Journal of Pharmaceutical Innovation (2027) 22:106
https://doi.org/10.1007/s12247-026-10967-3

RESEARCH

Integrating Business Impact Analysis, Scenario-Based FMEA, and Business Continuity Planning in Pharmaceutical Manufacturing: A Product-Level Case Study

Ivana Mitrevska[1,2] · Sandra Boshnachki[2] · Sonja Burcevska[2] · Elizabeta Karadzinska[2] · Olivera Paneva[2]

Received: 23 April 2026 / Accepted: 4 August 2026

Abstract

Purpose This study evaluated the product-level integration of Business Impact Analysis (BIA), scenario-based Failure Mode and Effects Analysis (FMEA), and Business Continuity Planning (BCP) for a selected finished medicinal product.

Methods A single-site case study was conducted for cefixime 400 mg film-coated tablets in a GMP-regulated pharmaceutical organization. Data were collected over approximately six months through four structured questionnaires, documentary and operational-record review, facilitated interviews, and cross-functional consensus sessions. BIA established Maximum Tolerable Downtime (MTD), Recovery Time Objective (RTO), and Work Recovery Time (WRT). Twenty-five de-identified scenarios, were assessed using predefined 1–4 scales for severity, frequency, and detectability; RPN was calculated as S × F × D.

Results IT and Technology had the shortest recovery requirement (MTD 48 h, RTO 24 h, WRT 24 h). Twelve scenarios were low risk and 13 were medium risk; none was high or critical. Material-transport interruption and adverse commercial and market conditions had the highest RPN of 16. Thirteen scenarios required additional controls. Sensitivity analysis showed that selected medium risks could move to high risk after a one-level score increase.

Conclusion The integrated approach supported transparent recovery prioritization and translation into product-specific continuity actions. Findings are context-specific and require prospective testing and replication.

Keywords Business impact analysis · Business continuity planning · Failure mode and effects analysis · pharmaceutical manufacturing · Operational resilience · Quality risk management

Abbreviations

API	Active Pharmaceutical Ingredient
BCDR	Business Continuity and Disaster Recovery
BCP	Business Continuity Plan/Business Continuity Planning
BIA	Business Impact Analysis
CSV	Computerized System Validation
D	Detectability
EMA	European Medicines Agency
EU	European Union
F	Frequency
FDA	U.S. Food and Drug Administration
FMEA	Failure Mode and Effects Analysis
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HAZOP	Hazard and Operability Study
HVAC	Heating, Ventilation, and Air Conditioning
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
IT	Information Technology
MTD	Maximum Tolerable Downtime
NIST	National Institute of Standards and Technology

✉ Ivana Mitrevska
ivana.mitrevska@ugd.edu.mk;
i.mickoska@Alkaloid.com.mk

[1] Faculty of Medical Sciences, Goce Delcev University, Krste Misirkov, 10A, Stip 2000, North Macedonia

[2] Quality Assurance, Alkaloid AD Skopje, Blvd. A. Makedonski 12, Skopje 1000, North Macedonia

Published online: 22 August 2026

QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RPN	Risk Priority Number
RTO	Recovery Time Objective
S	Severity
WHO	World Health Organization
WRT	Work Recovery Time

Introduction

The continuous availability of medicines depends on coordinated raw-material sourcing, transport, manufacturing, quality control, batch certification and release, warehousing, distribution, regulatory maintenance, and validated information systems. Shortages generally arise from interacting manufacturing, quality, supply, demand, commercial, regulatory, and logistical causes rather than from a single isolated event [1–4]. Their consequences may include treatment delay, substitution, medication error, increased workload and expenditure, and adverse patient outcomes [5–8]. These effects make product-specific knowledge of the complete operational pathway important for prevention and recovery planning.

For this study, an operational disruption was defined as an unplanned event or condition capable of interrupting, materially delaying, or reducing the capacity of activities required to manufacture, test, certify, release, maintain the regulatory status of, store, distribute, or supply the selected product. Internal causes may include equipment, utility, staffing, analytical, procedural, or computerized-system failures; external causes may include supplier interruption, transport blockade, geopolitical instability, market change, or extreme weather.

Regulatory policy increasingly emphasizes proactive shortage prevention. Regulation (EU) 2022/123 strengthened the European Medicines Agency role in crisis preparedness and shortage management [9]. EMA guidance and the Shortage Prevention Plan and Shortage Mitigation Plan pilot require product-specific vulnerability assessment, responsibilities, escalation, prevention, and mitigation arrangements [10–12]. The European Court of Auditors and subsequent European policy initiatives have also highlighted structural vulnerabilities, diversification, strategic capacity, and supply-chain transparency [13–15]. FDA guidance similarly recommends proactive risk-management plans for hazards that may cause drug shortages [16].

Business Continuity Management provides the organizational system for preparing for, responding to, and recovering from disruption. ISO 22,301 establishes requirements for a business continuity management system, ISO/TS 22,317 guides BIA, and ISO/TS 22,318 addresses supply-chain continuity [17–19]. NIST IR 8286D and quantitative BIA research further relate organizational objectives, dependencies, impacts, and recovery priorities [20, 21]. BIA establishes time-based requirements through MTD, RTO, and WRT, but does not by itself identify the specific scenarios that may interrupt a process.

Pharmaceutical Quality Risk Management provides the complementary scenario perspective. ICH Q9(R1) supports proportionate, knowledge-based risk assessment, control, communication, and review [22], while IEC 60,812 describes systematic FMEA practice [23]. Conventional RPN remains useful but has recognized limitations because ordinal ratings are subjective, different score combinations can yield the same product, and equal mathematical treatment does not imply equivalent operational meaning [24–26]. Component scores, uncertainty, controls, and scenario context must therefore accompany the numerical result.

BIA, FMEA, and BCP answer different but connected questions. BIA determines what must be recovered and by when; FMEA identifies what may prevent continuity and where additional controls are required; BCP defines who acts, how escalation occurs, and how recovery is implemented. Integrated continuity research and organizational-resilience literature support linking impact assessment, risk treatment, and recovery planning [21, 27–30]. Pharmaceutical resilience studies additionally emphasize inventory, dual sourcing, agility, API visibility, and upstream concentration [31–35], while WHO and GDP guidance reinforce consistent terminology and controlled distribution arrangements [36, 37]. Validated systems and data integrity are also central because digital disruption may affect multiple regulated processes simultaneously [38].

