

Automated Print Inspection in Pharmaceutical Packaging – From Batch Release to Data-Driven Quality Control

Pharmaceutical packaging occupies a critical position in the product lifecycle. From both a regulatory and quality control perspective, it is a critical component of the finished medicinal product. Errors in labelling, content information, 1D/2D codes, or Braille embossing can trigger product recalls and, in severe cases, directly endanger patient safety. Incorrect codes can also compromise traceability systems for medications throughout the supply chain, with significant downstream implications for pharmacovigilance and serialisation compliance.

Against this backdrop, automated print inspection systems have become the established standard in modern pharmaceutical packaging, replacing time-consuming and error-prone manual visual inspection. These systems deliver standardised, reproducible inspection results and are capable of simultaneously assessing print image integrity, code legibility and grading, and Braille embossing compliance in a single pass. Beyond efficiency gains, they generate comprehensive, audit-proof inspection reports. The inspection data accumulated by these systems represents a largely underutilised asset that, when systematically consolidated and analysed, can yield significant insights into process quality, recurring defects, and systemic risks.

Regulatory Framework

Any use of automated inspection data within a pharmaceutical quality context must be grounded in the applicable regulatory framework. Two primary regulatory instruments define the requirements for computer-based inspection systems and their data outputs:

In Europe, EU GMP Annex 11 and Annex 15 are most directly applicable. Annex 15 requires that quality-critical systems and processes be formally qualified (for systems) and validated (for processes), with supporting documentation maintained on a risk-based basis. Packaging quality characteristics must be reproducibly present and systematically tested. Annex 11 governs computer-based systems, including complete and consistent

data recording, traceability, protection against unauthorised access or alteration, regular data backup, and the maintenance of an audit trail. Inspection decisions and batch release actions must be documented in an audit-proof manner. Inspection reports, typically stored as PDF files immediately upon test completion, satisfy these requirements by default, though digital backup of extensive reports is advisable.

In the United States, 21 CFR Part 11 (in effect since 1997) sets out the equivalence of electronic records and signatures with their paper-based counterparts. Key requirements applicable to inspection systems include system validation (§11.10(a)), access controls (§11.10(d)), audit trails (§11.10(e)), sequential use of test steps and status indicators (§11.10(f)), and documented user training and qualification (§11.10(i)). A significant regulatory gap is identified: neither Annex 11 nor 21 CFR Part 11 explicitly addresses the procedures for retrospective analysis or secondary use of inspection data. This gap represents both a limitation and an opportunity, as there is substantial analytical potential between regulatory minimum requirements and data-driven quality assurance.

Types of Data Generated

Modern automated print inspection systems operate on the principle of digital comparison: a camera or scanning line captures the actual printed image, which is compared pixel by pixel against a pre-approved digital template (the "golden master"). Deviations exceeding defined tolerance thresholds are flagged for user evaluation or automatically rated as failures depending on system configuration. All systems generate several structured categories of data. Understanding the analytical potential of inspection data requires first mapping the categories of records produced by modern print inspection systems.

- Unit-level inspection records include a unique identifier (item or batch number), an automatically generated timestamp, an overall pass/fail result, results for each inspected feature (artwork, codes, Braille), any deviations between the approved template and the inspected sample, and quantitative measurements

such as code grading values and Braille dot heights.

- Batch-level reports aggregate individual unit tests and include count data (total samples, rejection rates, error type frequencies) as well as trend data. For example, how rejection rates increased progressively across a batch, at what points errors occurred most frequently, and how error types changed over the inspection run.
- Audit trail and event logs record system start/stop events, user actions, parameter changes, and modifications to inspection configurations. Although primarily required for regulatory purposes, this contextual data is critical for analysing anomalies and non-conformities.
- Pixel-level difference data is generated through digital comparison of an approved print template (the "golden master," typically a structured PDF) against the captured print image. The raw data of high value for root cause analysis shows not only the occurrence of a deviation but its precise location and magnitude.
- Quantitative code quality metrics are reported in accordance with ISO/IEC 15416 (linear barcodes) and ISO/IEC 15415 (2D codes), providing graded assessments (A to F) for parameters such as modulation, decodability, and print quality. Braille inspection systems generate analogous quantitative outputs, including dot height deviations, grid conformity, and geometric measurements.

