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Risk-Based Lifecycle Management of Chromatographic Methods for Generic API Quality: A Systematic Review

Punnaiah Chowdary Ravi[1]; Md Jamil Ahmmed[2];

[1]. Senior Research Scientist – Analytical Development; Laurus Labs Ltd., India;
Master of Science (M.Sc.) in Chemistry, Acharya Nagarjuna University, India;
Email: punnaiahchowdaryravi@gmail.com

[2]. Business Systems Analyst; Dotz IT, Dhaka, Bangladesh;
Email: jamilahmmed20@gmail.com

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Abstract

Risk-based lifecycle management of analytical procedures, formalised by ICH Q14 and Q2(R2) in 2020, rests on a literature written before those guidelines. This systematic review maps that evidence for chromatographic methods in small-molecule and generic active pharmaceutical ingredient (API) quality and derives a lifecycle framework mapped to the guidelines. Twenty-eight strings were run against the title and abstract fields of the OpenAlex index for works published before 2020; 3,433 records were retrieved, 2,405 were unique, 621 were removed by logged automated rules, 1,784 were title-screened, 515 were screened on the abstract, and 381 studies were included and coded for six lifecycle stages, risk tools, experimental designs, software, acceptance-criterion approaches, transfer, monitoring and ten reporting-quality items. The literature is recent (75% from 2013 to 2019) and concentrated in few journals and groups. It is strong at one stage: an optimisation design is reported by 44% of the studies and a design space or method operable design region by 21%, It is weak at the stages that make the lifecycle a lifecycle: an explicit analytical target profile in 7%, a risk assessment in 10%, verification of the robust region in 1%, transfer or verification in 6% and continued performance verification in 1%; only 6 studies report the chain from target profile through risk assessment and design space to validation, and validation is mostly reported against classical limits rather than total-error criteria. Reporting is thin on the items that make a method reusable (mean reporting score 0.6 of 10 from abstracts). The guidelines are therefore ahead of their evidence base at the ends of the lifecycle. The derived framework takes the mature design stage as practised and specifies the under-evidenced stages as deliberate capabilities for a generic API organisation, with the analytical target profile as the regulatory object, an explicit statistics role, equivalence-based transfer and a ten-item reporting checklist. Limitations are a single index, single-reviewer screening assisted by language-model agents, and abstract-based extraction.

Keywords

Analytical Quality By Design; Analytical Target Profile; Method Lifecycle; Chromatography; HPLC; Generic Active Pharmaceutical Ingredients; Quality Risk Management; Design Of Experiments; Method Validation; Systematic Review

Introduction

Chromatographic procedures carry most of the quality decisions made about a generic active pharmaceutical ingredient (API) and the products made from it: the assay that releases a batch, the related-substances method that controls process impurities and degradation products against the thresholds of ICH Q3A and Q3B, the residual-solvent and dissolution tests, and the stability-indicating methods on which shelf life rests (International Council for Harmonisation, 2006a; International Council for Harmonisation, 2006b; International Council for Harmonisation, 1999; International Council for Harmonisation, 2003). For a generic manufacturer the burden of these procedures is heavier than for an innovator in three respects. The impurity profile of an API made by an alternative synthetic route differs from the innovator's, so pharmacopoeial and innovator methods must be shown to separate the impurities that the generic route produces (Rao & Nagaraju, 2003; Görög, 2008; U.S. Food and Drug Administration, 2009). The same method is often run at several sites and by contract laboratories, so transfer and verification are routine rather than occasional (United States Pharmacopeial Convention, 2018c; United States Pharmacopeial Convention, 2018b). And the margins of the generic business reward methods that are fast, robust and cheap to run for a decade, which makes the cost of an unrobust method, of repeated out-of-specification investigations and of failed transfers a direct commercial loss (Woodcock & Wosinska, 2013; Lionberger et al., 2008).