The present study addresses a practical reporting gap by documenting how recovery parameters, scenario-level FMEA, evidence triangulation, and BCP actions were connected within a single finished-product case study. Accordingly, the objective was to evaluate the product-level integration of BIA, scenario-based FMEA, and BCP for cefixime 400 mg film-coated tablets within one GMP-regulated organization. The study addressed the following research questions: (i) Which product-supporting functions have the shortest recovery requirements? (ii) Which disruption scenarios have the highest priority under the predefined FMEA scales? (iii) How can BIA and FMEA findings be translated into product-specific continuity arrangements? (iv) How stable are the resulting priorities under plausible variations in scenario scores and recovery parameters? The numerical results are case-specific and require reassessment before application to other products, manufacturing sites, or organizational settings.

Materials and Methods

Study Design and Setting

A single-site, single-product organizational case-study design was used to examine the integration of BIA, scenario-based FMEA, and BCP in a GMP-regulated pharmaceutical manufacturer. The unit of analysis was the end-to-end pathway for cefixime 400 mg film-coated tablets, extending from procurement and inbound transport through receipt, storage, manufacture, quality-control testing, batch certification and release, distribution, regulatory maintenance, commercial activities, Quality Assurance, finance, and IT. The final controlled BIA report was completed on 24 February 2025. The analytical structure was informed by ISO 22,301, ISO/TS 22,317, ICH Q9(R1), and IEC 60,812 [17, 18, 22, 23]. The study workflow is summarized in Supplementary Material, Table S1.

Governance Structure and Expert Panel

Quality Assurance coordinated the assessment. The core panel comprised the responsible manager and deputy manager from each of six principal functional domains, providing 12 senior subject-matter experts, each with more than 15 years of organizational and process experience. The six principal domains represented manufacturing, quality control and quality assurance, supply and procurement, logistics and distribution, regulatory affairs, and IT and technology. The work was facilitated by the Qualified Person responsible for the product, with more than 15 years of pharmaceutical experience, and the company risk-management and business-continuity coordinator, with more than five years of relevant experience. The approximately six-month process was prepared by the facilitators, reviewed by Quality Assurance management, and approved at executive-management level. Roles and governance are detailed in Supplementary Material, Table S1.

Data-Collection Instruments and Procedure

Four structured, process-specific questionnaires covered raw and packaging material supply; manufacturing; finished-product testing, release, storage, and distribution; and commercial, regulatory, market, and financial processes. They addressed suppliers and alternatives, lead times, transport routes and environmental conditions, warehouse capacity, staffing and competence, equipment and spare parts, utilities, validated systems, backup and recovery, laboratory resources, regulatory maintenance, market conditions, financial exposure, and existing controls. Questionnaire domains and evidence sources are presented in Supplementary Material, Table S2.

Information was collected through completed questionnaires, facilitated interviews, cross-functional working sessions, joint risk-assessment meetings, documentary review, follow-up communication, and consensus review of the draft findings. The exact number of meetings was not retained as a research variable because the assessment was iterative. Sessions clarified incomplete responses, reconciled interdependent assumptions, and established the rationale for recovery parameters and FMEA scores.

Documentary and Operational Evidence

Expert judgments were triangulated, where available, against approved procedures and process maps, supplier and transport information, procurement and delivery records, inventory and storage data, equipment maintenance, qualification and validation records, change controls, environmental monitoring, laboratory records, IT backup and recovery procedures, regulatory information, transport qualification, and previous operational events. The evidence distinguished observed events, non-observed scenarios, active risks, and risks controlled through monitoring or contingency arrangements. This supported internal plausibility but was not treated as external predictive validation or as a statistically representative event database. Examples are provided in Supplementary Material, Table S7.

Process and Dependency Mapping

The pathway was mapped from material supply to market availability, including manufacturing, laboratory, release, storage, transport, regulatory, commercial, financial, Quality Assurance, and IT dependencies. Ishikawa analysis organized vulnerabilities under Manpower, Methods and processes, Materials and supply, Machines and technologies, Measurements and information, and Environment and infrastructure. The principal factors are shown in Fig. 1, while the integrated BIA-FMEA-BCP framework and detailed dependency map are provided in Supplementary Material, Fig. S1 and Table S3. The domains encompassed staffing and competence; procedures and restart arrangements; materials, suppliers, transport routes and spare parts; equipment, utilities and validated systems; monitoring, records and data integrity; and infrastructure, environmental and geopolitical conditions.

Business Impact Analysis

BIA proceeded from scope definition and process mapping to identification of critical activities and dependencies, assessment of disruption consequences, determination of recovery requirements, scenario risk assessment, risk treatment,