Retrospective Analysis: Opportunities and Application Areas

The systematic cross-batch analysis of inspection data is not conceptually novel. Statistical process control (SPC) has been standard practice in semiconductor manufacturing and other high-volume, highly automated sectors for decades. Its application to pharmaceutical packaging inspection data, however, has been limited despite the availability of a suitable data foundation. Several factors contribute to

this gap: inspection systems have historically been optimised as approval tools rather than analytical platforms; the necessary data infrastructure has only recently been established as companies transition from manual to automated inspection; and the methodological frameworks for analysing this data within a GMP context are not yet widely embedded in quality management practice.

Once these conditions are addressed, retrospective analysis opens several concrete opportunities:

- 1. Identification of recurring defects:** Statistical evaluation across batches can distinguish systematic error patterns (e.g., consistent legibility failures for a specific code type or print deviations in a defined region of a carton) from random process variation.
- 2. Assessment of process stability:** Continuous evaluation of quantitative measurement variables, such as code print quality grades or Braille dot height measurements, over extended time periods allow determination of whether a packaging line is operating within its qualified process limits. Deviations correlated with specific time points

can be linked to change events such as supplier changes, maintenance intervals, or process modifications.

- 3. Support for qualification and validation:** Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) are required during initial system of qualification. Retrospective inspection data from routine production can provide supporting evidence of sustained process performance within PQ parameters, strengthening both initial validation and periodic revalidation. Systematic ongoing data evaluation expands the evidentiary base compared with relying solely on discrete revalidation batches.
- 4. Risk Assessment and CAPA Support:** Failure Mode and Effects Analysis (FMEA) in packaging processes is typically qualitative. Inspection data enables quantitative estimation of defect occurrence frequencies, providing an empirical basis for risk prioritisation. Corrective and Preventive Action (CAPA) effectiveness can similarly be objectively demonstrated by showing a statistically significant reduction in the frequency of the addressed failure mode following implementation.

