRACTICE

Good Regulatory Practice (GRP) guidelines define the role and position of the Regulatory Affairs Department (RAD) within the organisation.

Appropriate and effective management of the regulatory process is mandatory for bringing a medicinal product or a medical device to the market and keeping it there in compliance with legal, scientific, ethical and administrative requirements. It is also fundamental to ensure the compliance of the relevant company's activities to the local and global regulations in terms of official and company regulations. The involvement of GRP in the concept of Total Quality Management (TQM) is essential from the initial development phase of the product and continues for its entire life

Efficient RAD organisation and working methods are mandatory in order to ensure adaptation and effectiveness towards continuous changes and increasing complexity of regulation requirements especially as RAD operates numerous interfaces within a pharmaceutical company.

RAD skills for communication and communicating information to other departments are a key parameter to ensure compliance with regulatory requirements, which involves particularly aspects of Regulatory Intelligence (see section 1.4).

Implementation of Good Regulatory Practice essentially contributes continuous Total Quality Assessment of all aspects of regulatory affairs and is the essential link between each discipline in Total Quality Management.

1. ACTIVITIES

The activities of RAD, depending on each company's structure and organisation, start at the initial development of medicinal products and continue through until the launch of the product. Once launched the RAD is fully involved in Marketing Authorisation (MA) maintenance and post-marketing activities.

GRP is based on sound science, coupled with organisational ability, to steer and maintain an application through the legislative framework which allows a Competent Authority to reach a scientific decision.

Pivotal to GRP is the need to keep abreast of world-wide legislation including potential changes and the interpretation of possible consequences in the event of failure to meet requirements. The communication of all relevant information including its evaluation and relevance for the existing product portfolio to all interested parties within the organisation is a pre-requisite to GRP.

1.1 Product Development

RAD should be involved in the creation and evolution of all aspects of research and development plans and advise departmental heads and project managers on the current requirements and any upcoming legal changes with potential impact for registration.

RAD should give advice for optimising development plans, in particular by an accurate interpretation of the requirements of the existing guidelines, which may ideally be done within the scope of a Regulatory Strategy Document (see section 1.2).

RAD is in charge of organising scientific advice with Competent Authorities on any aspect of the future Marketing Authorisation (MA) dossier and of coordinating with the other departments the briefing document including the questions and company's positions.

1.2 New Registrations

RAD is responsible for proposing the best registration strategy, taking into account the possible registration procedures, the impact of intellectual property rights, the particularities of the product and the scientific content of the different parts of the dossier.

RAD should prepare a Regulatory Strategy Document (RSD) which will contain all the essential global regulatory aspects of product development incl. scientific advice meeting with Competent Authorities, submission strategies (timing, responsibilities, choice of countries, free sale certificates and answers to Authorities' questions, intellectual property), dossier updates (variations and safety), dossier renewals, Periodic Safety Update Reports (PSURs) planning and a contingency plan. The document should address the proposed labelling also for discussion with Marketing and Sales and its impact on discussion with pricing and reimbursement authorities in the different countries. The RSD should be reviewed and updated on a regular basis.

RAD should participate in interdisciplinary project teams and collect and verify all scientific and technical product information needed to prepare investigator's brochures and clinical approvals, such as CTAs and INDs, as well as the paediatric investigational plan.

RAD should ensure that all activities related to obtaining Marketing Authorisations comply with existing legislation i.e. laws, regulations, directives and guidelines taking into account particular requirements of the intended regions and countries where Marketing Authorisations are proposed to be submitted. Consideration must be given on a pro-active basis to such recommendations, comments and developments as they arise.

RAD should establish ethical, practical, technical and regulatory standards to be laid down in policies and standard operating procedures (SOP) which specify the

responsibility of each staff involved, describe the processes and guarantee that the content of dossiers is in compliance with existing legislation and of the standard needed to obtain registration of the product (see section 4).

RAD is responsible for writing, co-writing, editing and/or authorising all documents for use in registration dossiers or communication with Authorities e.g. manuscripts, expert reports, methods of use, standard advice for patients and labels.

RAD should strive for world-wide implementation of harmonised prescribing information.

RAD should be responsible for the accurate planning and coordination of compiling the dossier.

