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GOOD MANUFACTURING PRACTICE DEFICIENCIES CITED IN REGULATORY INSPECTIONS: A THEMATIC ANALYSIS

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Abstract

Good manufacturing practice (GMP) inspections by national and international regulators repeatedly identify the same kinds of failure. This review synthesises published regulations, guidance documents, case investigations and commentary to group commonly cited deficiencies into themes: weak quality systems, data integrity breaches, contamination and cleaning failures, laboratory control lapses, and gaps in validation, change control and supplier oversight. The literature suggests that most citations trace back to organisational culture and risk management rather than to missing equipment or missing written procedures. Published evidence is largely descriptive and drawn from public documents, which limits comparison between agencies. The article is a narrative thematic review and reports no new data.

1. INTRODUCTION

A tablet that is safe in the clinical trial can still be unsafe in the pharmacy if the factory that made it was careless. Good manufacturing practice, usually shortened to GMP, is the set of rules meant to prevent that outcome. It covers premises, personnel, equipment, documentation, production, quality control and the handling of complaints, and it exists in broadly similar form in the United States, the European

Union and the World Health Organization framework [1, 2, 3]. Regulators check compliance by inspection, and the findings of those inspections, recorded as observations, deficiency reports or warning letters, offer a rare window onto how manufacturing quality fails in practice [4, 5].

Inspection findings are public in some jurisdictions and confidential in others, and they are written for the manufacturer rather than for researchers. Even so, repeated reading of them produces a recognisable pattern. A small number of themes account for a large share of the serious citations, and the themes recur across continents, product types and company sizes. This review treats that pattern as a thematic problem. It asks which categories of deficiency are described most often in the regulatory and scientific literature, what the documents say about their causes, and how the corrective approach has changed over time [4, 6, 7].

GMP regulation has a history of reacting to harm. The sulfanilamide elixir deaths in the United States in 1937 led to the Food, Drug, and Cosmetic Act of 1938, and thalidomide led to stronger controls on drug approval and manufacture in the early 1960s. European law followed the same pattern, and the principles were later set out in a Directive [5, 8]. This reactive history helps to explain why GMP rules read like a catalogue of past mistakes, and why each new category of failure tends to produce a new guidance document [5, 8].

The scope needs stating plainly. This is a narrative review of published regulations, guidance, case reports and commentary available up to 2023. It does not report a new count of inspection citations and does not rank agencies or companies. Findings are grouped into five themes that follow the structure of GMP itself and are collected in table 1, while fig. 1 shows how the entries are distributed between themes. Where the literature is thin, the text says so, because several of the commonly repeated claims about inspection trends rest on opinion rather than on systematic data [4, 7].

Vocabulary differs between agencies, and it can mislead. A form 483 observation in the United States, a major or critical deficiency in a European report and a non-compliance statement from a WHO prequalification inspection are not identical, and they should not be added together as if they were. The common thread is simpler. In each case an inspector has found evidence that a procedure, a record or a control did not meet the written standard, or that the written standard itself was inadequate for the risk involved [1, 2, 8].

2. QUALITY SYSTEMS AND OVERSIGHT

The most frequent root of a serious citation is not a broken machine but a weak quality system. United States regulations make the quality control unit responsible for approving or rejecting components, in-process materials, finished products and the procedures that govern them, and for reviewing production records and investigating discrepancies before a batch is released [1]. Inspectors regularly report that this independence is more nominal than real. Quality staff sit under production management, release is driven by shipping targets, and investigations close with a conclusion that does not follow from the evidence [5, 9]. The rules are not obscure. They are simply not followed under pressure.