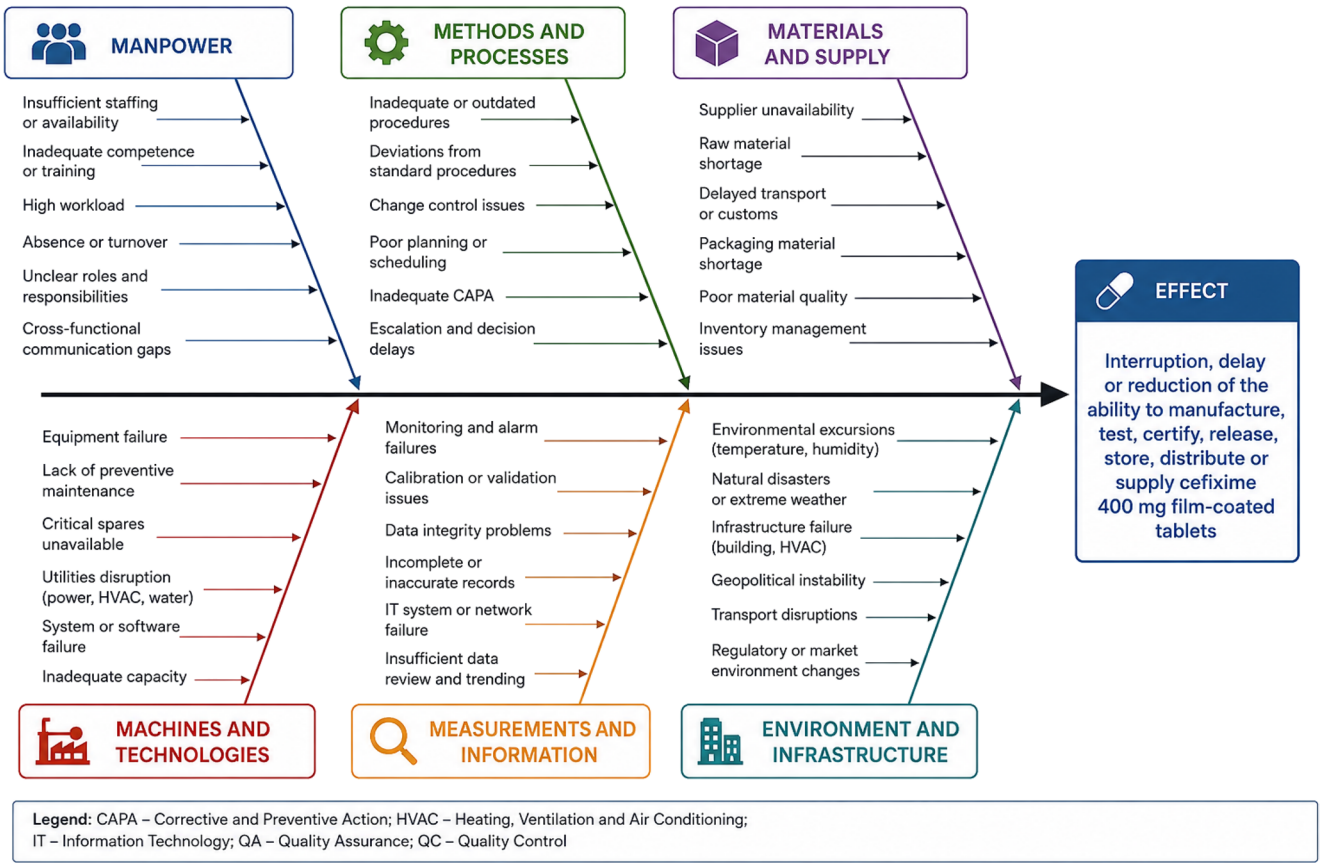

Fig. 1 Ishikawa cause-and-effect analysis of factors that may disrupt manufacture, batch release, and market supply of cefixime 400 mg film-coated tablets

and translation into continuity arrangements. MTD was the longest tolerable interruption before consequences became unacceptable; RTO was the targeted restoration period; and WRT was the additional time required to clear backlogs, reconcile data and records, and return to acceptable operation. Values considered stocks, supplier and transport lead times, warehouse capacity, manufacturing and service requirements, alternatives, testing and release timelines, IT recovery, regulatory deadlines, market consequences, and normalization time. Final values were established by cross-functional consensus. Principal values are reported in Table 1 and detailed rationales in Supplementary Material, Table S4.

Scenario-based FMEA

FMEA was conducted at scenario level rather than by assigning one aggregate RPN to each broad function. Twenty-five completed scenarios covered supply, inbound logistics, storage, manufacturing, quality control, finished-product distribution, commercial and regulatory continuity, finance, Quality Assurance, and IT. For publication, the de-identified scenarios were renumbered consecutively from 1 to 25 to remove a gap in the controlled internal sequence; this editorial renumbering did not change scenario content, scores, controls, or results. The full register is provided in Supplementary Material, Tables S6A and S6B.

FMEA Scales and Decision Rules

Severity, frequency, and detectability were scored from 1 to 4 using predefined company anchors. Severity ranged from negligible impact to major or potentially irreversible impact. Frequency ranged from an event considered unlikely or not previously observed to an event occurring approximately monthly. Detectability ranged from detection at process initiation to near-impossibility of detection before impact. RPN was calculated as S × F × D. Scores of 1–4 were low, 5–16 medium, 17–32 high, and 33–64 critical; the associated action expectations are reproduced in Supplementary Material, Table S5.

Consensus and Management of Differing Judgments

Participants did not complete independent score sheets. For each scenario, the panel reviewed the failure, causes, consequences, existing controls, prior experience, documentary evidence, dependencies, quality and regulatory implications,

Table 1 Product-level recovery parameters

Function/process	MTD	RTO	WRT	Interpretation
IT and Technology - disaster, major failure, or incident	48 h	24 h	24 h	Highest urgency
Finished-product transportation - environmental/temperature conditions	10 days	2–3 days	7 days	Highest urgency
Inbound material transportation - environmental/temperature conditions	11 days	3–4 days	7 days	Highest urgency
Manufacturing equipment, machinery, and servicing	20 days	10 days	10 days	High priority
Delivery of materials to the company	8 months	60 days	6 months	Extended buffering
Receipt and storage of raw materials	8 months	60 days	6 months	Extended buffering
Business development and sales	Approx. 3 years	1–2 years	8 months	Long-horizon strategic impact
Regulatory maintenance and sales support	Approx. 3 years	1–2 years	8 months	Long-horizon market-access impact
Medical marketing	Approx. 3 years	1–2 years	8 months	Long-horizon market-position impact
Quality Assurance - GMP certification	Approx. 3 years	1–2 years	8 months	Strategic GMP-certification maintenance and long-horizon compliance governance

and scoring anchors. Differences were resolved by returning to the relevant anchor and evidence until consensus was reached on scores, recovery values, actions, owners, and target periods. Because independent ratings were not generated or retained, ICC and Kendall concordance could not be calculated. Consensus reduced dependence on one assessor but could not eliminate subjectivity or group effects.

Risk Treatment and Continuity Planning

The register recorded whether additional controls were required, the proposed action, the score component or recovery capability targeted, the responsible function, implementation period, and residual-risk reassessment status. BIA and FMEA outputs were then translated into a draft product-specific BCP with activation criteria, escalation, responsibilities, communication, alternative resources, recovery activities, and return-to-normal criteria. Existing controls, planned measures, and actions awaiting prospective effectiveness verification were distinguished. Scenario actions are detailed in Supplementary Material, Table S6B, and BIA-to-BCP traceability in Table S9.

Sensitivity and Robustness Analysis

A deterministic analysis varied S, F, or D separately by one adjacent level within the permitted 1–4 range for each scenario. Resulting RPNs, category transitions, and retention in the highest-priority group were recorded. Weighted additive scoring analyses used equal, severity-dominant, frequency-dominant, and detectability-dominant weights without replacing the approved multiplicative RPN method. Rank stability was evaluated using Spearman correlation. MTD, RTO, and WRT were additionally varied by ±20%. Secondary weighted additive scoring analyses were performed using equal weighting and three illustrative criterion-emphasis assumptions. For each scenario, the weighted score was calculated as $WS = {}_{wS}S + {}_{wF}F + {}_{wD}D$, where ${}_{wS} + {}_{wF} + {}_{wD} = 1.00$. Equal weighting assigned one-third of the total weight to each criterion. In the severity-, frequency-, and detectability-dominant analyses, a weight of 0.50 was assigned to the emphasized criterion and 0.25 to each of the other two criteria. The alternative scores were calculated directly from the verified scenario-level S, F, and D values and were used only to examine ranking robustness; they did not replace the company-approved multiplicative RPN method. Spearman's rho was used descriptively to quantify rank concordance between the baseline RPN ordering and the alternative weighted rankings, with tied scores assigned average ranks. Full results are reported in Supplementary Material, Table S8.

