Review article

Rapports De Pharmacie Vol.1 (3), 2015, 122-129
ISSN: 2455-0507

SMART REVIEW OF MARKETING AUTHORISATION APPLICATIONS AND PRODUCT LIFECYCLE MANAGEMENT: FUTURE AND CHALLENGES

T. Sankarankutty Subin.

Regulatory Consultant, Health Sciences Authority, Singapore

ABSTRACT

Competent regulatory authorities are responsible for ensuring the product quality of all marketed products in their country. Product quality is achieved by meeting expected requirements for quality safety and efficacy. Risk assessment principles are by regulatory authorities all over the world for both pre-registration quality risk assessment as well as in post registration for assessment and management of risk in the product lifecycle. Pre-registration, risk assessment is applied to understand the product risks and determine the extent of review required as well as the need for preapproval manufacturing site inspection for ensuring compliance to good manufacturing practices. Post approval of a product, a systematic risk assessment is vital to assess the risk to the end users due to various product defects which includes product instability, contamination and impurities that may be potentially harmful to the patient and/or causes reduced efficacy of the formulation. These assessment should also cover the impact to the products in the market in the event of a GMP deficiency alerts from international counterparts. An independent risk assessment is conducted based on the basis of decision from international counterpart and the proposed response to the deficiency letter and an independent decision will be taken.Such risk assessments are conducted to protect public safety, but these have a big impact on the product availability and cost. In order to ensure speedy availability of medicines that meets quality safety and efficacy standards, and also to enable regulators to take better risk assessment post approval and to enable for faster market actions, all regulators are now working towards regulatory convergence and smart review process where the regulators work towards convergence of requirements, guidelines and speed-up the review process by joint reviews/inspections and sharing of review reports and post market alerts.

Keywords:Risk Based Review, International Collaborations, Smart Review

INTRODUCTION

A systematic process which covers the assessment, control, communication and review of factors that affect the product quality throughout the entire lifecycle of a therapeutic product is called as Quality Risk Management (QRM) [1]. Although these principles primarily intended for application to the pharmaceutical manufacturers, it is also widely applied by the regulators. International regulatory agencies are responsible to ensure the availability of medicines with quality safety and efficacy at an affordable price. The principles of quality risk management are used to effective identification and management of the risk during pre-registration as well as its lifecycle management in post registration.

Regulatory Review Process- Current System and Challenges:

All pharmaceutical manufacturers submits their marketing authorisation applications with the documentation covering the quality, safety and efficacy of their proposed product in the form of a dossier [2,3]. This information will be reviewed and regulatory decisions were made in the form of a marketing authorisation or a rejection. Regulatory review process is a highly complex, multifaceted assessment of the marketing authorisation applications to ensure that the proposed medicinal product meets the international standards for quality, safety and efficacy [4].On site audits are also a part of these reviewers to ensure compliance to Good Manufacturing Practices [5]. These reviews have big impact on the public health due its effect on both safety as well as healthcare costs.

Post marketing of a medicinal product, the manufacturers will be performing lot of changes to the product for which, the manufacturers will be producing evidence that such changes will not affect the target product profile of the drug product in the form of a variation application [6]. Intended quality safety and efficacy requirement for a product is often called as target product profile. At the same time, all regulatory agencies need to monitor the marketed products for any changes to safety [7] as well as any quality changes and/or defects [8]. A systematic

Address for correspondence:
T. SankarankuttySubin,
Regulatory Consultant,
Health Sciences Authority,
Singapore.
Email:subin_sankarankutty@hsa.gov.sg.

review process and systems will be in place in all regulatory agencies to identify the potential risk, work with the manufacturers for risk mitigation measures or in some situations, performs risk-benefit assessment to allow the continual availability of the product. Quality risk management principles forms the basis of all such risk reviews or assessments.