Table 1: Principal GMP deficiency themes described in the published literature

Theme and example	Typical finding or consequence	Ref.
Quality unit authority release decisions	Quality control unit not independent; discrepancies closed without adequate investigation before batch release.	[1, 9]
CAPA effectiveness root cause	Corrective actions aimed at operators, never checked for effectiveness, recurrent events logged as separate.	[9, 10, 11]
Shared logins and deletion electronic records	Analysts able to delete or overwrite raw data; audit trails absent or unreviewed.	[3, 12, 13]
Testing into compliance laboratory data	Repeated or trial injections used to obtain passing results; failing data discarded.	[12, 14, 15]
Aseptic processing sterile products	Weak environmental monitoring, unjustified interventions and gaps in media fill design.	[16, 17]

Theme and example	Typical finding or consequence	Ref.
Compounding outbreak 2012	Contaminated injectable steroid linked to fungal meningitis; sterility assurance inadequate.	[18]
Cleaning validation shared equipment	Acceptance limits unjustified, swab recovery not shown, hold times not studied.	[19, 20]
Out-of-specification results investigation	Results invalidated without cause; retesting until a passing value is obtained.	[21, 22]
Stability programmes expiry dating	Missing time points and non-stability-indicating methods leave shelf life unsupported.	[23, 24]
Process validation lifecycle	Reports written late; critical parameters unjustified; no continued verification.	[20, 25]
Supply chain oversight heparin	Contaminated ingredient from remote supplier reached patients; audits not risk based.	[26, 27, 28]

Pharmaceutical quality system guidance describes the intended arrangement. The European GMP chapter on the pharmaceutical quality system asks for management responsibility, continual improvement, and an effective process for corrective and preventive action (CAPA), and it asks senior management to take part in review of the system rather than delegate it [10]. Deficiency reports often show the reverse: CAPA records that blame an individual operator, actions that are never verified for effectiveness, and recurrent events logged as unrelated ones. An FDA approach to quality systems published in 2006 had already stressed that CAPA should address root causes and not symptoms [9, 10].

Behind these failures lies a question of culture, which regulators now discuss openly. Woodcock framed the desired state of manufacturing as one that reliably produces high-quality product without extensive regulatory oversight, and later authors argued that reaching it requires measurable quality metrics and a management that rewards problem reporting [6, 7]. Yu and Woodcock note that regulatory oversight alone cannot inspect quality into a product, and that persistently poor compliance usually reflects management choices about staffing, maintenance and investment [4]. These claims are plausible and consistent with inspection narratives. They are also difficult to test, which is a recurring limitation of this literature.

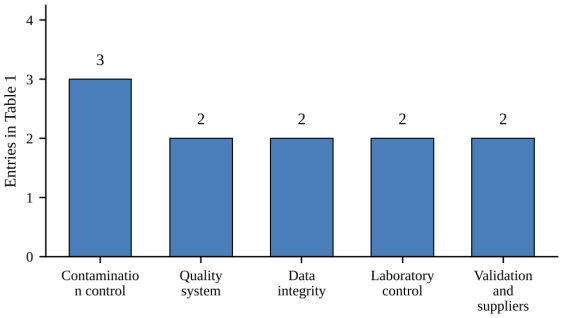


Fig. 1: Number of entries in table 1 by GMP deficiency theme

Documentation is the practical evidence of a quality system, and gaps in it are cited constantly. Batch records that omit steps, entries made out of sequence, unexplained corrections and blank fields signed as complete show that review was cursory [1, 2]. The saying that a task not written down was not done is a fair summary of the inspector's attitude. A deviation system that records events promptly, classifies them by risk and links them to batch disposition is the usual expectation, and gaps there often surface later as recalls [2, 9].

3. DATA INTEGRITY

Data integrity has become the most visible theme in the past decade. The principle is simple. Records that support a decision to release a batch must be attributable, legible, contemporaneous, original and accurate, a set of attributes often shortened to ALCOA, and they must be complete, consistent and enduring [12, 13]. Typical deficiencies include shared user accounts on chromatography software, the ability of analysts to delete or overwrite raw data, audit trails that are disabled or never reviewed, and paper records completed from memory after the event [12, 13, 14].