Ethical and Confidentiality Considerations

The work evaluated an internal organizational quality-risk and business-continuity process. Employees contributed professional operational information within established responsibilities; no patients, interventions, biological materials, health information, or individually attributable employee outcomes were involved. Formal ethics-committee approval was therefore not required. Only aggregated and de-identified findings are reported. Supplier identities, prices, exact stock levels, customers, internal security details, and confidential procedure codes were excluded. The organization authorized scientific publication of the aggregated non-confidential findings.

Results

Product Pathway and Dependencies

The mapping confirmed that continuity depended on a connected pathway rather than manufacturing alone. Material availability and inbound transport constrained production scheduling; manufacturing recovery did not

restore supply unless testing, certification, storage, and distribution were available; and IT supported documentation, traceability, communication, and access across functions. The complete pathway and cross-cutting dependencies are shown in Supplementary Material, Fig. S1 and Table S3.

Recovery-Time Priorities

The final BIA contained recovery parameters for ten product-supporting functions. IT and Technology had the shortest tolerance for interruption, followed by finished-product transport, inbound material transport, and manufacturing equipment and servicing (Table 1).

These long-horizon values apply to the cumulative strategic consequences of prolonged loss of the specified support capability and do not represent an acceptable period of complete absence of routine QA, regulatory, commercial, or medical activities. To compare recovery horizons ranging from hours to years, the values were converted to days and plotted on logarithmic scales in Fig. 2; ranges were plotted at their midpoint and bubble area represents WRT. The figure separates immediate operational recovery from longer-horizon strategic continuity.

Overall FMEA Risk Profile

RPN values ranged from 2 to 16, with a median of 6. Twelve scenarios were low risk and 13 were medium risk; none was high or critical (Table 2). All medium-risk scenarios were assigned additional treatment, whereas low risks remained under established controls and routine monitoring. The complete de-identified dataset is provided in Supplementary Material, Tables S6A and S6B.

Distribution by operational domain

Materials, supply, and inbound logistics contained the largest number of scenarios. Commercial, regulatory, market, and financial processes contained four medium risks, while Quality Assurance contained two medium risks and IT one (Table 3). Grouping was descriptive and did not replace scenario-level assessment.

Highest-Priority Scenarios

Scenarios 2 and 16 had the maximum baseline RPN of 16: interruption of material transportation and adverse commercial and market conditions. Scenarios 14 and 21 had RPN 12 for equipment and spare-part availability and currency

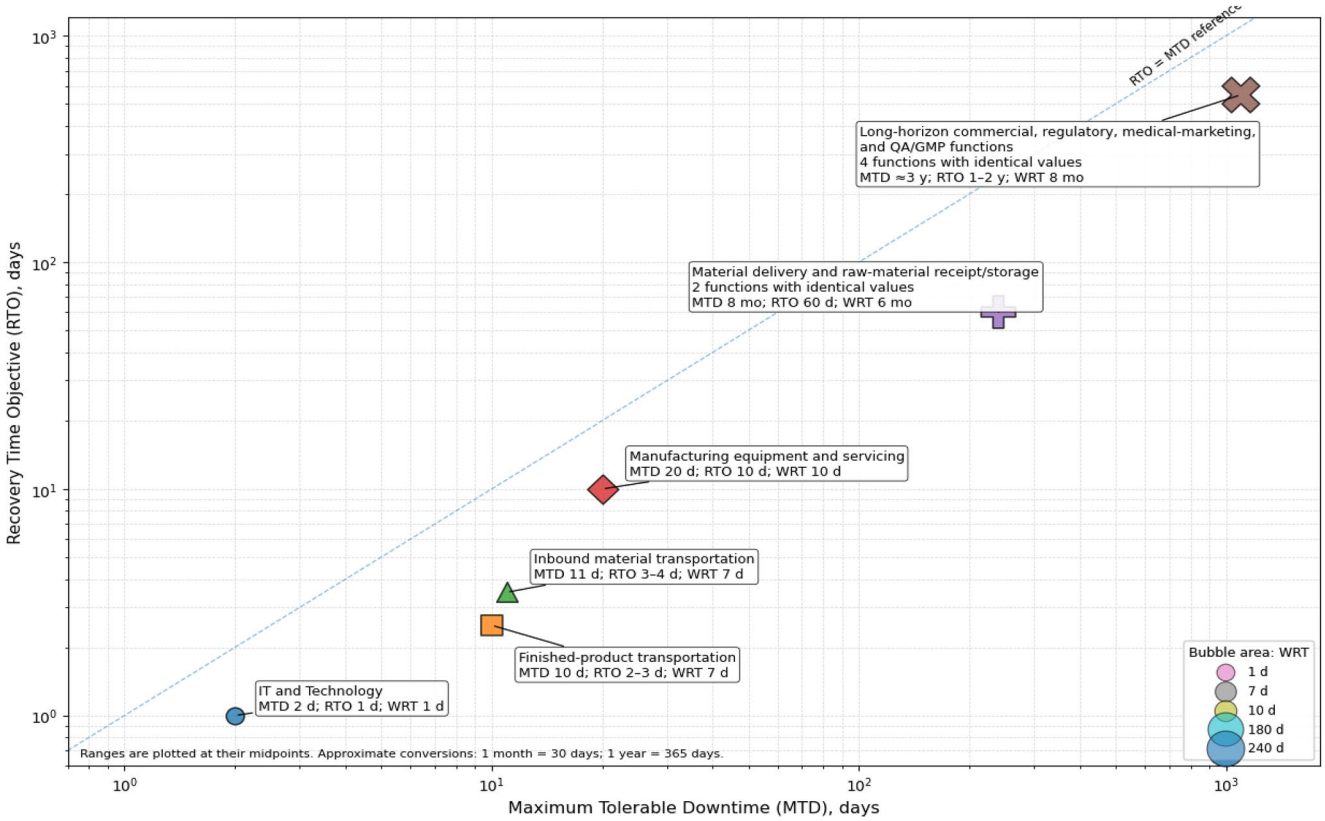

Fig. 2 Recovery-priority matrix for product-supporting functions. MTD and RTO are shown in days on logarithmic scales; bubble area represents WRT. Ranges are plotted at their midpoint

Table 2 Distribution of the 25 FMEA scenarios

Risk category	RPN range	Number	Proportion
Low	1–4	12	48%
Medium	5–16	13	52%
High	17–32	0	0%
Critical	33–64	0	0%
Total		25	100%

Table 3 Risk distribution by operational domain

Operational domain	*n*	Low	Medium	Highest RPN	Additional measures
Materials, supply, and inbound logistics	8	4	4	16	4
Manufacturing	3	2	1	8	1
Quality control	2	2	0	4	0
Finished-product storage and distribution	2	1	1	8	1
Commercial, regulatory, market, and financial	6	2	4	16	4
Quality Assurance	2	0	2	8	2
IT and Technology	2	1	1	9	1
Total	25	12	13	16	13

devaluation, respectively. Scenario 24, concerning IT continuity during disasters or major incidents, had RPN 9. Table 4 summarizes the principal medium risks and controls.