Pre-Registration Phase:
Regulatory authorities are responsible for timely review of all new marketing authorisation applications and major changes so as to ensure the timely availability of medicines that meets quality safety and efficacy. All regulatory authorities are nowadays seeking innovative and improvised methods to enhance their performance still meeting the quality of review.
Preregistration, review of regulatory authorities covers the review of quality system which is done by manufacturing site inspection and review of dossier which includes target product profile of the proposed product. It is the responsibility of the marketing authorisation holders to ensure that the manufacturers intended for manufacturing of drug product comply with the good manufacturing practice (GMP) for medicinal products. Many regulatory authorities also require the same for active substances. The guidelines for GMP are established by EMA which is adopted by PIC/s and its member states. In a site inspection, the inspector will verify the quality system for compliance with this guidance. At the same time, the quality and clinical dossier section will be reviewed by the agency using various guidelines adopted by the respective agencies. This entire process may take long time to complete which hinder the availability of promising therapy or cheaper alternatives [13].

The GMP status of the manufacturers will be routinely verified by the national regulatory authority of the country where the manufacturing site is situated. However when the product is supplied overseas, many national regulatory authorities conduct their own inspections due to the absence of mutual recognition.The inspection is a tedious process which starts with the receipt of an application and fees. Subsequent to the review of site master file, an onsite inspection will be done by auditing the actual manufacturing site, documentation and records and compare them against the manufacturer's SOPs and QMS Standard requirements stated in the GMP guidance [14]. The cost incurred will be higher if the manufacturing site is located overseas and an overseas site audit is required. It further adds to the burden for the manufacturers to host multiple inspection teams throughout the year. Various international industry associations alreadyraised this as a potential issue and highlighted duplication of inspection and wastage of resources on many occasions [16].

The quality and clinical review of the dossier submitted for the marketing authorisation applications are affected by the complex manufacturing and supply chains as well as complexity in medicinal products and their ingredients [22]. These risks attributed to the long review timelines which delay the patient's access to the quality and promising medicines which he could have obtained in a cheaper price.

Post-Registration Phase:
Post registration, regulatory authorities need to timely detect the signals that pose a risk to the patients and implement risk mitigation measures. These generally involve adverse events monitoring, quality defect monitoring, periodic testing of marketed products and periodic verification of the GMP compliance status of the manufacturers. It is not possible to manage these risks without sharing of information among the regulators.

Adverse drug reaction is an unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicine, whether or not considered related to this medicine [29]. All regulatory agencies maintain a voluntary reporting system and database for healthcare professionals to report the adverse events and medication errors. These databases serve as a tool for identifying new safety concerns in relation to a product in the market and if required, the product label will be amended[29,30,31].

A product defect is a suspected deficiency that may produce an impact, whether directly or indirectly, on continuing safety, quality and efficacy of a product [9]. In most countries, it is a legal obligation for Marketing Authorisation Holders, manufacturers and importers to report to the drug regulatory authorities about any product defect which may or may not result in a recall or restriction of supply [8,9]. Product defect classification by EMA [10] is widely adopted by many competent regulatory authorities. Upon receipt of such reports, a review is generally conducted to ensure the adequateness of the proposed action plan by the reporter.

In addition to the voluntary reporting of product defect, competent regulatory agencies also practice

sampling and testing of products using registered specifications and test procedures [11]. The sampling of marketed products for these testing will be based on its risk profile, various alert reports and

manufacturer's reputation will contribute generally as risk factors. Any deficiencies if detected, will lead to further investigation to the manufacturer's GMP practices and product's testing program's capability to detect the defects.

In addition to the above mentioned methods for detection of quality, safety and efficacy deficiency signals, all competent regulatory agencies also performs environmental scanning [7]. This is done by active surveillance which covers collection and review of scientific and medical literature, international media reports and regulatory alerts from other international partners. All such signals from such environmental scanning will be highlighted to the respective marketing authorisation holders to provide information for review.

All manufacturers of medicinal products must meet acceptable compliance standard of Good Manufacturing Practices as required by the competent authorities.The competent regulatory authorities are also required to conduct inspections of the manufacturing sites proposed in the marketing authorisation applicationto ensure compliance with Good Manufacturing Practices (GMP) for bothDrug Products as well as for Drug Substances (APIs).Review of Site Master File (SMF) is a part of the pre-inspection preparedness process. Data and information submitted in dossiers and SMFs will be verified during inspections [14,19]. The information collected during such inspections will be used for the risk assessment to decide the re-inspection frequencies [15]. During such re-inspection, if a major deficiency is observed by the inspection agency, the finding may result in global restrictions which may result in shortage of medicines [12]. The management of such shortage will also need to be managed by liaising with manufacturers and importers.

