
Regulatory Intelligence
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The articles contained in this e-book have been written by members of our expert staff. These articles, and many more, are available online at the **Acorn Regulatory** website.

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Welcome

Welcome to the first edition of 'Regulatory Intelligence'. Our team, based at our offices in Ireland and sites across the world, is regarded as one of the leading regulatory affairs teams in Europe. They have worked on many projects and have amassed a level of expertise that, we believe, is unrivalled.

In **'Regulatory Intelligence'** we are sharing some of our expertise on issues such as quality systems for the pharmaceutical sector, clinical trials, the need to consult with target patient groups on package leaflets and pharmacovigilance audits.

I hope that you find this useful and informative.

Dr. Gemma Robinson,
Managing Director,
Acorn Regulatory.

How Do You Translate Your Non-EU Dossier For The EU Market?

Gillian Prendergast,
Regulatory Affairs Advisor

Regulatory professionals will tell you that when you're developing your new medicinal product your developmental R&D strategy should have your regulatory strategy firmly in sight. How does a smaller company achieve this when they have limited resources and perhaps limited regulatory expertise? The answer is "it is possible, but you need correct advice"

The Issue for SME's

SME's tend to develop a product with one region/market in mind and then once regulatory approval in that market is achieved, their focus moves to registration in a different region. SME's are then left with the task of trying to tailor their existing dossier for the proposed region. This can be a difficult, but with the correct regulatory assistance it can be done successfully.

In Europe the first step for any new registration is to ascertain the legal basis of the application. The legal basis will dictate the dossier content, market exclusivity and paediatric requirements in a very profound way. Directive 2001/83/EC as amended outlines the various "legal basis" that a new application can adopt. It is also important to note that in Europe the legal basis is independent of the procedural route that your company wishes to take. Whether you decide the Centralised, Decentralised or National route, your choice in legal basis will remain the same.

In the main, only one legal basis will be appropriate whereby your product only fits into one category. What happens when your product doesn't fit nicely into one of the legal basis categories. You can be left navigating the intricacies of Directive 2001/83/EC and finding more questions than answers.
When your product is an established active substance where there are no current patent's, but includes a new dosage form, strength, route of administration, a new indication or any combination of these, your product cannot be considered as a generic medicine.

Three possible legal basis's may be open to you:

Article 8 (3) Full Dossier Mixed Marketing Authorisation
Article 10 (a) Full Dossier Well established use
Article 10 (3) Abbreviated Dossier (hybrid application)

Limitations

Awareness of the limitations to each option will help you determine which is the best approach or appropriate choice for you and your business. **The table on the following page** outlines various differences in the dossier requirements between each legal basis.

While the eAF is not a difficult document to complete it prompts the user regarding the associated documentation for the Annex. Generating this document early in the regulatory process it allows adequate time to request English translations etc.

Module 2

Module 2 is generic across all the proposed legal basis and all documentation should be supplied as outlined in the eCTD guidelines.

Module 3

While the large proportion of any Module 3 dossier is consistent irrespective of where the dossier is registered it is important to note the following points:

All non-EU references must be removed and replaced with the EU equivalent. Appropriate EU Guidance documents must be referred tothroughout each document in module 3.
European specifications and associated limits as detailed in the various EMA guidance documents must be adhered to.

Obtaining an EU authorisation for a non-EU product is possible. It takes careful planning it is achievable for an SME company.

	Article 8 (3) Full Dossier Mixed Marketing Authorisation	Article 10 (a) Full Dossier Well Established Use	Article 10 (3) Abbreviated Dossier (hybrid application)
Dossier Requirements	Company's own studies + published peer-reviewed literature No reliance on EU Reference product. Paediatric regulation 1901/2006 is applicable PIP/waiver must be submt-ted Advantages due to certain data protection and market exclusivity	Must demonstrate "well established use" of the active substance in the community over a 10 year period. This use must also demonstrate that the active substance has a recognised efficacy and an acceptable level of safety. Proposed indication must be aligned with the existing recognised indica-tion within the EU Risk of rejection in certain member states if an alternative route of ad-ministration is proposed No reliance on an EU refer-ence product	EU reference product is required and must be referenced in the dossier Company's own studies which must have been conducted using the EU reference product (i.e. bioequivalence) Reference is made in the dossier to the Non-clinical and Clinical data of the EU reference product Paediatric regulation 1901/2006 is not applicable No PIP/waiver is required

Clinical Trials: Is Ireland The Place To Be?