Action Status and Documentary Triangulation

All 13 medium-risk scenarios had additional measures assigned, but numerical post-implementation S, F, D, and residual RPN values were not yet complete. Four scenarios were explicitly recorded as not yet accepted after treatment and one residual-risk field remained incomplete. These actions therefore represent planned or ongoing treatment rather than demonstrated risk reduction. Ownership, targets, and residual-risk status are provided in Supplementary Material, Table S6B.

Documentary and historical evidence supported scenario plausibility and scoring. Examples included a prior communication failure, one finished-product storage event, no reported HVAC failure, a 2024 equipment-related change control, regulatory and market experience, and the estimated rarity of a major IT disaster (Table 5). This evidence was internally informative but not externally predictive.

Sensitivity and Recovery Robustness

Across 123 feasible one-level perturbations, 67 (54.5%) retained the original category, 30 (24.4%) moved from low to medium, 17 (13.8%) moved from medium to low, and 9 (7.3%) moved from medium to high; none became critical. Medium-to-high transitions involved scenarios 2, 14, 16, 21, and 24. Therefore, baseline absence of high risk depended partly on consensus-derived component scores, particularly for RPN 9–16.

Table 4 Principal medium-risk scenarios and controls

No.	Scenario	S/F/D	RPN	Established controls	Additional measure
2	Material-transport interruption	4/2/2	16	Alternative routes, modes and carriers	Maintain feasible alternatives and activation capacity
16	Adverse commercial/market conditions	4/2/2	16	Positioning, education and market monitoring	Indication/market development and stakeholder coordination
14	Equipment or critical spare parts unavailable	3/2/2	12	Stock planning and supplier monitoring	Critical-spare strategy and qualified alternative equipment
21	Currency devaluation	2/3/2	12	Daily monitoring, financial analysis and stable-currency invoicing	Reduce exposure to high-risk markets
24	Major IT disaster or incident	3/1/3	9	BCDR procedures, backup and recovery controls	Periodic restore tests and scenario exercises
3	Material-transport environmental conditions	2/2/2	8	Carrier qualification and temperature monitoring	Rapid carrier escalation and alternative transport
5	Interdepartmental communication failure	2/2/2	8	Enterprise-system notifications	Warehouse communication action plan
7	Manufacturing-equipment failure	4/1/2	8	Emergency service, spares and restart procedure	Additional spares and alternative equipment
15	Finished-product transport conditions	2/2/2	8	Qualified transport and monitoring	Carrier escalation and corrective response
23	Product/process quality failure	4/1/2	8	Pharmaceutical Quality System and GMP controls	Continual process and technology improvement

Scenarios 2 and 16 remained within the highest-priority group under equal weighting and under the three criterion-dominant assumptions. Spearman's rank correlations with the baseline RPN ordering were 0.953 for equal weighting, 0.746 for severity-dominant weighting, 0.940 for frequency-dominant weighting, and 0.966 for detectability-dominant weighting. These coefficients

Table 5 Examples of documentary and historical triangulation

No.	Risk topic	Evidence	Use in assessment
5	Warehouse communication	A prior communication failure	Supported F = 2
12	Finished-product storage conditions	One event during the prior year	Supported F = 2 and strong detectability
8	Manufacturing HVAC	No reported failure	Supported low frequency and early detection
14	Equipment/spares	2024 equipment transition managed by change control	Supported medium risk and additional equipment strategy
17	Marketing-authorisation maintenance	No event detected in 2024	Supported low frequency with significant consequence
20	Prescribing environment	No product event, but restrictions in some markets	Supported horizon monitoring
24	IT disaster/major incident	Estimated once in 10–20 years; limited pre-event detection	Supported S = 3, F = 1, D = 3
1	Material availability	No complete supply failure observed	Supported low frequency with stock and alternatives

were interpreted descriptively as measures of rank concordance rather than as inferential validation of the risk model. Under ±20% variation, IT remained most time-critical; the two transport processes remained in the highest recovery group but could exchange order; manufacturing equipment remained next; and long-horizon functions remained separated. Spearman's rho was used descriptively to quantify rank concordance between the baseline RPN ordering and the alternative weighted rankings. Full calculations are in Supplementary Material, Table S8.

Translation Into Continuity Planning

The combined findings were translated into a draft product-specific BCP defining activation triggers, response levels, accountable functions, communication and escalation, quality and regulatory controls, alternatives for suppliers, routes, storage and technical resources, IT backup and recovery, return-to-normal criteria, testing, and periodic review. The plan prioritized IT, temperature-sensitive transport, and manufacturing equipment. It demonstrated structured translation from analysis to continuity planning, but not verified effectiveness through repeated exercises or actual activation. The traceability matrix is provided in Supplementary Material, Table S9.

Discussion

Principal Findings and Integrated Interpretation

The principal finding was that recovery-time priority and scenario risk priority were complementary rather than interchangeable. IT had the shortest RTO, whereas material-transport interruption and adverse commercial conditions had the highest RPN. A low-frequency event may require immediate recoverability because its occurrence could interrupt several regulated processes simultaneously. Conversely, a longer-horizon commercial or regulatory function may receive a high scenario score because sustained disruption threatens market availability and business viability. This distinction supports ICH Q9(R1) expectations that decisions consider impact, uncertainty, knowledge, and context rather than a numerical score alone [22].

The profile of 12 low and 13 medium risks indicates an established control environment with remaining vulnerabilities. Equal RPNs did not imply equivalent treatment: material transport required logistical redundancy, whereas adverse commercial conditions required market, regulatory, medical, and financial action. This illustrates the recognized mathematical and interpretive limitations of conventional RPN [24–26]. Sensitivity analysis strengthened interpretation by showing that principal priorities were generally stable while selected boundary scenarios could move to high risk after modest score changes.