RAD should take care of compilation, translation, reproduction and shipment of new dossiers to the relevant countries. Account should be taken of the possibilities for electronic submission of the dossier or parts of it, especially in terms of submission of eCTDs and submission of labelling information as part of PIM-activities.

RA is responsible for ensuring administrative validation, chasing up the dossier throughout the assessment and anticipating the possible questions from the Competent Authorities in order to optimise the timing, the quality of the answers and the Marketing Authorisation (MA) approval and Summary of Product Characteristics (SPC) wording.

Queries from registration authorities should be answered in a consistent manner and within the time limits set by the agency when indicated and in any case according to internal guidelines.

Status reports should be issued regularly in order to provide information on the world-wide registration situation.

1.3 MAINTENANCE OF EXISTING REGISTRATIONS

All existing dossiers should be carefully archived, maintained and regularly updated to reflect the current standards and knowledge.

Variations and change control: management of change control forms an important element of GRP. Such changes include product data or specifications, manufacturing or analytical methods, facilities or suppliers as well as line extensions, additional indications etc.. All such changes have to be communicated to the appropriate regulatory authorities in accordance with the respective legal requirements of the countries affected.

RAD and quality assurance department should liaise closely on all aspects affecting variations and change control to ensure timely and appropriate answers

to the queries raised by the Competent Authorities and to ensure regulatory compliance.

It is the responsibility of RAD, the Qualified Person and QA to ensure manufacturing and QC are conforming, at all times, with the registration file and the authorisation granted (regulatory compliance).

RAD should assure regulatory compliance by the manufacturer, packager and marketing department.

Changes of SPC and/or patient leaflet labelling: such changes might be initiated by marketing or medical departments, but can also be requested for new safety data. For these changes RAD and medical / pharmacovigilance will liaise closely for the preparation and timely implementation once the revised wording is approved.

RAD should establish, in close collaboration with the Drug Safety department and the Qualified Person for Pharmacovigilance, renewal and PSURs planning on a yearly basis for each product and collect all the information needed for their submission, also taking into consideration post-approval commitments or follow-up measures.

RAD should ensure that activities related to post marketing studies are carried out in compliance with, and reported according to, existing legislation

It is the duty of RAD to inform the Regulatory Authorities of any pharmacovigilance issue and to implement and file the necessary data into the official documents. This will be done in close cooperation with the Drug Safety department and the Qualified Person for Pharmacovigilance.

1.4 REGULATORY INTELLIGENCE

RAD should have a system in place and ideally a specific organisation to ensure the tracking without delay of all the versions, either approved or as a draft for comment, of regulations, guidelines, and concept papers.

A systematic review of the relevant world-wide legislation, guidelines, discussion papers, codes of conduct etc. should be made within the timeline with 2 objectives:

1. RAD should interpret the scope and possible consequences arising from such legislation and codes and inform the organisation accordingly:
 - RAD should be aware and retain all relevant world-wide legislation and codes of conduct or guidelines which may affect the activities of the organisation

- RAD is in charge of the interpretation, evaluation of the impact on the company's portfolio and decision of the implementation when relevant. Close cooperation with the appropriate departments within the company is vitally important
- RAD should inform, explain, describe the content of the regulatory texts to the other appropriate departments concerned
- RAD should also ensure and coordinate the necessary activities arising from changes to ensure that compliance with regulations will be met.

2. RAD should furthermore comment on new draft guidelines / draft legislation and take an active role in participating in the outcome of final regulatory documents. For this purpose, RAD will preferably join pharmaceutical associations to represent the needs of pharmaceutical industry on a higher level.

Records should be kept and made accessible of all such legislation and codes.

2. PERSONNEL

There should be sufficient personnel at all levels within the organisation with the ability, education, training, experience and appropriate professional skills to perform the tasks assigned to them.

All personnel should be trained regularly in the tasks assigned to them. Such training should be verified to ensure that all persons possess sufficient skill and knowledge of the procedures and policies of the organisation.

Ideally, all graduate personnel should have a multidisciplinary background, scientific expertise, communication and negotiation skills, regulatory knowledge, planning capacity and be able to work in teams, to organise multidimensional projects and to work in a multidimensional manner.

Standard operating procedures should be designed to deal with communication and flow of information.

