



TATA ELXSI

Pharmacovigilance Compliance - Changing Regulatory Landscape during Pandemic

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ABSTRACT

The onset of the COVID-19 pandemic has a serious impact on the healthcare system, regulatory compliance management, and socio-economic environment across the globe. While the world witnessed short-term and long-term effects due to COVID-19, European countries witnessed significant changes in terms of regulatory obligation due to BREXIT.

The majority of the Health Authorities worldwide released guidance to ensure pharmacovigilance is driven in a risk proportionate manner and focused on safety information processing of the COVID-19 treatments. Pharma companies faced challenges in integrating digital transformation with regulatory compliance management, safety analysis of Advance Therapy Medicinal Products (ATMP), and ensure inspection readiness. Diligent use of regulatory compliance flexibilities and return to normal business process through gap analysis becomes the need of the moment.

Automation in business transformation, risk management, and signal detection of new drugs for increased efficiency and compliance with regulatory requirements will be the key success criteria for a robust pharmacovigilance process.



INTRODUCTION

Since the initiation of the COVID-19 outbreak in China in Dec 2019 to 15 Jan 2021, there were more than 83 million affected people all over the world as per an estimate by the Centers for Disease Control and Prevention (CDC).

83.1 Million Estimated Total Infections	70.4 Million Estimated Symptomatic Illnesses	4.1 Million Estimated Hospitalizations
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Fig1. Covid-19 Disease Burden

For more information, please refer to estimated disease burden of Covid-19 shared by the Centers of Disease Control and Prevention (CDC)

<https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html>

COVID-19 resulted in many short terms and long-term effects. The main short-term effect of COVID-19 was an increased demand for prescription medicines, vaccines, and medical devices. Demand change, supply shortages, panic buying and stocking, regulation changes, and shift of communication and promotions to remote interactions through technology and research and development (R&D) process. The long-term impact included approval delays, moving towards self-sufficiency in the pharma-production supply chain, industry growth slow-down, and possible trend changes in consumption. In terms of regulatory compliance, it has impacted clinical trial, pharmacovigilance, and inspection process. There is an increase in demand for regulatory intelligence to comply with new regulatory requirements.



IMPACT OF COVID-19 PANDEMIC ON PHARMACOVIGILANCE PROCESS

During the COVID-19 pandemic, pharma companies were struggling to manage regulatory compliance due to mass absenteeism, optimum usage of key resources on treatment and vaccine development. Few of the major changes in the PV obligation are as follows:

Coding of indication, event, medical history, and lab test :

- MedDRA version 23.1 was implemented on 01 Sep 2020 to include COVID-19 related event terms, indication, medical history, and lab test. COVID-19 can be coded as COVID-19 aggravated, pneumonia aggravated or precise LLT, and condition aggravated. For indication, there are three options—prophylaxis, immunization, or treatment. For medical history, there is an option to code occupational exposure to COVID 19. Lab test parameters specific to COVID were also created.

Management of literature, Digital media and follow up report:

- During the pandemic, there is a surge of reporting of cases in scientific literature as well as on social media platforms.

- The focus for the literature article should be on the new information which is not part of MLM service. Also, ensure truly valid cases are sent to the Health authority to avoid unnecessary burden on the analysis.
- For social media screening, the scope of compliance is limited to company-sponsored digital media.
- Follow-up should be focused on risk proportionate manner. Priorities for follow-up are Serious ICSRs, Events of special interest as per the RMP, Prospective reports of pregnancy & cases related to COVID-19.

Reporting obligation:

- There are some flexibilities from major Health Authorities for reporting obligations. In the USA, reporting obligation will continue for COVID-19 cases and products approved within 3 years. Periodic Adverse Drug Reaction Report (PADAR) and other ICSR reports can be stored.
- In Europe, serious Covid-19 cases will be prioritized over non-Covid serious cases. Pharmacovigilance System Master File (PSMF) will include a note on the prioritization criteria.
- Reports should not be submitted for the misuse of non-medicinal products which may contain substances also present in medicinal products.
- If the product is approved for COVID-19 treatment, LOE should be considered for expedited reporting. If the product is not approved for COVID -19 and there was an off-label use, the LOE is not required.
- As per the USFDA enforcement approach, all the stored cases need to be submitted within 6 months of the restoration to their pre-pandemic state

Flexibilities in Risk Management and Periodic Safety Update Report

- MHRA has published flexibilities in terms receipts of Risk Minimization Measure (RMM), survey and Direct HealthCare Professional (DHCP) letter dissemination to ensure optimum use of Healthcare professional resources. MHRA waived requirements for evidence of receipt of RMM by HCPs.