Pearl Casey,
Regulatory Affairs Manager

Great progress has been made in recent years in Ireland to advance the capability in design, conduct, analysis and reporting of clinical trials. Patients, researchers, academics, clinicians and industry along with the Health Research Board have worked tirelessly to develop this framework. Yet, with all of these developments, Ireland still only participates in less than 2% of studies in Europe (**clinicaltrials.gov**).

ICORG (The All Ireland Cooperative Oncology Research Group) created the template for research in Ireland. More than 10,000 Irish cancer patients have participated in Irish cancer trials and enabled access to treatments and changed the landscape of cancer care in Ireland. This has not been replicated in general medical clinical trials. Some works have been completed to address this with namely the Health research board (**HRB**) funding three clinical research centre facilities (CRFs) in accordance with three centres of excellence (SVUH, CUH and UCHG), alongside two research centres (CRCs) that complement these CRFs (**Mater** and **Beaumont**). These world-class centres of excellence facilitate the infrastructure, specialist research staff and practical knowledge needed to carry out the research. With this infrastructure, gaps still exist and there is a need for research dedicated clinicians in line with other countries. This vital link has been missing for so long.

New Funding Streams

In January, 2017 Ireland secured €13m in funding from a combination of **The Wellcome Trust** and HRB, **HSE** and the Health and Social Care Research Development office, Northern Ireland, and their partner Universities.

This funding will enable a fundamental change in the training of future clinicians on an all-Ireland basis. Eight postgraduate trainee doctors per year, over a period of 5 years will be provided with fully integrated clinical and research training up to consultant level.

This programme will identify, recruit and mentor doctors during their postgraduate training who have the potential to become future academic leaders.

This programme will position Ireland to meet the future challenges and demands in excellence and clinical innovation in healthcare, and the diverse needs of patients.

With this dedicated continued investment and focus on the grassroots of clinical research in Ireland, the future is extremely bright and enables Ireland to obtain access to more than the 2% of the studies that we currently have access to.

Are You Prepared For An Inspection?

Dr. John McIntyre,
Senior Regulatory Affairs Advisor

A pharmacovigilance inspection can be a daunting prospect for many companies. Since 2002 we have worked with countless companies to guide them through their inspections. In this article, we look at the measures that your company can take to be prepared.

MHRA Metrics

In the UK, the **MHRA** publish pharmacovigilance inspection metrics each year. 2015-2016 has seen the number of inspections continue to fall with 34 inspections in this period compared with 47 for 2014-2015 and 56 for the period 2013 to 2014. These yearly reports, together with our own experience of **MHRA** pharmacovigilance audits over the years, have given us an insight on the changing focus of the inspectorate since the introduction of the revised **Good Pharmacovigilance Practice** in June 2012.

In the latest reporting period (April 2015 to March 2016), the most commonly cited critical finding was 'Supervision and oversight' at 28%. This category includes issues related to the provision of complete and accurate information to national competent authorities and inspectors, maintenance of the PSMF and QPPV/ MAH oversight of the pharmacovigilance system. 'MAH oversight' accounted for 11% of critical findings in 2014-2015 and was not listed as a category in the 2013-2014 report. This represents an upward trend in findings in this area. The second most cited category for critical findings in 2015-2016 was both 'Data management' and 'Reference safety information (RSI)', both at 18%. RSI includes failures and significant delays to submit safety variations to update the safety sections of SPCs and PILs. RSI seems to have seen an improvement in MAH compliance in recent years, as it represented 29% and 42% of critical findings in 2014-2015 and 2013-2014, respectively. Data management was not a category in previous reports, and includes issues with collation and integrity of the global safety dataset, ICSR handling and safety database validation, configuration and control.