The regulatory model of the analytical procedure has changed over the period this review covers. Until the mid-2000s the procedure was developed by experience, validated once against the checklist of ICH Q2(R1) and then frozen, with changes handled by revalidation (International Council for Harmonisation, 2005a; Shabir, 2003; Ermer, 2001). The quality-by-design guidelines for products (ICH Q8, Q9, Q10 and Q11) introduced the ideas of a target profile, risk assessment, design space, control strategy and continual improvement, and a group of papers from industry and the United States Pharmacopeia argued that the same ideas apply to analytical procedures: an analytical target profile (ATP) that states what the procedure must deliver, risk assessment of the method parameters, designed experiments that establish a method operable design region (MODR), validation understood as the qualification of the procedure's performance against the ATP, and continued verification during routine use (International Council for Harmonisation, 2009; International Council for Harmonisation, 2005b; International Council for Harmonisation, 2008; International Council for Harmonisation, 2012; Borman et al., 2007; Schweitzer et al., 2010; Nethercote & Ermer, 2012; Martin et al., 2013; Barnett et al., 2016). The ICH took the lifecycle view into its work programme in 2018 and adopted ICH Q14 on analytical procedure development and the revised ICH Q2(R2) on validation in November 2020, after the period covered by this review (International Council for Harmonisation, 2018; International Council for Harmonisation, 2020b; International Council for Harmonisation, 2020a). The literature that this review examines is therefore the evidence base on which those guidelines were built: what was proposed, tried and reported about risk-based, lifecycle management of chromatographic methods before the guidelines made it an expectation.

That literature has been reviewed narratively several times, usually from the perspective of analytical quality by design (AQbD) and design of experiments in method development (Vogt & Kord, 2011; Orlandini et al., 2013; Rozet et al., 2013; Peraman et al., 2015a; Sahu et al., 2018; Deidda et al., 2018; Parr & Schmidt, 2018). Those reviews are expert syntheses rather than systematic ones: they do not report a search strategy, eligibility criteria or a flow of records, and they do not quantify how often the lifecycle stages are actually implemented in the published work, how risk is assessed, which experimental designs and acceptance approaches are used, or how far the reporting of the studies allows a reader to reuse their methods. A systematic review of this literature is therefore useful on four counts: to map the evidence base on which ICH Q14 and Q2(R2) now rest; to quantify the gap between the lifecycle model as proposed and the lifecycle model as practised; to identify the stages (transfer, continued verification, change management) that the evidence covers least; and to derive from the evidence a framework that a generic API organisation can implement.

This article reports such a review. It asks four questions. RQ1: what is the volume, growth and distribution of the literature published before 2020 on lifecycle and risk-based approaches to chromatographic methods for small-molecule pharmaceutical quality? RQ2: which lifecycle stages and which quality-risk-management tools are reported, and how often? RQ3: how are validation and

acceptance criteria handled, and what evidence exists on transfer, verification and monitoring? RQ4: what is the reporting quality of the studies, and which framework for risk-based lifecycle management of chromatographic methods for generic API quality do the findings support, mapped to ICH Q14 and Q2(R2)? The review follows the PRISMA reporting conventions adapted to a bibliographic source and a single reviewer (Moher et al., 2009; Liberati et al., 2009), and it is explicit about its limits: the search ran in one bibliographic index, screening and extraction were done by one reviewer with a structured form, and extraction relied on abstracts where full texts were not openly accessible.