Several practices appear again and again in public descriptions. Analysts run test injections of a sample before the official run and discard results that do not please. Failing results are repeated until a passing one is found, a habit sometimes called testing into

compliance. Records are backdated, signatures are applied for tasks not witnessed, and electronic raw data are replaced by printed summaries. None of this requires sophisticated deception, which may be why it persists, and the guidance documents describe these behaviours in detail so that inspectors and auditors know where to look [12, 15].

Why do people do it? The guidance documents are surprisingly frank about motive. Production deadlines, fear of reprimand for a failing result, inadequate staffing and a belief that the data would have passed anyway all appear in discussions of behaviour behind falsification [12, 14]. This is why the more recent documents recommend management behaviours such as protecting staff who report errors, reviewing the workload of analysts, and designing processes that make the honest action the easy one. Technical controls on their own do not remove the incentive to alter a record [14, 15].

The regulatory response has been to spell out expectations for computerised systems. Annex 11 of the European GMP guide requires that systems be validated, that changes be controlled, and that audit trails be available and reviewed [3]. The data integrity literature and the GAMP guide extend the same ideas to paper and hybrid systems and treat data governance as a management duty and not an information technology one [14, 15]. Evidence on whether these documents have reduced the number of citations is limited, and the commentary available is mostly descriptive. A cautious reading is that awareness has risen, while behaviour has been slower to change.

4. CONTAMINATION AND CLEANING CONTROL

Contamination is the deficiency theme with the clearest link to patient harm. Sterile products carry the greatest risk, and the European Annex 1 and the United States aseptic processing guidance both describe the expected controls: classified cleanrooms, environmental monitoring, personnel gowning and behaviour, and media fills that simulate the process [16, 17]. Inspectors frequently cite inadequate smoke studies, interventions in grade A areas that are not justified, trending of environmental data that misses repeat isolates, and aseptic technique that departs from the written method [16, 17]. Lapses are seldom limited to a single control, and inspectors often find several weaknesses stacked together.

Basic facility conditions also draw citations in non-sterile areas. Inspectors describe water systems without adequate sanitisation and trend review, air handling that lets dust move between rooms, damaged surfaces that cannot be cleaned, pest control gaps and poor personnel hygiene [1, 2]. These findings seem mundane beside a data integrity scandal, but they point to the same weakness, which is that routine upkeep is treated as optional until something goes wrong. Maintenance programmes with documented preventive tasks and clear ownership are the standard remedy, and are required by the regulations [1, 2].

The cost of such failures is not abstract. In 2012 contaminated methylprednisolone from a compounding pharmacy in the United States was linked to a multistate outbreak of fungal meningitis and joint infections, with many patients affected and a substantial number of deaths [18]. Investigators described inadequate sterility assurance and facility conditions that would not have met GMP expectations for sterile manufacture. The episode led to a change in legislation on compounding, and it is still cited as a reason for taking environmental control findings seriously [16, 18]. Reports on the episode also stress how long the contaminated lots remained in use before the signal was recognised.

Cross-contamination in multiproduct plants is the second large concern. Cleaning procedures must be validated, and acceptance limits should be based on the toxicology of the previous product, the batch size of the next one and the shared equipment surface area [19, 20]. Deficiencies include visual inspection as the only criterion, swab recovery that was never demonstrated, hold times that were not studied, and cleaning methods that were changed without revalidation. In the more severe cases, potent compounds such as hormones or cytotoxics

have been made in shared equipment without adequate separation [1, 19].

5. LABORATORY CONTROLS

Laboratory deficiencies are among the most common in published warning letters because the laboratory is where the decision to release is made. Regulations expect scientifically sound specifications, validated or verified methods, calibrated instruments and reference standards that are qualified and traceable [1, 22]. The WHO good practices for quality control laboratories add expectations for sample management, reagent control, and the training of analysts [22]. Typical citations include out-of-date standards, uncalibrated balances, system suitability criteria that were applied inconsistently, and methods changed informally between batches [1, 22]. Laboratory findings are also easy for inspectors to verify from records, which partly explains how often they are cited.