IMPACT OF BREXIT ON PHARMACOVIGILANCE PROCESS

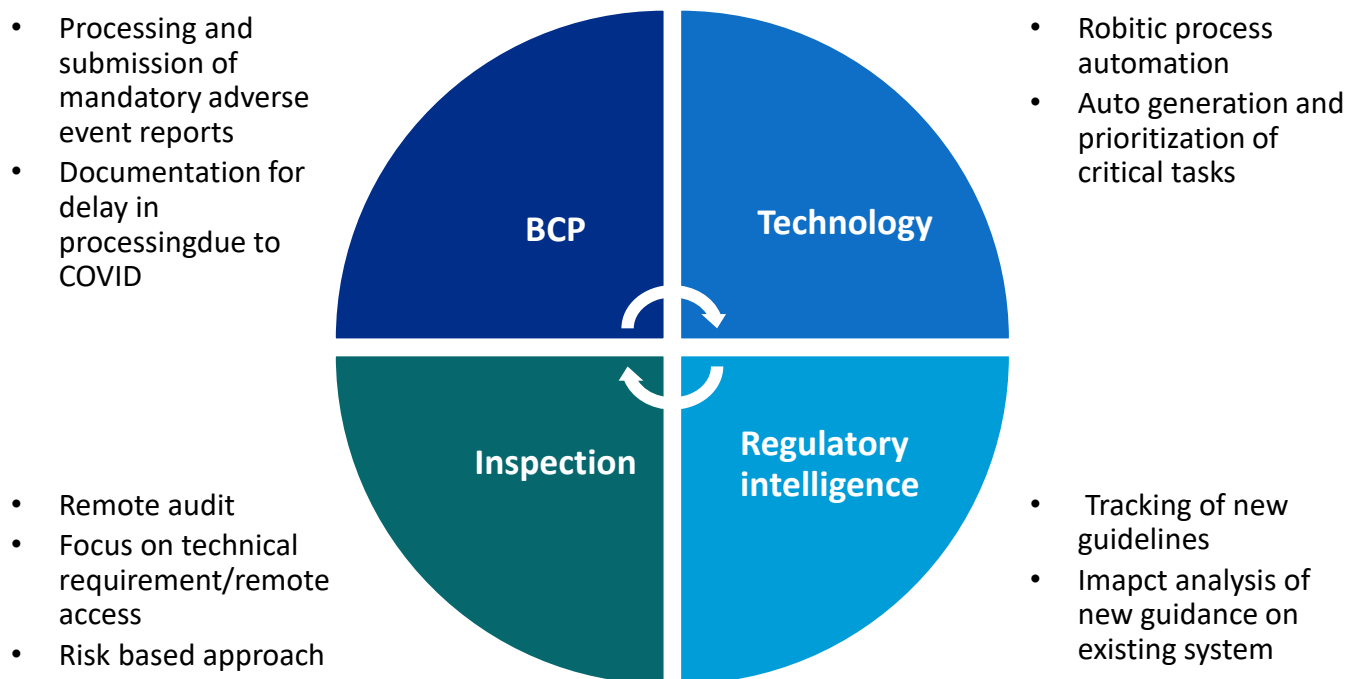
There are several important changes in terms of PV operation due to BREXIT:

- It is now mandatory that UK QPPV should be located in the UK. Otherwise, there should be a UK national who can work as a PV contact person.
- There should be a separate PSMF based on UK authorized products. The template can be as per EU regulation. The PSMF should include a unique PSMF number which will be provided by MHRA. Use of the MHRA portal for submission of ICSR and aggregate report is mandatory.
- MAH needs to notify MHRA about any new signals within 3 working days.
- RMPs can be prepared in the EU template. If required MHRA specific additional information can be included in a specific annex.
- Imposed PASS protocol to be submitted via type II variation. Final study report required to be submitted to MHRA within 12 months of the end of data collection

Access Tata Elxsi's on-demand webinar to learn about the [new impact areas under the MHRA's post-transition guidelines and how to optimize implementation overheads with innovation in processes powered by digital technologies](#).