Background

From validated procedures to managed procedures

ICH Q2(R1) defines validation as demonstrating that an analytical procedure is suitable for its intended purpose and lists the characteristics to be evaluated: specificity, linearity, range, accuracy, precision (repeatability and intermediate precision), detection and quantitation limits and robustness (International Council for Harmonisation, 2005a). The guideline is silent on how the procedure was developed, on acceptance criteria and on what happens after validation, and the practice that grew around it treated validation as a one-time event documented in a report (Shabir, 2003; Ermer, 2001; Rozet et al., 2007). Three lines of criticism accumulated. Statisticians pointed out that the characteristics are evaluated separately and compared with limits that have no link to the decision the result supports, and proposed instead that validation should establish, with a stated probability, that future results will fall within an acceptance interval around the true value: the total-error and accuracy-profile approach of the SFSTP commissions and the tolerance-interval formulation of Hoffman and Kringle (Hubert et al., 2004; Hubert et al., 2007; Feinberg, 2007; Hoffman & Kringle, 2005; Hoffman & Kringle, 2007; Rozet et al., 2012). Metrologists argued that fitness for purpose is a statement about measurement uncertainty and the decision rule, which the Eurachem and ISO guidance and the GUM already provided for other sectors (Magnusson & Örnemark, 2014; Ellison & Williams, 2012; Joint Committee for Guides in Metrology, 2008; International Organization for Standardization, 2017; Thompson et al., 2002). And practitioners of quality by design argued that a procedure developed without a target profile, a risk assessment and designed experiments cannot be robust by construction and will fail in transfer and routine use whatever its validation report says (Borman et al., 2007; Schweitzer et al., 2010; Nethercote & Ermer, 2012; Vogt & Kord, 2011).

The lifecycle model that emerged from these lines has three stages in the formulation of the USP stimuli articles: procedure design and development, procedure performance qualification and continued procedure performance verification, with the ATP as the anchor and knowledge management and quality risk management as continuous activities (Martin et al., 2013; Barnett et al., 2016). ICH Q14 structures development as the definition of the ATP, knowledge and risk management, the identification of analytical procedure parameters and their ranges (including, for the enhanced approach, a MODR), the control strategy and the documentation of established conditions; ICH Q2(R2) revises the validation characteristics, admits the evaluation of validation data against ATP-derived criteria and covers newer technologies; and ICH Q12 provides the regulatory mechanism for changes within established conditions (International Council for Harmonisation, 2020b; International Council for Harmonisation, 2020a; International Council for Harmonisation, 2019). Figure 1 gives the lifecycle in the six-stage form used throughout this review (ATP, risk assessment, method design, validation, transfer and verification, continued performance verification) around a governance and knowledge core, with the regulatory anchors and the generic-API context noted. Table 1 lists the guidance documents and standards in chronological order with the lifecycle element each introduced or formalised.

Figure 1: Risk-based lifecycle framework for chromatographic methods: six stages around a governance and knowledge core, with stage gates, regulatory anchors and the generic API context