The resource requirements to perform these operations are tremendous in the current pharmaceutical market where supply chains are becoming increasingly complex. It is not possible for any single regulatory agencies to inspect all manufacturing sites related to all marketed products since they may be situated in different geographical locations and performing an overseas site audit is extremely costly and resource intensive both for the company as well as the pharmaceutical company who need to support such inspection with both inspection fees and support staff. Facing multiple inspections from various competent regulatory agencies throughout the year is emerged as anissue for pharmaceutical manufacturers. Furthermore, if one of such inspection is resulting in a regulatory action which potentially leading a supply shortage, timely communication and preparedness are required between regulators and with manufacturers to face such shortage. Therefore, there is an increasing call for collaboration among international regulatory agencies to provide access to collective resources that availbetter and most effective usage of available scientific and technical expertise [22] so as to enable faster approval of the marketing authorisation applications.

SMART Review, Inspections and Post-approval Alerts:

All regulatory agencies are exploring ways to improve their performance while ensuring the same quality of their regulatory systems. In order for performance improvement, a faster review is required with effective usage of the available resources without compromising the quality of review. Work sharing with regulatory convergence is getting popular among regulators as a solution to the issues faced currently.

Work sharing initiatives- Assist in Faster Registration:

For an effective work sharing, understanding of the fellow regulators evaluation strategies, policies and procedures should be assessed for better convergence. The preliminary step towards work sharing is a confidence building exercise by comparing the review principles of either parties and then followed by signing memorandum of understanding and/or confidentiality agreements which facilitates the information exchange [24]. A comparison of the review principles and guidelines, joint review and/or participating in the review, exchange of the review reports etc., are widely used as the tools for confidence building. Once attain confidence, the certificate and/or review report issued by the agency is acceptable without the need for re-review and a review will be conducted only to the aspects which are not covered in the earlier review. This makes the review process faster.Certifications and sharing of review reports is currently used as effective work sharing methods. Certifications are issued by international non-regulatory independent bodies such as European Directorate of Quality if Medicines (EDQM) and

United States Pharmacopoeia (USP) whereas the sharing of review reports will be between the regulatory authorities. Below are some of the certifications that are already established.

Certificate of Suitability (CEP) issued by EDQM:
'Certification of Suitability to the monographs of the European Pharmacopoeia' is a certificate which can be used in lieu of drug substance sections of the quality dossier. This was established to control the chemical purity of pharmaceutical substances, evaluation of products with a risk of transmissible spongiform encephalopathy (TSE) and evaluation of products with risk of transmitting agents of animal spongiform encephalopathy. Inspection of the manufacturing sites is a part of this certification. CEPs are recognised by the various regulatory agencies such as all member states and the European Union, Canada, Australia, New Zealand, Tunisia, Morocco and many more. This certification is widely used in lieu of the drug substance section including sterile drug substances and drug substance GMP inspection as well as to replace the TSE/BSE risk assessment for materials of animal origin [24, 25].

USP Verified Pharmaceutical Ingredients:
Similar to CEP which offers certification for pharmaceutical ingredients for compliance to European Pharmacopoeia, USP verified pharmaceutical ingredients are a similar certification offered by United States Pharmacopoeia. Similar to CEP certification, this is certifies the quality of pharmaceutical ingredients by conducting an independent review of drug substance chemistry, manufacturing and controls (CMC) documentation, GMP compliance audit of manufacturing sites, laboratory testing of pharmaceutical ingredientsto ensure conformance to intended specifications and lifecycle management for ongoing change monitoring and surveillance. Therefore this certification can also be used to replace the need for submission and review of drug substance dossiers and/or drug master files [26].

WHO-Prequalification of Active Pharmaceutical Ingredients:
The prequalification of medicines programme (PQP) is initiated by World Health Organisation (WHO) to enable the access to quality medicines through assessment of APIs and inspection of drug substance manufacturing sites. WHO-prequalified drug substances are listed on the WHO List of Prequalified Active Pharmaceutical Ingredients. This list provides the information on drug substances that already evaluated and meeting the required quality standards to the medicines regulatory authorities. This certification consists of a thorough evaluation procedure which covers both the assessment of the Drug Master File as well as the assessment of the manufacturing sites of drug substancefor its compliance with GMP requirements. The successful applicant will get a WHO Confirmation of Active Pharmaceutical Ingredient Prequalification document which can be used by the applicants in lieu of the drug substance sections in the dossier.