On major findings in 2015-2016, the top two cited were signal management (24%) and ICSR management (18%). Here in Ireland, the **HPRA** conduct a limited number of PV inspections each year, with only 2 pharmacovigilance inspections taking place in 2015 (HPRA Annual report 2015).

From our experience with the **MHRA**, a key focus at present is QPPV oversight and influence. The QPPV must continue to be aware of all aspects of safety related to the medicinal product(s). This is an extremely wide net and QPPVs should be able to satisfy themselves with all of the following, as outlined in GVP module 1:

•Does your QPPV have the skills for the management of the phamacovigilance system and have adequate theoretical and practical knowledge? Simply assigning a member of staff to this position that does not have extensive experience in the area is not acceptable, and will be cited by national competent authorities.

•Is the information in the PSMF accurate and up to date at all times? Is it a true reflection of the how the pharmacovigilance system is executed on a day-to-day basis?

•Do you have sufficient oversight of all third parties, for example distributors? Have you got robust safety data exchange agreements in place? Are you performing reconciliation activities at appropriate intervals? Have you ensured all third parties have received initial and refresher pharmacovigilance training? Have all third parties been included on your audit schedule? Have you assessed risks when deciding on your audit plan for third parties?

•Do you have oversight over the functioning of the system in all relevant aspects, including its quality system (e.g. standard operating procedures, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to pharmacovigilance)?

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The Pharmaceutical Quality System

A New Approach

Christine McGrath,
Regulatory Affairs Advisor

Currently, pharmaceutical manufacturers are not fully utilizing modern manufacturing technologies and quality management approaches; there is a lot of pressure on regulators and manufacturers for a change in approach. In this article, we look at the pharmaceutical quality system and its merits in a manufacturing environment.

The **ICH Q10** guideline describes a model for an effective quality management system for the pharmaceutical industry or a 'pharmaceutical quality system'. It advocates preventative action culture to ensure that actions are taken before problems happen. It also facilitates the use of ICH Q8 and Q9.

It is based on ISO 9000 with an emphasis on management responsibilities, improvement of QS and improvement of product quality over its lifecycle. Its scope is across pharmaceutical drug substances (API) and drug products, including biotechnology and biological products.

The Elements of a pharmaceutical quality system (PQS) encourage the use of scientific and risk-based approaches at each lifecycle stage.

Three main objectives:

Achieve Product Realisation: Having a system in place that allows delivery of products with the quality attributes appropriate to meet the needs of the patient.

Establish and Maintain a State of Control: To develop and use effective monitoring and control systems for process performance and product quality ie. Use of QRM (Quality risk management).

Facilitate Continual Improvement: Identify and implement appropriate product quality improvement, process improvement, variability reduction, innovation and pharmaceutical quality system enhancement.

The PQS covers the entire lifecycle of the product including:

- Pharmaceutical development
- Technology transfer
- Commercial manufacturing
- Product discontinuation

ICH Q10 is used in conjunction with regional GMPs for the technology transfer, commercial manufacturing, product discontinuation and investigational products stages of the process.

Management responsibilities are critical to all stages of the life cycle and the PQS elements which are a very important part of the structure supporting the PQS model.

The PQS elements are used in each lifecycle stage to identify areas for continual improvement, these include:

•Process performance and product Quality monitoring system - ensure that a state of control is maintained, provide assurance of continuous capability of process controls to produce a product of the desired quality.

•**Corrective Action/Preventative Action** (CAPA) system. This system should result in product and process improvements.

•Change management system- System to evaluate, approve and implement changes identified from innovation, CI, CAPA, Audits. Must be implemented ensuring no unintended consequences from the change.

•Management Review- Product quality review must be carried out at various levels of investigation, deviation, Audit findings and **CAPA** effectiveness.

The enablers of ICH Q10 are:

•Knowledge management – Product and process knowledge should be managed and developed through the commercial life of the product and up to discontinuation.

•Quality risk management - This is integral to an effective PQS. Applying QRM provides a proactive approach to identifying, scientifically evaluating and controlling potential risks to Quality. (ICH Q9)

•These support the PQS goals of achieving product realisation, establishing and maintaining a state of control and facilitating continuous improvement.