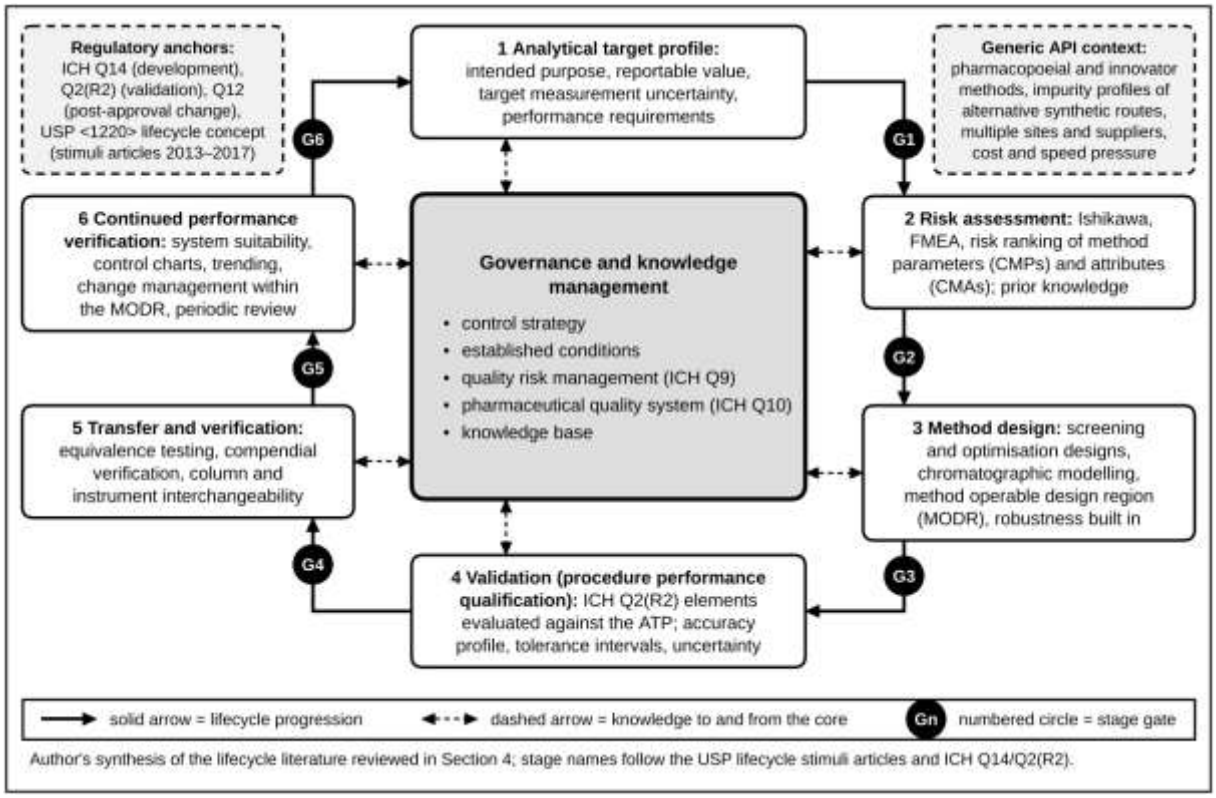


Table 1: Guidance documents and standards relevant to the lifecycle of chromatographic procedures, in chronological order, with the lifecycle element each introduced or formalised

Year	Document	Lifecycle element introduced or formalised	Relevance to generic API methods
1994	ICH Q2A (text) and 1996 Q2B (methodology), consolidated as Q2(R1) in 2005 (International Council for Harmonisation, 2005a)	Validation characteristics: specificity, linearity, range, accuracy, precision, detection and quantitation limits, robustness	The checklist against which pharmacopoeial and in-house methods for generics were validated for two decades
1999	ICH Q6A (International Council for Harmonisation, 1999)	Specifications as the link between the test procedure, its acceptance criteria and the decision about a batch	The reportable value and the decision rule that an analytical target profile must serve
2002	IUPAC harmonised guidelines for single-laboratory validation (Thompson et al., 2002)	Fitness for purpose, measurement uncertainty and the use of validation data to estimate uncertainty	Metrological alternative to the checklist; basis of the Eurachem guidance
2003	ISPE good practice guide on technology transfer (International Society for Pharmaceutical Engineering, 2003)	Comparative testing, co-validation and revalidation as transfer designs; acceptance criteria to be set in advance	Multi-site and contract-laboratory transfers routine for generics
2004 to 2007	SFSTP harmonisation of validation strategies (Hubert et al., 2004, 2007)	Accuracy profile and beta-expectation tolerance interval as the validation decision; total error as the criterion	Validation as a guarantee about future results rather than a set of separate statistics

