Crisis Planning for pharmacovigilance compliance management due to COVID-19 pandemic

The purpose of this document is to provide guidance to pharmaceutical companies if their PV system is compromised due to the COVID-19 pandemic. The guidance is based on principles that put patient safety first while acknowledging the critical importance of compliance with global regulations. The guidance spans the PV system and suggests possible approaches to mitigate issues arising from potential significant and sudden resource capacity reduction. The guidance also takes into account the current external environment where HCPs are needing to focus on saving lives and should not be unnecessarily burdened with non-critical requests from industry.

The main approach proposed is to prioritise PV obligations. It is acknowledged that prioritisation may indeed result in non-compliance, so careful consideration is needed of what activities are likely to protect patients the most and plans should be made that monitor and document any resultant non-compliance with appropriate rationale for decisions made and justification for approaches to mitigation of impact strategies.

It is recognized that every company will need to determine their own approach based on the company size, product portfolio, extent of clinical trial programmes, level of automation, geographic spread and extent of outsourced PV activities however the guidance aims to drive some consistency in approach. This will also assist regulatory authorities understanding of how the industry managed this unprecedented situation in the context of future PV inspections. Companies should adopt a risk-based approach and determine how best to implement chosen strategies to suit their situation i.e. one size will not fit all. The strategy should include a recovery plan that determines how to return to business as usual. This should include justification for circumstances where

retrospective remediation is not proposed. Companies should exhaust all alternative solutions e.g. technology, process efficiencies before making decisions that could impact compliance. The overall approach should be managed through each company BCP.

Different parts of the PV system may be differently impacted by resource levels and therefore contingency strategies may need to be started earlier in some functional area than others. It is therefore essential that careful planning and oversight of the overarching approach is in place throughout the crisis. In addition, it is recognised that prioritising one part of the PV system may have downstream impact on other parts therefore it is important to understand impact of risk-based decisions with pragmatic mitigations to address.

In addition, it should be understood that any PV system depends in large parts on Health Care Providers (HCPs) who under the current crisis situation need to be focused on patient care. Therefore, industry aims to minimize any non-essential administrative burden on HCPs. Industry proposes that this principle based and pragmatic approach to managing compliance activities during the COVID-19 pandemic be adopted globally.

Crisis Planning Principles

	Principles	Examples	Possible Approaches	Mitigations/ Comments
1	Patient safety comes first, all activities should be prioritised to those that drive safe use of medicines and investigational products for patients and study subjects.	Risk minimization activities	Continue where patient at risk Evaluate activities that need to be prioritised and those that may be paused or stopped since they do not impact safe use of medicines but may burden HCPs in a time of crisis	Identify priority product/situation
2	Some activities are critical and should be maintained at all times, these activities should be clearly identified, and contingencies should be in place to ensure these activities are resourced. A risk-based approach to maintaining these activities should be used.	Processing of AEs	When necessary prioritise ICSR processing 1. Clinical trial serious and non-serious cases for products developed/tested for COVID-19 2. Clinical trial serious cases 3. Serious spontaneous cases 4. Serious solicited cases 5. Non-serious cases Further prioritization may be required if resource levels fall to a critical level. This could include: 1. Limited data entered into database for non-serious cases – this could be further limited to certain substances e.g. < 5 years on market, 2. Reduce/stop follow-up activities on all non-serious or non-serious expected, except of COVID-19 treatments & vaccines, expected or prioritize according to time on the market. Postpone all non-urgent contacts with HCPs 3. Reduce reconciliation activities 4. Conduct duplicate checks on serious cases only	Impact of pandemic on HCPs should be taken into account when determining the extent of follow-up activities.

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			5. Reduce quality control checks	
		Medical review of individual cases	Prioritise cases for review: 1. Serious unlisted cases/unexpected 2. Serious listed/expected 3. Non-serious adverse events of special interest	
		Risk Management	Maintain provision of additional Risk Minimization Measures. Prioritise products with significant risk minimization programmes e.g. Pregnancy Prevention Programmes vs provision of educational materials. Deprioritise RMPs for established products without additional PV or risk minimisation measures.	Route of delivery of aRMMs may need to be amended if feasible e.g. digital vs paper vs hand delivered Consider priorities of HCPs in pandemic situation and assess if materials could be provided at a later date
		Signal detection activities	Prioritize activities: 1. Focus internal signal detection on substances < 5 years on market unless signal is medically important e.g. could have potential to impact benefit:risk (see section on benefit:risk evaluation) 2. Deprioritize EVDAS activities	
		Safety label updates (including both existing marketing authorisations and important new safety information to investigators in the IB)	Prioritise new information in the RSI accordingly: • Safety amendments to RSI that would require additional risk minimisation activities including further HCP or investigator communications • Identification of new adverse effects or potential risks that are serious and warrant a warning /precaution • Medically Serious ADRs • ADRs that involve non-serious events would be processed only if staff capability allows.	