The handling of out-of-specification (OOS) results has a long regulatory history. The EU chapter on quality control requires that out-of-specification results be investigated and the outcome recorded [21]. Regulators in the United States have long expected a phased investigation: a laboratory check to find an assignable cause, then a full-scale investigation involving production if none is found, and rules limiting retesting and averaging. Inspectors report that firms often invalidate OOS results without evidence, retest repeatedly until a pass is obtained, or treat the first result as an error because it is inconvenient. That practice is the laboratory counterpart of data integrity failures, and the two themes frequently appear in the same letter [12, 21].

Sampling and the identity testing of incoming materials are a quieter source of citations. Regulations expect each container of a component to be sampled according to a documented plan, and the identity of at least one container from each lot to be confirmed by a specific test [1, 22]. Where a supplier's certificate of analysis is relied on in place of testing, the supplier must have been qualified. The heparin contamination of 2008 passed through supply chains in which such checks had been inadequate, and it showed how a missed identity or purity test can have consequences across several countries [22, 27].

Stability programmes and retained samples also attract citations. Firms may lack a protocol, miss time points, or use methods that are not stability indicating, which means that expiry dates are not supported by data [23, 24]. For active pharmaceutical ingredients, the WHO guidance on active pharmaceutical ingredients repeats similar expectations and adds specific controls for intermediates and for the reprocessing of failed batches [23]. In all these areas the underlying demand is the same: a conclusion about quality has to be supported by a record that someone else could follow and, if necessary, repeat [21, 23].

6. VALIDATION, CHANGE CONTROL AND SUPPLIERS

Process validation was reframed in the 2011 FDA guidance as a lifecycle activity, running from process design through qualification to continued verification, in place of the older three-batch exercise [25]. The WHO guidance on non-sterile process validation takes a similar line [20]. Deficiencies that inspectors still report include validation reports written after commercial distribution has started, critical process parameters that were never justified by development data, and no routine monitoring of variability once the product is on the market [20, 25, 29]. Many firms treat the validation report as a one-off hurdle and not a living document.

Quality by design offers a way to avoid several of these problems. Where a company has defined a design space and has understood the link between material attributes, process parameters and quality, a change is easier to assess and fewer surprises appear at scale [29, 30]. The same understanding supports risk-based decisions about what to validate and how often to monitor [30, 31]. Inspection narratives, on the other hand, describe companies that apply the vocabulary of quality risk management to justify skipping a test, which is the opposite of the intended use [31, 32].

Change control sits between validation and the quality system. A modification to a

supplier, a solvent, a piece of equipment or a software setting should be assessed for its effect on quality before implementation, and the impact should be documented. Deficiencies include changes made informally, with no evaluation of downstream effects, and changes made in one site that were not applied or tested at another. The nitrosamine problem is the best known recent case in which a change in manufacturing route went unassessed for a critical impurity [28, 31]. Small, apparently harmless alterations accumulate and are rarely reassessed together.

7. ROOT CAUSES AND REMEDIATION

When the individual citations are set side by side, the root causes group into a few ideas. Management did not provide the resources, time or independence that quality required. Risk was assessed superficially or after the fact. Staff did not understand why a rule existed. Systems were designed for audit and not for use. These causes appear in reviews of pharmaceutical quality and in regulatory commentary, though neither source provides quantified attribution [4, 6, 7]. The common theme is that missing procedures are rarely the problem, and the tidy folder of standard operating procedures can conceal a weak practice.