Material Supply and Transportation Vulnerabilities

Material transport was both the highest-ranked scenario and one of the most urgent recovery processes. Pharmaceutical supply depends on suppliers, routes, carriers, customs, storage conditions, geopolitical stability, and qualified alternatives [14, 15, 19, 31–35]. The findings support qualified route and carrier alternatives, escalation pathways, route and geopolitical monitoring, contingency transport capacity, defined temperature-excursion responsibilities, and stock decisions linked to actual lead time. GDP requirements further require suitable vehicles, environmental control, documentation, traceability, deviation management, and allocated responsibilities [37]. Long MTD values for material delivery and storage reflected buffering through stock and planning, not low importance; they should be reassessed when demand, suppliers, lead times, or market coverage change.

Manufacturing Equipment and Digital Resilience

Equipment and spare-part availability combined an RPN of 12 with a relatively short recovery horizon. Preventive

maintenance reduces failure likelihood but does not guarantee timely restoration. Recovery also depends on critical spares, service response, technical competence, approved restart and line-clearance procedures, material disposition, alternatives, and qualification, validation, and change control. Severity-dominant weighting appropriately increased the prominence of high-impact, low-frequency manufacturing and quality scenarios [22]. Proposed alternative equipment and spare-part arrangements should remain classified as planned controls until implementation and residual-risk reassessment are documented.

IT occupied the most time-critical position because validated systems, networks, backup, communication, and electronic records support multiple functions. Recovery requires more than hardware restart: systems, data, interfaces, audit trails, configurations, access, and downtime records must remain reliable and fit for use [38]. Periodic exercises should test backup restoration, failover, manual contingencies, cybersecurity escalation, record reconciliation, return-to-service criteria, and achievement of the 24-h RTO. A documented backup alone does not demonstrate recoverability.

Commercial, Regulatory, and Market Continuity

The maximum RPN for adverse commercial and market conditions broadened continuity beyond physical manufacture. A technically manufacturable medicine may still become unavailable because of regulatory delay, prescribing restriction, reimbursement or market change, currency instability, or commercial unsustainability [1–4, 13]. EMA shortage-prevention guidance expects companies to assess vulnerabilities across the full supply chain and distinguish preventive from mitigating arrangements [10–12]. Regulatory horizon scanning, timely maintenance of authorisations, stakeholder engagement, market diversification, medical monitoring, and financial controls were therefore legitimate continuity measures rather than peripheral business activities.

Translation into BCP and Managerial Implications

The practical contribution was the traceable conversion of BIA and FMEA outputs into a draft BCP. BIA identified what required recovery and by when; FMEA identified which scenarios required additional prevention or mitigation; BCP assigned activation, action, communication, and recovery. This sequence is consistent with continuity-management models that treat BIA as an input to strategy and planning [17–21, 27]. It also creates an operational bridge between pharmaceutical quality risk management and product-specific shortage prevention [10–12].

Management should distinguish administrative action closure from demonstrated effectiveness. IT performance should be verified through restoration time and backup tests; transport controls through alternative-route activation and excursion performance; equipment controls through downtime, repair time, and spare availability; supply controls through stock coverage and qualified alternatives; and regulatory, commercial, and quality controls through overdue actions, emerging restrictions, release backlog, inspection commitments, and residual-risk status (Table 6).

Because the BCP remained a draft implementation document, its effectiveness should be established through tabletop and targeted scenario exercises, restoration and failover testing, supplier and transport contingencies, measurement of actual recovery time, residual-risk reassessment, and management review of differences between planned and demonstrated performance.

Robustness and Internal Validation

Documentary and historical triangulation allowed the panel to distinguish observed events, non-occurrence during the reviewed period, active risks, and scenarios managed by established controls. Sensitivity analysis provided a second layer of robustness: principal priorities were not products of one weighting assumption, but several middle rankings remained sensitive to modest score changes. These analyses do not support probabilistic prediction because historical data were not standardized or sufficient for reliable distribution estimation. Internal triangulation is therefore evidence support, not external validation. Reassessment is required when operations, technologies, suppliers, markets, or controls change.

Transferability and Relationship to Supply-Chain Resilience

The findings align with resilience models emphasizing awareness, mitigation, preparedness, response, adaptation, and proportionate allocation of resources [28–35]. The product-level approach adds operational detail by identifying the processes supporting one medicine, tolerable interruption, required controls, accountable functions, and evidence of recovery readiness. It can inform broader shortage-prevention and vulnerability assessments but cannot replace national or international analyses [33–36].

The analytical sequence may be configured for other products, but the numerical values are not directly transferable. Recovery priorities depend on dosage form, process complexity, stock coverage, supplier geography, transport and storage requirements, alternative sites and equipment, testing and release timelines, digital architecture, regulatory

Table 6 Managerial priorities from the integrated analysis

Priority area	Main implication	Accountable functions	Effectiveness indicators
IT and Technology	Demonstrate restoration within 24 h	IT, system owners, QA/CSV, process owners	Restore-test success, actual recovery time, unresolved deviations
Material transport	Maintain feasible routes, carriers and escalation	Supply Chain, Logistics, QA	Activation time, carrier availability, interruption duration
Finished-product transport	Protect conditions and customer continuity	Logistics, QA, distributors	Excursions, delays, alternative-carrier activation
Manufacturing equipment	Ensure service and critical-spare capacity	Production, Engineering, Maintenance, QA	Downtime, repair time, spare availability
Material supply	Link stock and alternatives to lead time	Procurement, Supply Chain, Planning, QA	Coverage, supplier performance, qualified alternatives
Commercial/regulatory/market	Maintain horizon monitoring and timely action	Business Development, Sales, Regulatory, Medical, Finance	Restrictions, overdue actions, concentration, currency exposure
Quality and GMP	Protect certification, product quality and release	QA, QC, QP, Production	Critical deviations, release backlog, commitments
Risk governance	Reassess after change, event or exercise	Risk coordinator, QA, process owners, management	Open risks, overdue actions, residual-risk acceptance

obligations, patient need, therapeutic substitutes, and organizational maturity. Sterile, biological, cold-chain, sole-source, or globally concentrated products may require markedly different priorities.

Unlike HAZOP, fault tree analysis, and bow-tie analysis, which primarily examine hazards, causal pathways, failure propagation, and control barriers, the present approach was selected to integrate time-dependent recovery requirements with scenario-level prioritization and the assignment of operational continuity responsibilities [39–41]. The study does not claim superiority over these methods; rather, it addresses a complementary decision-making need by linking impact tolerance, risk treatment, and recovery planning.