Year	Document	Lifecycle element introduced or formalised	Relevance to generic API methods
2005	ICH Q9 (International Council for Harmonisation, 2005b)	Quality risk management: risk assessment, control, communication and review; tools such as FMEA and Ishikawa diagrams	The risk-ranking step of analytical quality by design
2008 and 2009	ICH Q10 and Q8(R2) (International Council for Harmonisation, 2008, 2009)	Pharmaceutical quality system, knowledge management and continual improvement; target profile, design space and control strategy for products	Concepts transposed to analytical procedures by the stimuli articles
2007 to 2012	Industry papers on analytical quality by design (Borman et al., 2007; Schweitzer et al., 2010; Nethercote & Ermer, 2012; Vogt & Kord, 2011)	Analytical target profile, method operable design region, control strategy and lifecycle verification for procedures	First explicit programme for managing methods rather than validating them once
2012	ICH Q11 (International Council for Harmonisation, 2012)	Development and manufacture of drug substances; control strategy for the substance	Impurity control strategy of the generic route
2013 and 2016	USP stimuli articles on lifecycle management of analytical procedures (Martin et al., 2013; Barnett et al., 2016)	Three-stage lifecycle (procedure design, performance qualification, continued performance verification) anchored on the ATP	Model adopted as the structure of this review
2014 and 2012	Eurachem guides on method validation and on measurement uncertainty (Magnusson & Örnemark, 2014; Ellison & Williams, 2012)	Fitness for purpose defined through target uncertainty; uncertainty budgets; decision rules	Target measurement uncertainty as a component of the ATP
2015	FDA guidance on analytical procedures and methods validation (U.S. Food and Drug Administration, 2015)	Lifecycle language for validation; expectations for procedure changes and revalidation	Applies to ANDA submissions
2018	USP General Chapter <1210> (United States Pharmacopeial Convention, 2018d)	Statistical tools for procedure validation: tolerance intervals, prediction intervals, combined accuracy and precision	Statistical basis for ATP-derived acceptance criteria
2018	ICH concept paper for Q14 and Q2(R2) (International Council for Harmonisation, 2018)	Decision to write a development guideline and revise the validation guideline	End of the period covered by this review
2019	ICH Q12 (International Council for Harmonisation, 2019)	Established conditions and post-approval change management protocols	Mechanism for changing methods within established conditions
2020	ICH Q14 and Q2(R2) (International Council for Harmonisation, 2020a, 2020b)	Analytical procedure development (minimal and enhanced approaches, ATP, risk assessment, MODR, control strategy) and revised validation	Guidelines against which the framework of Section 6 is mapped; outside the review period

Risk-based development of chromatographic methods

The technical core of the lifecycle literature is the use of quality risk management and designed experiments in chromatographic method development. Risk assessment identifies the method parameters (mobile-phase composition and pH, gradient slope, temperature, flow rate, column chemistry, detection wavelength, sample preparation) whose variation could affect the method's

critical attributes (resolution, tailing, retention, sensitivity, run time), typically with an Ishikawa diagram followed by a ranking or a failure mode and effects analysis; the ranked parameters are then studied in screening designs (Plackett-Burman, fractional factorial) and the influential ones in optimisation designs (full factorial, central composite, Box-Behnken, D-optimal), with desirability functions to combine several responses (International Council for Harmonisation, 2005b; Vander Heyden et al., 2001; Dejaegher & Vander Heyden, 2007; Dejaegher & Vander Heyden, 2011; Hibbert, 2012; Bezerra et al., 2008; Ferreira et al., 2007; Derringer & Suich, 1980; Plackett & Burman, 1946; Box & Behnken, 1960; Sahu et al., 2018). Chromatographic modelling software that predicts retention from a small number of runs, in the tradition of DryLab, allows the design space of the separation to be mapped and its robustness assessed before the method is run (Molnár, 2002; Molnár et al., 2010; Monks et al., 2012; Snyder et al., 2009; Snyder et al., 1997). The design space of an analytical method was given a statistical definition by the Liège group as the region of parameter settings within which the method meets its performance requirements with a stated probability, estimated from predictive models with their uncertainty rather than from the mean response surface (Lebrun et al., 2008; Debrus et al., 2011; Rozet et al., 2013). Column interchangeability, a recurring transfer problem, is addressed by selectivity databases and column-classification schemes (Snyder et al., 2004; Euerby & Petersson, 2003).