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		Responses to regulatory authority safety questions	Prioritise according to the medical importance of the safety question including potential impact on benefit risk in the case of new safety signals. Questions for clarification of information on individual case reports would be deprioritized. Prioritize those questions that are part of a regulatory procedure Propose extension of due date for non-urgent requests.	
		Benefit: risk evaluation	Prioritise substances e.g. products tested or used to treat COVID-19, products <5years on market, medically important trigger or authority request Prioritisation based on e.g. • products of interest for special situations • medical needs, • any products with significant new populations • ongoing safety issues • significant clinical development • significant emerging data NB: these approaches to prioritization apply across all activities not just benefit:risk	
3	Compliance is critical to ensure patient safety therefore the aim should be to always be as compliant as possible.	Continuous assessment of resource availability and appropriate capability	Where possible, train staff to prioritize and complete different activities according to the potential impact on benefit risk of the product (investigational and marketed) or where there is greatest likelihood of impact to compliance	

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			Consider geographic opportunities e.g. utilize regional language capabilities	
4	Build prioritization framework with thresholds for moving to next level of plan implementation. The framework should describe how to return to normal activities once crisis has normalized.	Level 1 - resources levels moderately impacting compliance (e.g. resource levels 80%) Level 2 - resource levels severely impacting compliance (e.g. resource levels 50-80%) Level 3 – resource levels critically impacting compliance (e.g. resource levels 30-50%)	Framework should clearly describe which activities may be stopped, limited/amended or should be maintained. Limited activities may include: 1. Reduced follow-up for some case 2. Extension of deadlines for some safety deliverables e.g.3 yr. PSUR extended to 4 yr. for substances authorized > 5 years with established safety profile and no aRMMs 3. Use of Line Listings in place of IMD Safety reports to investigators and IRBs/ECs 4. Extension of PADER timeframes Submit 3-month PADER 6 or 12 monthly 5. Submission of on-time abbreviated PSURs and DSURs 6. Delay literature screening NB: There should be no limitation of activities for products use in the management of COVID-19 or where the virus is mentioned in the context of AE.	Decisions will be made on a company by company basis and the framework should be incorporated into BCP. Impact of resource availability may differ across functions within the same organization and therefore it is important to track at what Level each function is operating while BCP is active.
5	Document compliance strategy with rationale for thresholds applied and approaches to mitigation. The strategy should include a recovery plan to return to normal activities post crisis.	Inability to comply with regulatory requirements (e.g. no/late reporting of ICSRs)	Create an overarching Master deviation under which all decisions are captured and list key root causes	Include in BCP To be described in the PSMF

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6	Any major non-compliance that is driven by implementation of strategy should be tracked however usual deviation process should be delayed until crisis is over.	Inability to comply with regulatory requirements	Reduce level of investigation as root cause is known	Implement planned deviation against usual deviation process for key relevant/impacted processes
7	Maintain oversight and monitoring of all deviations from normal process across the Quality Management System.	Functional deviations, Affiliate deviations	Log deviation centrally but create standard root cause i.e. crisis situation Delay determination of any corrective actions until pandemic is declared over by WHO or capacity is back to normal and stable - corrective actions should typically not be required as strategy decisions should not require remediation activities. Deprioritise routine updates to PSMF e.g. annexes Pause activity on routine ongoing CAP actions except for critical findings and significant major findings	
8	Backlogs are inevitable, prepare for backlogs and define strategy for addressing; keep in mind the reason/value of proposed actions.	ICSRs, literature screening, reconciliations, deviation, investigations	Determine and document which backlogs will be addressed post crisis and which will not e.g. if non-serious cases limited data entry and reduced follow-up of non-serious cases then these cases will not be revisited but approach described in PSURs	

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	Those activities that are considered less critical and do not impact the safe use of medicines should be documented and it should be considered if these are temporarily halted and addressed post crisis or if these will not be addressed post crisis.			
9	Inform Partners of strategy for meeting contractual obligations during the crisis situation.	Conduct no partner audits until crisis over. Do not accept requests to be audited by partners.	Proactively communicate decision and principles with business alliance partners. Propose post crisis principles for addressing backlogs /noncompliance with the licensing agreement Circulate MOU to partners if appropriate Accept partner risk-based approach to meeting contractual obligations during COVID-19 crisis.	Agree on risk strategy to resolve issues arising
10	To maintain appropriate Safety Governance at all times e.g. senior safety committee, senior labelling committee.	Maintain oversight over global product benefit-risk and continue to review ad hoc safety topics as they arise; document decisions as appropriate.	Prioritize safety topics with potential adverse impact on benefit:risk profiles of products. Allowing a more flexible approach with regard to the minimum number of attendees/critical roles that should be represented.	

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11	Ensure optimal use of available resource at all times. Consider redeployment of staff from areas where workload may have fallen. Proactively identify staff with transferable skills capabilities and experience to enable fast reallocation of responsibilities.	Medical/scientific staff could be moved across drug/product safety teams or moved into data analytics to support key product activities.	All functions to identify staff with transferable capabilities and be ready to redeploy staff appropriately	Enhance cross collaboration opportunities
12	Reduce and/or postpone internal pharmacovigilance audits.	Allow for- cause audits, postpone all other or perform selected virtual audits considering resource availability and criticality of conducting the audit		