The responsibilities of the Qualified Person (QP) and the Qualified Person for Pharmacovigilance (QPPV) in relation to the RAD should be clearly defined. These responsibilities should be explained and written into the job description for each QP together with any training and education required on product registration.

Key personnel in responsible positions should be accountable for authorising procedures and tasks and have adequate supporting staff. Persons should be designated to deputise for them in their absence.

3. PREMISES

Premises should be designed and maintained in good order to provide sufficient space to suit the activities being carried out, should allow efficient work flow and should permit effective communication and supervision.

Physical and non-physical working conditions e.g. ergonomics, environmental factors, stress, etc., should be such that the quality of the activities carried out is influenced in a positive manner.

All necessary equipment for the activities to be performed efficiently should be provided, e.g. computer hard and software, printers, copiers, archives and means of communication.

Personnel should be instructed in the proper use of equipment and the risk of errors occurring should be minimised by effective systems.

4. QUALITY ASSURANCE

A good quality management system should be set up by RAD for all the activities under its responsibility.

4.1 PROCEDURES

Procedures should be laid down in writing in standard operating procedures, authorised by appropriate staff and communicated to the relevant personnel. They should be readily available and be checked and updated regularly.

Standard operating procedures should be adapted and /or renewed in the case of new or amended standards.

Standard operating procedures should be established on how to implement relevant legislation and codes and the consequences for the organisation's policy. RAD should develop policies for situations in which changing legislation and codes make it necessary or desirable to adapt to it.

Procedures should cover the different areas in RA to specify responsibilities and organisation (preparation MAA, regulatory development plan, development of SPC and PIL, preparation of CTD, compilation of Regulatory Application file, change control, preparation of response documents, maintenance of MA, preparation of renewal etc).

4.2 SELF-INSPECTION

Regular self-inspections should be performed by RAD in cooperation with QA to ensure compliance with the relevant regulations by staff at all levels and to check

the compliance with the procedures and, if relevant, to adapt the procedure according to current practices.

4.3 TRAINING

An initial training program should be in place for new employees to ensure a good understanding and therefore compliance.

All RAD staff should be regularly trained in the procedures, to ensure a good understanding and therefore compliance.

Each new procedure or an update of an existing procedure should also lead to a specific training on the changes implemented, which may be training in reading also.

Understanding of all the aspects of the procedure should preferably be assessed by knowledge control.

A tracking system of the annual training should be organised.

5. DOCUMENTATION

Good documentation is essential for the whole organisation and especially for the local RAD. All documentation should be prepared with great care and clearly written to prevent errors that can arise from oral communication.

Documents should contain all the information necessary for proper use.

Title, type and objectives should be unambiguous and clearly stated in standard operating procedures.

All documentation should be reviewed regularly and kept up to date. Amendments should be dated, authorised and signed by the appropriate personnel.

An appropriate system should be in place to ensure traceability of documents and their different versions, answers to the Competent Authorities, changes in SPC, variations etc. This may best be achieved by help of a commercially available electronic document management system.

All documentation should be securely stored. When prepared or stored electronically or optically error free validated processing programmes should be used. Data should be protected against loss or damage, e.g. use of backup procedures. Only authorised personnel should be allowed to enter or change data.

Documentation should be readily accessible to regulatory affairs personnel.

6. ARCHIVING

A good archiving system is mandatory. It should be described in a procedure which will describe, both for the documentation and the electronic documents, the archiving plan, the management of the different versions, the answers to questions from Competent Authorities, the traceability and the measures taken to ensure regular backup.

7. COMMUNICATION

Due to the multidisciplinary activities under the responsibility of RAD, close relationship with almost all the other departments (pre-clinical, medical, pharmacovigilance, production, quality control, quality assurance, marketing and sales etc.) is needed.

RAD skills for communication and communicating information to other departments, Competent Authorities, Professional Associations are a key parameter to GRP in terms of compliance with regulatory requirements, lobbying, negotiation, effective relationship with external bodies.

RAD should ensure that communication lines are as short as possible and no unnecessary delays in transfer of information occur.

Procedures should be developed to streamline internal and external flow of information. Classification should take place according to the type and source of information, the persons responsible for co-ordination and dissemination and the actions expected of receivers.