Validation, transfer and continued verification

Validation in the lifecycle model is the qualification of the procedure against the ATP. The accuracy-profile approach computes, at each concentration level, a tolerance interval for future results and compares it with the acceptance limits derived from the ATP; the method is valid over the range in which the profile stays within the limits, and the same profile gives the measurement uncertainty (Hubert et al., 2004; Hubert et al., 2007; Feinberg, 2007; Rozet et al., 2011; Rozet et al., 2012). The approach was extended to transfer, where the question is whether results at the receiving site meet the same acceptance limits, with equivalence tests replacing significance tests of mean differences (Dewé et al., 2007; Kaminski et al., 2010; Limentani et al., 2005; Chambers et al., 2005; United States Pharmacopeial Convention, 2018c; International Society for Pharmaceutical Engineering, 2003). Precision in routine use was studied from stability data, which showed that intermediate precision rather than repeatability is the quantity that acceptance criteria should rest on (Ermer & Ploss, 2005; Ermer et al., 2005). Continued performance verification applies the control-chart tradition of statistical quality control to the procedure's system-suitability and quality-control results, with Shewhart, EWMA and CUSUM charts and multi-rule schemes to detect drift and shifts (Shewhart, 1931; Roberts, 1959; Page, 1954; Lucas & Saccucci, 1990; Westgard et al., 1981; Montgomery, 2012). The statistical tools for these tasks (tolerance intervals, variance components, equivalence tests, detection and quantitation limits) have a long literature that the pharmacopoeial chapter on statistical tools for procedure validation summarises (Hahn & Meeker, 1991; Satterthwaite, 1946; Burdick & Graybill, 1992; Schuirmann, 1987; Currie, 1968; Currie, 1999; Armbruster & Pry, 2008; United States Pharmacopeial Convention, 2018d).