In addition to the above certifications, there are lot of associations of regulatory authorities coming up with the idea of regulatory convergence, work sharing and work together initiatives. Although a few are already implemented and working well, majority are still in initial pilot phase.

International Generic Drug Regulators Pilot (IGDRP):
The IGDRP was initiated in April 2012 to strengthen collaboration and convergence between regulatory agencies worldwide and mitigate challenges of global generic development and approval programs [20,21]. In the initial phase, the union is planning to make common set of review guidance especially in the area of drug master file, chemistry reviews, inspection of bioequivalence sitesand information sharing ofproduct quality alerts. Subsequently using the European Union decentralised procedure as a model, for the review which is based on one agency becomes the lead reviewer and others co-reviews based on the lead reviewer report and additional regional requirements. This sharing of assessments and co-review will allow faster approvalof medicinal products in partner countries in a harmonized and resource efficientmanner.International generic consortium which is also known as ACSS consortium is a group working closely with IGDRP formed by ‘like-minded' regulatory authorities comprising health regulatory agencies from Singapore, Australia, Canada and Switzerland, who already piloted the above plan [28].

International Coalition of Medicines Regulatory Authorities (ICMRA):
Similar to IGDRP, ICMRA is also a union of likely minded medicines regulatory authorities worldwide providing strategic coordination, advocacy and leadership [22]. It is a forum to support international cooperation among medicines regulatory authorities with the aim to avoid duplication and promotion of

better allocation of resources based on the better information and risk understanding for strengthening cooperation, enabletrusted information exchange and support better utilization of resources and work products of its members. It currently includes a number of European national competent authorities as well as medicines regulatory authorities in Australia, Brazil, Canada, China, Japan, Korea, Mexico, New Zealand, Nigeria, South Africa and the United States. The European Commission is also a member and the World Health Organisation (WHO) is an observer.

Work sharing initiatives- Assist in Life-cycle Management:

In the life-cycle management of the products, the biggest challenges faced by the regulators will be timely detection and handling of quality, safety and efficacy alerts. Regulators will be engaged in active and passive surveillance for timely detection of signals. However, for timely detection and to enable regulators to take suitable preventive measure, a greater international cooperation is initiated by lot of national regulatory agencies. These initiatives include a) sharing of product defect information, b) Joint review and sharing of review reports, c) Joint inspection and sharing of inspection reports, and d) Sharing of adverse reaction reports.

Sharing of product defect information:

Product defect reports that may potentially affect the quality, safety and efficacy are circulated widely through various international groups which are mainly by PIC/s and ASEAN. Upon receipt of such alerts, all competent authorities will conduct and independent assessment of the risks based on whether the product is available, and whether the risks applicable. Based on this independent assessment, component authorities decide to take market actions. These may either same as the agency initiated the alert or sometimes milder actions. Regulators need also to consider availability of alternative medicines and sometimes, a product with quality defect may need to be retained in the market if the risk from the quality defect outweighs the risk due to absence of effective treatment therapy.

Rapid Alert Notification (RAN) by Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S is a communication channel set under the PIC/s scheme[15]. ASEAN Post Market Surveillance System is a similar initiative amongst ASEAN member states for similar sharing of product defect information [33]. All defect reports that may pose a significant threat to the public health are circulated by the competent regulatory agency of the member country to all member states through these communication channels.

Joint review and sharing of review reports:

To effectively utilise the resources, all regulators are now exploring methods for smart review where regulators depends on the competencies each other and try to avoid duplication. If one agency reviewed a dataset, another agency can proceed based on the review reports, if both the agencies have common review standards, policies, procedures, report writing system and competencies [21, 23]. Many international associations of regulatory agencies are working towards this goal. With the implementation of common technical dossier formats like ICH CTD [2] and ASEAN CTD [3] the dossier format amongst the regulators are nowadays standardised. After getting a common dosser format, subsequently they started working to get common submission requirements and review process. ASEAN Variation Guidance [6] aligns the post approval change review system whereas consortium Initiatives [21, 22, 23, 28] are working on getting common review guidelines, reporting format and procedures for sharing of review reports. Joint reviews of products are done in order for the member states to get an understanding of each other. For review of drug substance section of the dossiers, already many regulatory agencies start accepting the certificates issued by independent bodies such as EDQM, USP and WHO [24, 25, 26 & 27]. With more sharing of review reports with the availability of common guidelines and mutual understanding, faster approvals with less regulatory cost will be possible. With the full implementation of common variation guidelines, many pharmaceutical companies will be benefitted since they need to make a single variation package for a product change if the product is marketed in many countries.