IMPACT PV Quality Management System (QMS)



The COVID-19 pandemic has highlighted the importance of having a robust business continuity plan (BCP), strong quality management system, efficient technology solutions and a proactive regulatory intelligence management process.

Business continuity plan (BCP) was essential part of Good Vigilance Practice as mentioned in “Good Pharmacovigilance Practices (GVP) Module I – Pharmacovigilance systems and their quality systems” to ensure Critical pharmacovigilance processes are not impacted during situations like COVID-19 pandemic. USFDA has emphasized implementation of Continuity of Operations Plan to ensure safety information for death cases and safety information of COVID-19 treatment/vaccine is processed accurately. Amalgamation of technology with regulatory compliance is the need of the moment to facilitate to reach out to patients to collect safety information and conduct audits or support inspection to ensure patient safety and efficacy and well being is maintained properly. Tracking of regulatory updates across globe, impact analysis of the new/updated regulations and update existing process as per latest requirements became more important.

CURRENT CHALLENGES IN PV PROCESS

PV process is a highly regulated and compliance-driven process. Mass absenteeism, working from home, remote working affected processes like case submission and audits. However, Health authorities have promptly taken this into account and provided flexibilities to manage critical compliance activities on a risk-based approach and digitally. European Medicines Agency has updated the “Questions and Answers on Regulatory Expectations for Medicinal Products for Human Use During the COVID-19 Pandemic” that allows conducting audits and inspections remotely because of the pandemic.

Pharmacovigilance workload in terms of processing spontaneous report, literature screening, digital media screening, and processing of COVID-19 reports resulted in skewed workload. There was a lot of fluctuation in the ICSR workload for non-COVID-19 products. In 2020, the remote collection of the adverse event information has increased and an increasing trend was observed for reporting adverse events on social media or through the company’s websites. There is an increasing focus on the enablement of the technology to harmonize patient data across the globe. Implementation of mandatory use of the ISO ICSR format for reporting individual cases of suspected side effects and implementation of the ISO IDMP standards by EMA are good examples.

During the pandemic pharmacovigilance departments witnessed 4 major challenges across the globe:

- Integrating technology with regulatory compliance
- PV of advanced therapy medicinal product/biologics
- Optimization of business process
- Audit/inspection readiness

SOLUTIONS TO ACHIEVE COMPLIANCE:

Blending regulatory compliance with digital transformation – We observed regulatory intelligence is a pain area for many pharma companies due to the vastness and complexity of the websites. Every day new regulations are coming up from advanced markets like USFDA, EMA, MHRA, TGA, and evolving clinical trial and PV regulations are published from the semi-regulated markets. To minimize the human effort, we have developed a regulatory intelligence tool - TEDREG. This tool provides regulatory updates from 50+ Health authority websites in a single click. You can get an impact analysis of the regulations on your existing process. Additionally, the dashboard will provide you a summary of changes. This reduced 90% of your manual effort to search regulatory information and perform impact analysis.