Regulators respond in a graded way. A routine inspection may end with a list of observations, to which the firm replies in writing within a set period. If the reply is inadequate, or the findings are serious, the agency can issue a warning letter, restrict imports from the site, suspend a licence, or request a recall [4, 33]. Published commentary suggests that the credibility of the response matters as much as the original finding. Firms that analyse root causes honestly and commit resources tend to be treated differently from those that offer a promise of retraining and little else [4, 9].

Remediation guidance has moved accordingly. The 21st-century initiative of the FDA proposed a risk-based approach to oversight and encouraged firms to adopt modern quality systems and science-based decisions [33]. Quality risk management as set out in the EU annex and the WHO guidelines gives a structured way to prioritise attention [31, 32]. For firms already under enforcement, consent decrees and third-party expert audits have been used, though published evidence on their long-term effectiveness is scarce. The more convincing remedies in the literature involve leadership change and investment in people, since technology without these tends to reproduce the same failures [4, 33].

8. LIMITATIONS AND FUTURE DIRECTIONS

The evidence base has clear limits. Most sources are guidance documents and regulatory commentary, not systematic studies, and inspection records are not collected or published in a uniform way across agencies. Citations depend on which sites are inspected, and agencies use risk-based schedules, so the observed pattern is shaped by inspection policy as well as by manufacturer behaviour. Selection effects are likely, and any apparent trend in a theme such as data integrity must be read with that in mind [4, 7, 8]. Some agencies also publish only a selection of letters, so absence of a theme in public records is not proof of absence in practice.

Several developments deserve attention. Quality metrics reported by manufacturers may allow earlier detection of trouble than inspection alone, and continuous manufacturing with real-time release changes where deficiencies arise [7]. Harmonised inspection frameworks and mutual recognition could reduce duplication and make findings comparable [2, 8]. Research that links specific deficiency categories to product recalls, shortages or patient outcomes would be especially valuable, because the policy case for particular inspection priorities currently rests on plausibility more than on measured effect [4, 18]. Each of these developments is plausible, though none has yet been evaluated rigorously.

Low- and middle-income settings deserve separate attention. Much of the published inspection commentary comes from the United States and Europe, yet a large proportion of active ingredients and finished generics are made elsewhere, often for supply

under procurement programmes that rely on WHO standards [2, 7, 8]. Findings from inspections of those sites are less often published, and limited regulatory capacity can leave gaps between the written standard and what is actually enforced. Without data from these settings the picture of global GMP compliance is incomplete, and conclusions drawn from one region may not transfer to another.

9. CONCLUSION

Published inspection findings point to a short list of recurring problems: quality units without real authority, data that cannot be trusted, contamination that was predictable, laboratories that reach the answer they wanted, and changes or suppliers that nobody assessed [1, 12, 16, 21, 27]. The documents agree on what good practice looks like. What they show less clearly is why firms depart from it, although the weight of commentary points to management choices and weak quality culture [4, 6, 7]. Where they diverge is in emphasis: agencies stress different details, while the underlying logic remains the same [1, 2, 8].

For practising pharmacists and quality staff the message is practical. Procedures alone do not protect patients, and real protection comes from independent quality oversight, honest investigation, validated and reviewed electronic records, and risk assessments that are used to find problems and not to excuse them [10, 15, 31]. Better public data on inspection outcomes, and studies that connect deficiencies to recalls and patient harm, would let future reviews move beyond narrative description [4, 8]. Until those data exist, readers should treat statements about inspection trends with some caution, and treat the stronger claims as informed opinion [7, 33].

10. ABBREVIATIONS

ALCOA-Attributable, legible, contemporaneous, original, accurate, API-Active pharmaceutical ingredient, CAPA-Corrective and preventive action, FDA-United States Food and Drug Administration, GMP-Good manufacturing practice, ICH-International Council for Harmonisation, MHRA-Medicines and Healthcare products Regulatory Agency, OOS-Out of specification, PIC/S-Pharmaceutical Inspection Co-operation Scheme, WHO-World Health Organization

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12. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

13. CONFLICT OF INTERESTS

Declared none

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