Joint Inspection and sharing of Inspection reports:

The international cooperation in the area of good manufacturing practice compliance started with the establishment of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) which are actually two international mechanisms between countries and inspectorates [19].The PIC/s developed GMP Guide which is actually a harmonisation of international GMP guides and guidelines. With the introduction of PIC/s GMP guide [5] and its implementation by all competent regulatory authorities, helped in the consistentinterpretation of GMP and Quality

Systems requirements for GMP Inspectorates. PIC/s also promotes voluntary sharing of inspection reports so as to enable the partner agencies to conduct
independent risk assessment so as to minimise the duplication and costly overseas GMP inspection [15]. Such sharing of information is more relevant nowadays where GMP inspection related deficiencies and warning letters are causing shortage of many important lifesaving medications [12]. Many agencies are also arranging joint inspections [16, 17, 18] which helped them to reduce the resources and in confidence building by understanding each other.

Sharing of adverse reaction reports:
Similar to many international associations among regulators discussed earlier, this is also a similar association started in 1971 with the objective to establish an international system for the monitoring of drug adverse reactions (ADRs). WHO Collaborating Centre for International Drug Monitoring in Sweden is responsible for the operational aspects of this joint program whereas the policy issues are handled by WHO Headquarters. The association stated with 10 member states who already had an established system of adverse reaction reporting and who are willing to share this information. In order for this sharing platform to become operational, they developed common reporting form, comeup with guidelines for entry of information, standardized the terminologies and classifications for use in the shared database, and also developed IT systems for management of database such as systems for storage, and data exchange.At present, this shared ADRs database contains over three million ADR reports [31, 32].

SUMMARY AND CHALLENGES AHEAD

With the increase in globalisation and resultant complex manufacturing and supply chains, national regulatory agencies are facing many challenges in product registration and its lifecycle management. They are trying to overcome these difficulties by performing a risk based review which is relaying on international cooperation and sharing of information. With the progress in international cooperation, slowly, the focus is shifting towards faster registration and inaway, increases the burden on post-market surveillance. With increase in product quality alerts, GMP alerts and related supply shortages, it has come to situation where the current international cooperation in the post market alerts and Inspection need to be further enhanced. Non-availability of information which is required to conduct an independent review in the event of a post market alert, through national authority websites or through international communication channels are increasingly appeared as a problem for regulators from rest of world. More close collaboration and voluntary sharing of information such as alerts, GMP inspection reports and other relevant pre or post market assessment reports can help to enhance the global public safety.

Declaration
The authors declare that they have no conflict of interests and are agreeable to the publication of this paper.

REFERENCES

[1] ICH Q9 Quality Risk Management; available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

[2] ICH M4 The Common Technical Document; available at http://www.ich.org/products/ctd.html

[3] ASEAN Common Technical Dossier ; available at http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Western_Medicines/Overview/Guidelines_on_Drug_Registration.html

[4] Annex 9 Good review Practices: guidelines for national and regional regulatory authorities, WHO Expert committee on specifications for pharmaceutical preparations-WHO Technical Report Series No. 992, 2015

[5] PIC/S GMP Guide PE 009-11; available at http://picscheme.org/publication.php?id=4

[6] ASEAN Variation Guideline ; available at http://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/ASEAN%20Variation%20Guideline%20for%20Pharmaceutical%20Products%207.2%20clean%20draft.pdf

[7] TGA, Product regulation according to risk-overview of the way the Therapeutic Goods Administration (TGA) considers risks and benefits during the evaluation

and post market monitoring of products; available at https://www.tga.gov.au/product-regulation-according-risk