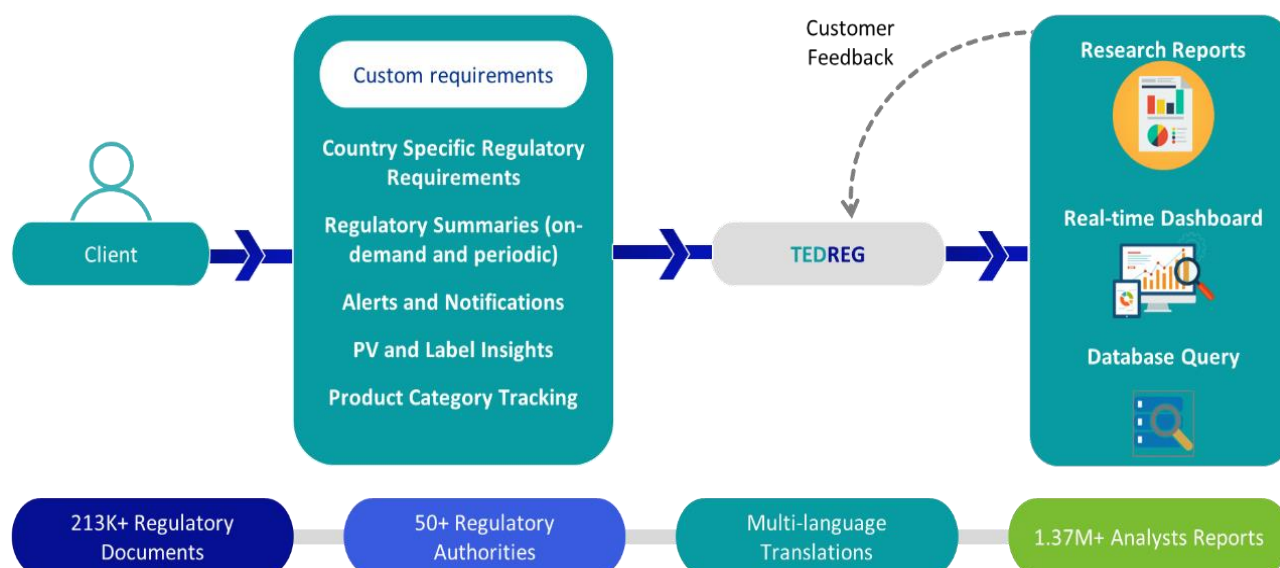


Fig 2: Framework of TEDREG

SOLUTIONS TO ACHIEVE COMPLIANCE:

Pharmacovigilance of Advance Therapy Medicinal Products – Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues, or cells. They offer groundbreaking new opportunities for the treatment of disease and injury.

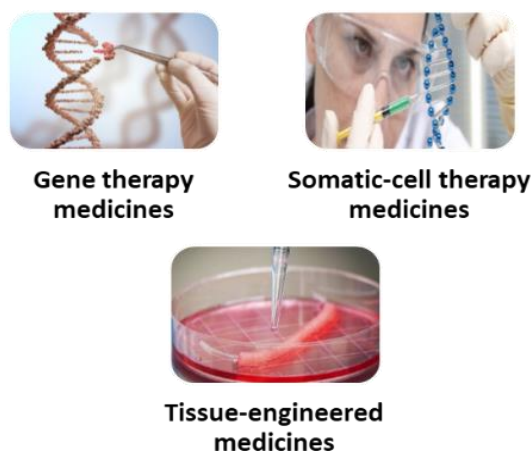


Fig 3: Types of ATMP

There are 5 key differences between the pharmacovigilance of small molecules and ATMP.

- Adverse event: If serious adverse events or reactions occur with a combined advanced therapy medicinal product, the agency shall inform the relevant national competent authorities responsible
- Follow-up of the efficacy of advanced therapy medicinal products and adverse reactions. Procedures for follow-up of reported ADRs at obtaining at least minimum information including product name and batch number
- Risk minimization activities included additional PV activities and the efficacy follow-up system. Elements of the PV system necessary to support additional PV and efficacy follow-up activities. The effectiveness of any risk management system shall be included in the PSUR
- Recordkeeping requirement is for a minimum of 30 years after the expiry date of the product
- Electronic exchange of pharmacovigilance information will need some adjustment

SOLUTIONS TO ACHIEVE COMPLIANCE:

Increasing efficiency and reduce cost:— Increasing workload and cost optimization are essential features of PV operational excellence. Three important parameters to achieve these objectives are increasing first pass yield, using automation to reduce cost, and business transformation with help of strategic partnerships to reduce the cost of compliance management.

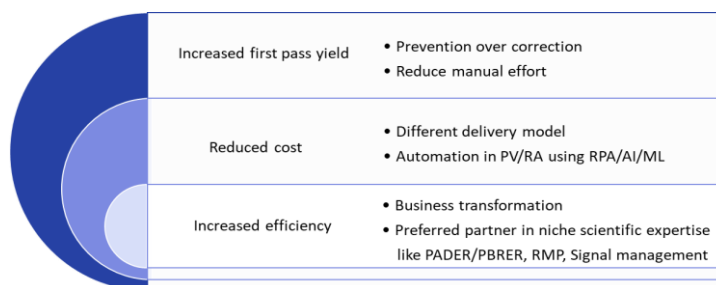


Fig 4: Optimized business model

Inspection readiness:— A robust PV system should be inspection-ready at any time. Audit and inspection readiness includes three components. The first component is the development and execution of an annual audit plan. In the EU, the requirement is to start with a strategic audit plan for 3-5 years followed by an annual tactical audit plan and then an individual audit plan. Audit outcome helps to identify the gap areas in the PV process. The next component is to design solutions to the gap areas through a corrective and preventive action plan. The third component is to ensure effective preventive actions are implemented to prevent the recurrence of the deviation.