Strengths, Limitations, and Future Research

A principal strength of this study was its complete coverage of the product pathway and the participation of experienced cross-functional experts. Additional strengths included the use of structured questionnaires, controlled company scoring anchors, documentary triangulation, a complete de-identified scenario register, sensitivity analysis, and translation of the findings into accountable continuity actions. Collectively, these features improved the transparency and traceability of the assessment beyond a purely conceptual framework.

Interpretation remains bounded by the single-product, single-site design. Scores were established by facilitated consensus and independent ratings were unavailable, preventing formal inter-rater reliability analysis. Historical evidence supported operational judgment but did not provide incidence rates or a probabilistic model. Dependencies were mapped qualitatively rather than by network centrality or cascade simulation. Several controls were planned or in progress, residual-risk reassessment was incomplete, and the draft BCP had not been validated through repeated exercises or actual activation.

Future studies should replicate the approach across products and sites, use independent preliminary scoring and inter-rater analysis, collect prospective disruption, near-miss, and actual recovery-time data, compare planned with demonstrated RTO, quantify dependencies where data permit, compare RPN with alternative multi-criteria methods, and evaluate controls before and after implementation. Exercises and actual disruptions should update BIA, FMEA, BCP, and Shortage Prevention and Mitigation Plans within a continual-improvement lifecycle.

Conclusion

This case study showed that product-level BIA, scenario-based FMEA, and BCP provide complementary information for pharmaceutical continuity management. IT had the shortest recovery requirement, while material-transport interruption and adverse commercial conditions had the highest RPN. The integrated analysis linked recovery urgency, disruption controls, accountable functions, and continuity arrangements. Sensitivity analysis supported the principal priorities but identified boundary scenarios capable of moving to high risk. The study demonstrates

structured assessment and planning, not post-implementation effectiveness or universal transferability. Prospective exercises, residual-risk reassessment, and replication across products and sites are required to establish broader applicability.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12247-026-10967-3.

Acknowledgements The authors thank the Quality Assurance, Quality Control, Production, Regulatory Affairs, business, fi-nance, logistics, and IT teams for their contributions to the questionnaires, interviews, working sessions, and risk assessment.

Authors contributions Conceptualization, I. M.; Methodology, I. M. and S. B.; Investigation, I.M. and S. B.; Writing-original draft preparation, I. M.; Writing-review and editing, E. K. and S. B.; Supervision, O. P. All authors have read and agreed to the published version of the manuscript.

Funding This research received no external funding.

Data Availability The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to confidentiality and proprietary restrictions related to the pharmaceutical manufacturing environment, the data are not publicly available.

Declarations

Ethics approval Formal ethics approval was not required because this was an internal organizational quality-risk and business-continuity assessment without patients, interventions, biological materials, health information, or individually attributable employee outcomes.

Consent to participate Not applicable.

Consent for Publication Alkaloid AD Skopje authorized publication of the aggregated and non-confidential findings.

Competing interests The authors declare no competing interests.

References

1. Shukar S, Zahoor F, Hayat K, Saeed A, Gillani AH, Omer S, Hu S, Babar ZUD, Fang Y, Yang C. Drug shortage: causes, impact, and mitigation strategies. Front Pharmacol. 2021;12:693426. https://doi.org/10.3389/fphar.2021.693426.
2. Cornelissen N, Zielhuis SW, van den Bemt PMLA, van den Bemt BJF. Causes and management of drug shortages: a scoping review. Res Social Adm Pharm. 2026;22(2):232–53. https://doi.org/10.1016/j.sapharm.2025.10.008.
3. Bade C, Olsacher A, Boehme P, Truebel H, Fehring L. Reasons for supply side driven drug shortages-a mixed-methods study on first-level, higher-level, and root causes from the perspective of marketing authorization holders. Res Social Adm Pharm. 2023;19(8):1218–27. https://doi.org/10.1016/j.sapharm.2023.05.007.
4. Tucker EL, Daskin MS. Pharmaceutical supply chain reliability and effects on drug shortages. Comput Ind Eng. 2022;169:108258. https://doi.org/10.1016/j.cie.2022.108258.
5. Phuong JM, Penm J, Chaar B, Oldfield LD, Moles R. The impacts of medication shortages on patient outcomes: a scoping review. PLoS ONE. 2019;14(5):e0215837. https://doi.org/10.1371/journal.pone.0215837.
6. Miljković N, Batista A, Polidori P, Kohl S, Horák P. Results of EAHP's 2019 medicines shortages survey. Eur J Hosp Pharm. 2020;27(4):202–8. https://doi.org/10.1136/ejhpharm-2020-002341.
7. Santhireswaran A, Chaudhry S, Ho M, Fuller K, Gaudette E, Burry L, Tadrous M. Impact of supply chain disruptions and drug shortages on drug utilization: a scoping review. Pharmacoepidemiol Drug Saf. 2025;34(7):e70178. https://doi.org/10.1002/pds.70178.
8. Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H. Association between US norepinephrine shortage and mortality among patients with septic shock. JAMA. 2017;317(14):1433–42. https://doi.org/10.1001/jama.2017.2841.
9. European Parliament and Council of the European Union. Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices. Off J Eur Union. 2022;L20:1–37. https://eur-lex.europa.eu/eli/reg/2022/123/oj.
10. European Medicines Agency. Guidance for industry on implementing Shortage Prevention Plans. EMA/436737/2024. Amsterdam: European Medicines Agency; 2024. https://www.ema.europa.eu/en/documents/other/guidance-industry-implementing-shortage-prevention-plans-spp_en.pdf.
11. European Medicines Agency Good practices for industry for the prevention of human medicinal product shortages. EMA/760980/2022. Amsterdam: European Medicines Agency. 2023. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practices-industry-prevention-human-medicinal-product-shortages_en.pdf.
12. European Medicines Agency. Shortage Prevention Plan and Shortage Mitigation Plan pilot report. Amsterdam: European Medicines Agency; 2025. https://www.ema.europa.eu/en/documents/other/shortage-prevention-plan-spp-shortage-mitigation-plan-smp-pilot-report_en.pdf.
13. European Court of Auditors. Critical shortages of medicines: EU measures were of added value, but structural problems remain. Special Report No.: 19/2025. Luxembourg: Publications Office of the European Union; 2025 https://doi.org/10.2865/1959835