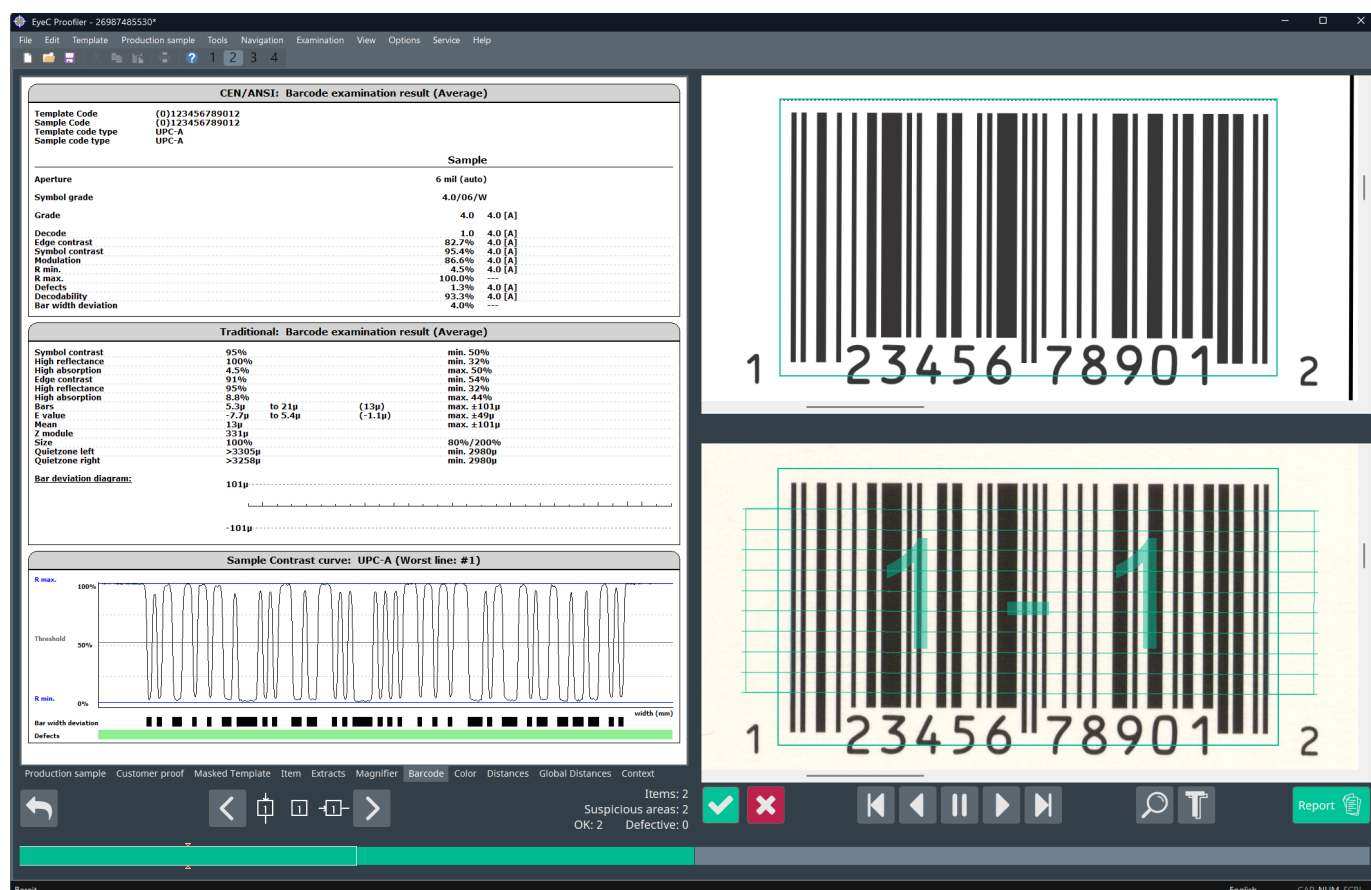
Analytical Methodology

The analysis described above can be conducted using a range of statistical and data management approaches. Method selection must be appropriate to the data type, the analytical question, and the regulatory context.

For pass/fail data, statistical process control methods are the primary tool. It is suited to statistical process control methods, enabling scrap rate calculations over time and differentiation between special-cause events and natural process variability. Common-cause variation can only be reduced through systematic process improvement; special-cause events require targeted investigation and, where appropriate, CAPA.

Quantitative measurements (code grades, Braille dot heights, pixel deviations) enable the calculation of sample statistics for comparison against specification limits, enabling assessment of whether processes are operating within specification limits and whether trends toward the specification boundary are emerging.

The temporal structure of inspection data is of particular methodological importance. Inspection data is time-bound, and trends can only be identified if the temporal context



is preserved and incorporated into the analysis.

In some cases, calculating rates is the method of choice, for instance, when output volumes vary between batches or time periods; absolute defect counts must be normalised to total units inspected to permit valid comparisons.

Finally, data quality considerations must be addressed explicitly. Inspection data generated under GMP conditions is generally of high quality, given the requirements of Annex 11 and 21 CFR Part 11. However, events such as maintenance, reference file updates, or changes to inspection parameters may introduce discontinuities in the measurement series. A rigorous analysis incorporates this contextual information and adjusts interpretations accordingly.

Infrastructure and Implementation

Practical implementation of data analysis depends on several infrastructure conditions. Inspection data must remain accessible and analysable beyond the batch release period, which is not always the case – some systems store data locally in proprietary or archive-optimised formats unsuitable for cross-batch analysis. Integration into databases and the use of standardised data formats are prerequisites. Regulatory data retention requirements must also be satisfied throughout: in Europe, records must typically be retained for at least one year after the product's expiration date, with longer periods

applicable to blood products and certain biologics.

A general implementation pathway is described in five steps:

1. Inventory of existing inspection data across systems
2. Formulation of a specific research question before analysis begins
3. Data preparation, including retrieval, supplementation with contextual metadata (batch, line, product, time period, change events), and format conversion – often the most time-consuming step
4. Statistical analysis interpreted within the context of inspection conditions, treating identified correlations as hypotheses