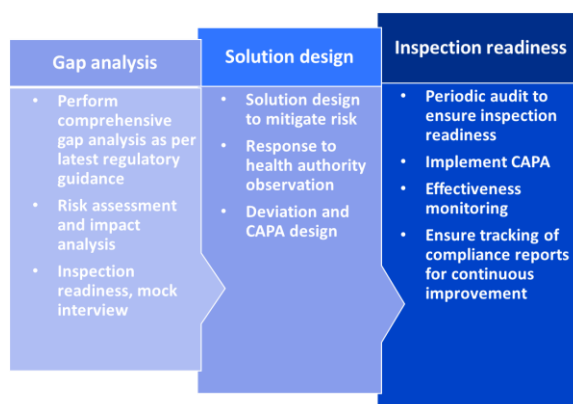


Fig 5: Inspection readiness strategy

These strategies can be used for all the different types of the inspections like for cause inspection or pre-authorization inspection

CONCLUSION

COVID-19 pandemic highlighted the importance of a risk-based approach for PV activities. Also, the pandemic demonstrated a roadmap for accelerated treatment/vaccine development pathway keeping the high focus on safety evaluation on a real-time basis. Health authorities pave the way for digital transformation in the PV domain. Digital transformation, automation solution to reduce the manual effort for routine PV tasks and use of Natural Language Programming/ artificial intelligence for advanced PV activities are on the cards.

An increasing trend of customized medicines and gene therapy requires rigorous scientific expertise for safety assessment. Continuous focus on process improvement, business transformation through digitalization, exploring innovative medicines like ATMP, and inspection readiness will ensure better patient safety and successful transition from COVID-19 Pandemic to the post-pandemic situation.



REFERENCES

1. <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html>
2. <https://www.meddra.org/COVID-19-terms-and-MedDRA>
3. Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products. EMEA/149995/2008
4. Regulation (EC) no 1394/2007 of the European parliament and of the council of 13 Nov 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004
5. Detailed guidance on ICSRs in the context of COVID-19 Validity and coding of ICSRs. EMA/174312/2020. 30 Oct 2020.
6. Questions and answers on regulatory expectations for medicinal products for human use during the COVID-19 pandemic.
7. Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic version 4 04 Feb 2021
8. MHRA regulatory flexibilities resulting from coronavirus (COVID-19). 4 Aug 2020
9. USFDA Post marketing Adverse Event Reporting for Medical Products and Dietary Supplements during a Pandemic. May 2020
10. Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorization holders and the licensing authority. 21 Dec 2020



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Prajeesh leads the Pharma presales & solutions at Tata Elxsi. He has a diverse experience of 15+ years in pharma R&D business process & technology across clinical operations, data management, pharmacovigilance, and regulatory services. He is responsible for pharma business growth and strategy in Tata Elxsi and develops strategic relationships with customers across the US, Europe, APAC, and Japan. He takes a special interest in the regulatory business and has hands-on experience in handling large customer relationships across the top 10 pharma companies.

ABOUT TATA ELXSI

Tata Elxsi, a part of Tata Group, is amongst the world's leading providers of design, engineering, and regulatory compliance services. With 15+ years of experience in catering to healthcare & life sciences companies, Tata Elxsi has built a strong services and solutions portfolio that adds value at every stage of the customer's product development lifecycle.

Tata Elxsi offers end-to-end regulatory service portfolio for global pharma companies to help them increase agility and lower operational costs while ensuring compliance with ever-changing global industry standards and requirements. We have extensive experience with regulatory agencies like FDA, EMA, PMDA, MHRA, BfArM, and other leading health agencies.

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