14. European Commission. Proposal for a Regulation of the European Parliament and of the Council laying a framework for strengthening the availability and security of supply of critical medicinal products as well as the availability of, and accessibility of, medicinal products of common interest, and amending Regulation (EU) 2024/795. COM(2025) 102 final; 2025/0102(COD). Brussels: European Commission; 2025 [cited 2026 Aug 8]. Available from: https://eur-lex.europa.eu/eli/C/2025/4214/oj/eng
15. European Medicines Agency. Methodology to identify vulnerabilities in supply chains of critical medicines. Report No.: EMA/344341/2025. Amsterdam: European Medicines Agency; 2025 Nov 17 [cited 2026 Aug 8]. Available from: https://www.ema.europa.eu/en/documents/other/methodology-identify-vulnerabilities-supply-chains-critical-medicines_en.pdf
16. U.S. Food and Drug Administration. Risk management plans to mitigate the potential for drug shortages: draft guidance for industry. Silver Spring: U.S. Food and Drug Administration. 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/risk-management-plans-mitigate-potential-drug-shortages. Accessed 20 Jul 2026.
17. International Organization for Standardization. ISO 22301:2019 Security and resilience-Business continuity management systems-Requirements. Geneva: International Organization for Standardization; 2019.
18. International Organization for Standardization. ISO/TS 22317:2021 Security and resilience-Business continuity management systems-Guidelines for business impact analysis. Geneva: International Organization for Standardization; 2021.
19. International Organization for Standardization. ISO/TS 22318:2021 Security and resilience-Business continuity management systems-Guidelines for supply chain continuity management. Geneva: International Organization for Standardization; 2021.
20. Quinn S, Ivy N, Chua JA, Barrett M, Feldman L, Topper D, Witte G, Gardner RK. Using business impact analysis to inform risk prioritization and response. NIST Interagency Report 8286D-upd1. Gaithersburg: National Institute of Standards and Technology; 2025. https://doi.org/10.6028/NIST.IR.8286D-upd1.
21. Torabi SA, Rezaei Soufi H, Sahebjamnia N. A new framework for business impact analysis in business continuity management—with a case study. Saf Sci. 2014;68:309–23. https://doi.org/10.1016/j.ssci.2014.04.017.
22. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH harmonised guideline Q9(R1): Quality risk management. Final version adopted 18 January 2023, corrected 15 January 2025. Geneva: ICH; 2025. https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guideline_Step4_2025_0115.pdf.
23. International Electrotechnical Commission. IEC 60812:2018 Failure modes and effects analysis (FMEA and FMECA). Geneva: International Electrotechnical Commission; 2018.
24. Liu HC, Liu L, Liu N. Risk evaluation approaches in failure mode and effects analysis: a literature review. Expert Syst Appl. 2013;40(2):828–38. https://doi.org/10.1016/j.eswa.2012.08.010.
25. Spreafico C, Russo D, Rizzi C. A state-of-the-art review of FMEA/FMECA including patents. Comput Sci Rev. 2017;25:19–28. https://doi.org/10.1016/j.cosrev.2017.05.002.
26. Bhattacharjee P, Dey V, Mandal UK. Risk assessment by failure mode and effects analysis using an interval number-based logistic regression model. Saf Sci. 2020;132:104967. https://doi.org/10.1016/j.ssci.2020.104967.
27. Sahebjamnia N, Torabi SA, Mansouri SA. Integrated business continuity and disaster recovery planning: towards organizational resilience. Eur J Oper Res. 2015;242(1):261–73. https://doi.org/10.1016/j.ejor.2014.09.055.
28. Duchek S. Organizational resilience: a capability-based conceptualization. Bus Res. 2020;13:215–46. https://doi.org/10.1007/s40685-019-0085-7.
29. Ponomarov SY, Holcomb MC. Understanding the concept of supply chain resilience. Int J Logist Manag. 2009;20(1):124–43. https://doi.org/10.1108/09574090910954873.
30. Ivanov D, Dolgui A. Viability of intertwined supply networks: extending the supply chain resilience angles towards survivability—a position paper motivated by COVID-19 outbreak. Int J Prod Res. 2020;58(10):2904–15. https://doi.org/10.1080/00207543.2020.1750727.
31. Lücker F, Seifert RW. Building up resilience in a pharmaceutical supply chain through inventory, dual sourcing and agility capacity. Omega. 2017;73:114–24. https://doi.org/10.1016/j.omega.2017.01.001.
32. Socal MP, Ahn K, Greene JA, Anderson GF. Competition and vulnerabilities in the global supply chain for US generic active pharmaceutical ingredients. Health Aff. 2023;42(3):407–15. https://doi.org/10.1377/hlthaff.2022.01120.
33. National Academies of Sciences. Engineering, and Medicine. Building resilience into the nation's medical product supply chains. Washington, DC: National Academies; 2022. https://doi.org/10.17226/26420.
34. Postma DJ, De Smet PAGM, Mantel-Teeuwisse AK, Leufkens HGM, Notenboom K. Upstream pharmaceutical supply chains of 10 high-use pharmaceuticals in the Netherlands: a cohort study. BMJ Open. 2025;15(4):e099697. https://doi.org/10.1136/bmjopen-2025-099697.
35. Chapman S, Dedet G, Lopert R. Shortages of medicines in OECD countries. OECD Health Working Papers, No. 137. Paris: OECD Publishing; 2022. https://doi.org/10.1787/b5d9e15d-en
36. World Health Organization. Meeting report: technical definitions of shortages and stockouts of medicines and vaccines. Geneva: World Health Organization; 2017. https://www.who.int/docs/default-source/medicines/meeting_report_october_shortages.pdf?sfvrsn=1a902eab_3.
37. European Commission. Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use. Off J Eur Union. 2013;C343:1–14. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C.:2013:343:0001:0014:EN:PDF.
38. Medicines and Healthcare products Regulatory Agency. GxP data integrity guidance and definitions. Revision 1. London: MHRA; 2018. https://assets.publishing.service.gov.uk/media/5aa2b9ede5274a3e391e37f3/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf. Accessed 20 Jul 2026.
39. International Electrotechnical Commission. IEC 61882:2016 Hazard and operability studies (HAZOP studies)-Application guide. Geneva: International Electrotechnical Commission; 2016. https://webstore.iec.ch/en/publication/24321.
40. International Electrotechnical Commission. IEC 61025:2006 Fault tree analysis (FTA). Geneva: International Electrotechnical Commission; 2006. https://webstore.iec.ch/en/publication/4311.
41. International Electrotechnical Commission. IEC 31010:2019 Risk management-Risk assessment techniques. Geneva: International Electrotechnical Commission; 2019. https://tc56.iec.ch/risk-assessment-standards/.