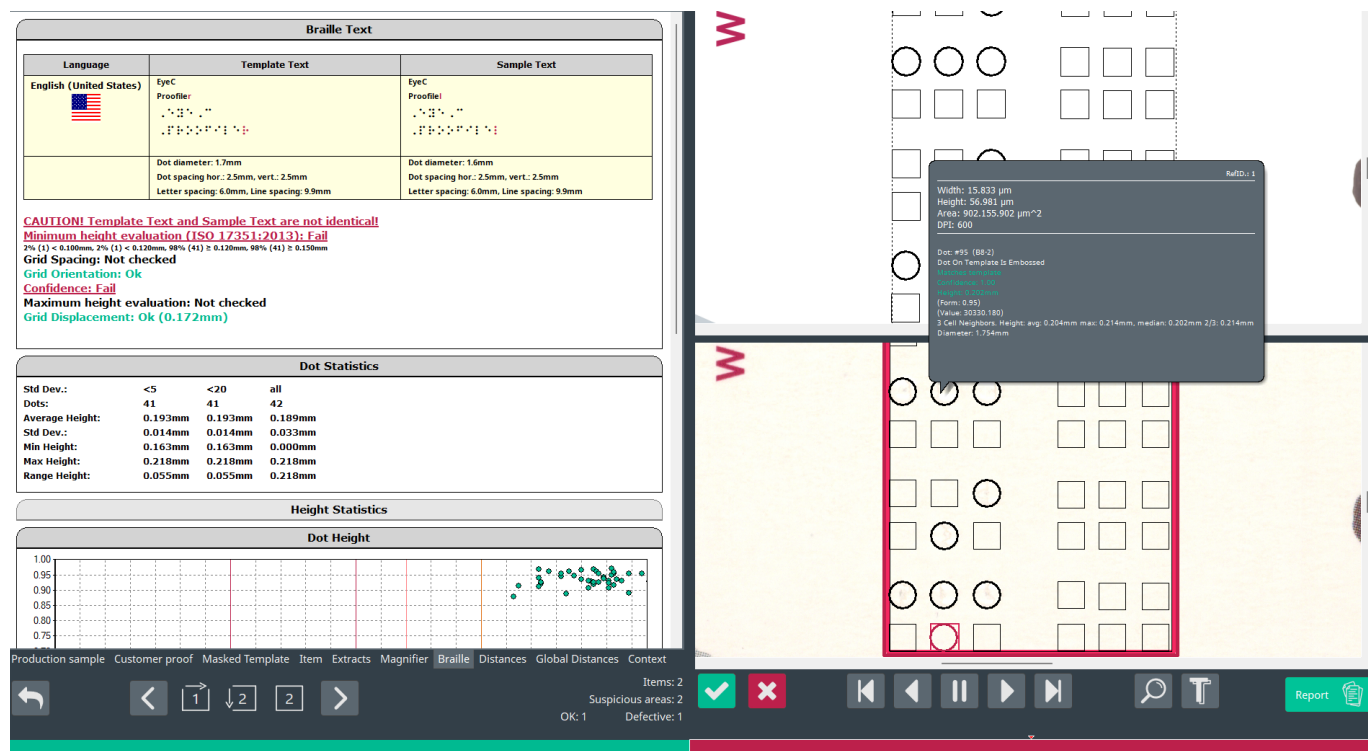
requiring further root cause investigation rather than as proof of causation

5. Documentation of analysis results in accordance with Good Documentation Practice (GDP)

Limitations

A balanced assessment of retrospective inspection data analysis requires acknowledging its inherent limitations.

First, inspection systems can only detect what they are configured to inspect. If inspection parameters or tolerance thresholds are not appropriately set for the relevant risks, the resulting data – however voluminous – cannot provide a complete picture of process performance. Data analysis cannot compensate for deficiencies in system configuration.



Second, statistical analysis identifies correlations, not causes. Detecting a recurrent defect pattern of the data is the beginning of an investigation, not its conclusion. Root cause analysis requires process expertise, contextual knowledge, and targeted investigation; data analysis can direct and support this process, but cannot replace it.

Third, the validity of retrospective analysis depends on data continuity and consistency. Changes in inspection systems, modifications to inspection parameters, or incomplete archiving can introduce discontinuities in time series data that limit the interpretability and comparability of results across time periods.

Conclusion

Automated inspection systems satisfy established regulatory requirements for audit-proof documentation of print quality, codes, and Braille in pharmaceutical packaging. The structured data these systems generate, however, exceeds its current use as a documentation and batch release tool. When systematically aggregated, temporally organised, and analysed using appropriate statistical methods, this data can support identification of systematic error patterns, objective process stability assessment, qualification and validation activities, and empirically grounded risk management. The primary gap is not in available data, but in the systematic transition from archiving to active analysis, a transition expected to gain regulatory and operational importance as pharmaceutical production continues to digitise and as regulatory focus on data integrity and continuous improvement intensifies.



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