•The use of knowledge management and risk management will allow the company to implement ICH Q10 effectively and successfully.

The system is greatly dependent on senior management commitment to provide leadership, resources, encourage internal communication on quality issues and ensure informed decision-making processes are carried out using process knowledge and risk management tools.

The system should be designed to be well structured and clear with a common understanding, size and complexity of the company's activities should be taken into account. The system should have the appropriate resources and process to assume the quality of outsourced activities and purchase of materials.

Quality Manual

The company must have an appropriate quality manual in place, which must include details of the:

*Quality policy
•Scope of the pharmaceutical quality system
*Identification of the PQS processes, sequences, linkages and interdependencies
*Management responsibilities within the pharmaceutical quality system.

Management Responsibilities

Management responsibilities are vital and must include:

*Leadership
*Management commitment
*Establishment of the Quality Policy
*Quality planning
*Resource management
*Internal communications and ensuring that all communications are understood by all levels of staff.
•Reviews to ensure continuing suitability and the effectiveness of the PQS and assessments of the conclusions of periodic reviews of the process and performance and product quality.
•Manage outsourced activities and purchase of materials
•Manage changes in product ownership.

For continuous improvement of the pharmaceutical quality system the below activities must be conducted:

Management Review

Management review of the pharmaceutical quality system, review must include:

•Measurement of achievement of pharmaceutical quality system objectives, assessment of performance indicators ie. Complaints, deviations, CAPA and change management process.
•Feedback on outsources activities
•Self-assessment process including risk assessments, trending, and audits.
•Monitoring of internal and external factors impacting the pharmaceutical Quality system
•Emerging regulations, guidance and quality issues
•Innovations that enhance PQS
•Changes in business environment and objectives
•Change in product ownership

Outcomes of Management Review

Outcomes of management review and monitoring should include

•Improvements to the pharmaceutical quality system and related processes.
•Allocation and reallocation of resources
•Revisions to quality policy and quality objectives
•Documentation and timely and effective communication of the results of management review and actions.

Implementation of ICH Q10

Implementation of **ICH Q10** throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. **ICH Q10** is signed up to as the quality system of choice by the regulatory authorities and industry representative for US, Europe and Japan as they are a permanent member of the ICH.

This is the first quality system that is ratified this way.

ICH Q10 provides a mechanism for having a quality system that covers the entire lifecycle of the product; from R&D to product discontinuation. The appropriate level and rigour being applied dependent on the stage in the lifecycle.

Q10 describes mechanisms with feedback and enablers to facilitate the continuously improve the quality system and increase product knowledge.

Package Leaflets

An Overview

Eileen Shortiss,
Senior Regulatory Affairs Advisor

What role do target patient groups have in the creation of a package leaflet? We look at the issue and the directives concerning package leaflets in our blog.

Council Directive 2001/83/EC as amended by the **Council Directive 2004/27/EC** includes the following requirements in terms of the legibility and understanding of the package leaflets;

•The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use" (Article 59(3)).

•The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority." (Article 61 (1))

Consultations with target patient groups are therefore required for all package leaflets included in national or community authorisation applications and where significant changes are made to an existing package leaflet (e.g. new indications, new safety issue).

So how can MAHs meet these requirements?

One option is to submit a User Test Outcome Report. User testing is a process to test the readability of a package leaflet with a group of selected test participants.

Key safety issues associated with the specific medicine (e.g. side effects, warnings and precautions) are identified prior to commencement of the user testing. A questionnaire covering a balance of general and specific issues is then prepared. Testing takes the form of a series of one to one, face-to-face interviews and involves at least two rounds of 10 participants each.

A satisfactory test outcome is when at least 90% of literate adults are able to find the information requested within the package leaflet, of whom at least 90% can show that they understand it.

The User Test Outcome Report should be presented in Module 1.3.4 of a new application or as Type IB variation procedure under category C.I.z.

While all package leaflets for medicines must reflect the results of consultation with target patient groups, not every package leaflet needs to be subjected to a separate test.

Alternative evidence may take the format of a Bridging Report which will be discussed in a further publication.


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