[8] EMA Notifying suspected quality defects or product recalls; available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/wrapper_product_defects_notifying.jsp&mid=WC0b01ac058006bf88

[9] Health Sciences Authority- Guidelines on Product Defect Reporting and Recall Procedures; available at **http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_andProduct_Recalls/Guidelines_on_Product_Defect_Reporting_and_Recall_Procedures.html**

[10] European Medicines Agency- An analysis of quality product defects in the centralised procedure; available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004420.pdf

[11] European Medicines Agency- Sampling and Testing of Centrally Authorised Products- Development of risk based approach for the selection of products; available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500005114.pdf

[12] European Medicines Agency- Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems; Available at http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500135113

[13] Applying for EU marketing Authorisation; available at http://www.jpsr.pharmainfo.in/Documents/Volumes/vol5issue06/jpsr05061302.pdf

[14] TGA- Guidance on licensing/certification inspections, Published April 2013; available at https://www.tga.gov.au/file/4850/download

[15] TGA Manufacturer inspections - a risk-based approach to frequency; avauilable at https://www.tga.gov.au/manufacturer-inspections-risk-based-approach-frequency

[16] EMA- EMA / FDA joint GMP inspection pilot programme, 27 September 2010 available at http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500098837

[17] EMA- Joint Audit Programme For EEA GMP Inspectorates, 19 September 2006 available at http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004862

[18] Final report on the International API inspection Pilot Programme- 16 June 2011, available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500108655.pdf

[19] The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme; available at http://picscheme.org/benefits.php

[20] EMA- International Generic Drug Regulators Programme (IGDRP) Information Sharing Pilot published 15 January 2015; available at http://igdrp.com/sites/default/files/media-2015-eu-dcp-ip-150119.pdf

[21] HSA- International Consortium Aims to Facilitate Availability of Generic Drugs for Patients Through Focus on Generic Drug Review Collaboration published 29 June 2012; available at http://www.hsa.gov.sg/content/dam/HSA/News_and_Events/HSA_Updates/2012/HSA%20Website%20Update%20_Generic%20Drug%20Review%20Collaboration.pdf

[22] International Coalition of Medicines Regulatory Authorities (ICMRA) Factsheet, published Sept 2014 available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000626.jsp&mid=WC0b01ac058085284f#

[23] EMA Press Release- Europe to boost international cooperation on generics, published 19 Jan 2015; available at http://www.ema.europa.eu/ema/index.jsp?

curl=pages/news_and_events/news/2015/01/news_detail_002251.jsp&mid=WC0b01ac058004d5c1

[24] Health Canada's exploration of the use of European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability (CEP); available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/int/edqm_2007-eng.php

[25] EDQM Certification of Suitability-Background and Legal Framework; Available at http://www.edqm.eu/en/certification-background-77.html

[26] The USP Pharmaceutical Ingredient Verification & Qualification Processes; available at http://www.usp.org/usp-verification-services/usp-verified-pharmaceutical-ingredients/verification-qualification-processes

[27] WHO Technical Report Series TRS953, Annex 4Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products; available at http://apps.who.int/prequal/info_general/documents/TRS953/TRS_953-Annex4.pdf

[28] Swissmedic- Multilateral co-operation with international organisations / initiatives; available at https://www.swissmedic.ch/ueber/01398/01401/01939/index.html?lang=en

[29] FDA Adverse Event Reporting System (FAERS), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm

[30] TGA Reporting medicine and vaccine adverse events; available at http://www.tga.gov.au/reporting-medicine-and-vaccine-adverse-events

[31] WHO Adverse Drug Reactions Monitoring; available at http://www.who.int/medicines/areas/quality_safety/safety_efficacy/advdrugreactions/en/

[32] About Uppsala Monitoring Centre; available at http://www.who-umc.org/DynPage.aspx?id=96979&mn1=7347&mn2=7469

[33] Asean Policy Guideline ON STANDARDS AND CONFORMANCE; available at https://www.google.com/url?q=http://www.asean.org/archive/20531.pdf&sa=U&ved=0CAwQFjADahUKEwjSy-_c-YTIAhVQ1I4KHRnGBSE&client=internal-uds-cse&usg=AFQjCNFPp63Qr1XNhkRVTzV19TgIOVAl1w