The generic API context

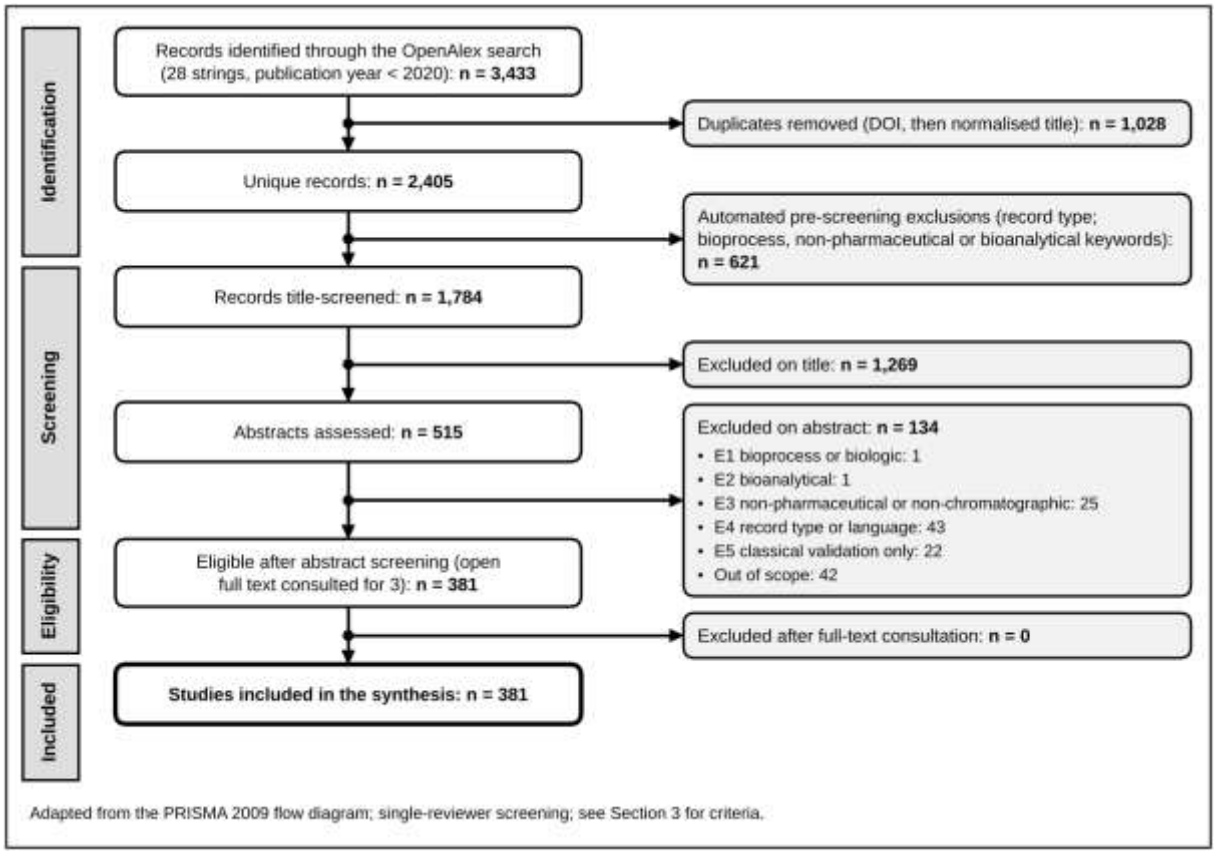
For generic APIs the lifecycle has specific features. The impurity profile is route-dependent, so the related-substances method must be shown to resolve the process impurities and degradation products of the generic route, often with forced-degradation studies and hyphenated identification, against the ICH Q3A and Q3B thresholds (International Council for Harmonisation, 2006a; International Council for Harmonisation, 2006b; Bakshi & Singh, 2002; Blessy et al., 2014; Alsante et al., 2007; Reynolds et al., 2002; Singh et al., 2012; Görög, 2018; Baertschi et al., 2011). Pharmacopoeial methods are verified rather than validated when they are used as published, but a generic manufacturer frequently adapts them, which moves the procedure from verification to validation and transfer (United States Pharmacopeial Convention, 2018a; United States Pharmacopeial Convention, 2018b; United States Pharmacopeial Convention, 2018e). The quality-by-design framework for abbreviated new drug applications formulated by the FDA's Office of Generic Drugs placed the analytical procedure inside the product's control strategy, so that the method's design space and the product's are developed together (Lionberger et al., 2008; Yu, 2008; Yu et al., 2014; Woodcock & Wosinska, 2013). And the multiplicity of sites, suppliers and contract laboratories makes transfer, verification and continued performance verification the stages at which a generic organisation gains or loses most from the lifecycle model.

Methods

Protocol and reporting

The review followed a protocol written before the search (file protocol.md in the supplementary material) and is reported with the PRISMA 2009 items that apply to a review of a bibliographic index by a single reviewer (Moher et al., 2009; Liberati et al., 2009). The protocol fixed the research questions, the information source, the search strings, the eligibility criteria, the screening stages, the extraction form, a ten-item reporting-quality score and the synthesis plan. Conventions for systematic reviews outside clinical medicine, where the evidence consists of methodological and applied studies without a common outcome, were followed for the structure of the synthesis (Tranfield et al., 2003; Kitchenham & Charters, 2007; Petticrew & Roberts, 2006; Grant & Booth, 2009). Figure 2 gives the flow of records.

Figure 2: PRISMA-style flow of records through identification, automated pre-screening, title screening, abstract screening and full-text checks



Information source and search

The single information source was the OpenAlex works index (https://openalex.org), queried through its public application programming interface on 25 and 26 October 2020. PubMed, institutional repositories and publisher metadata and was chosen because it can be queried reproducibly by uniform resource locator without a subscription; its coverage of the pharmaceutical analytical literature is broad but not complete, and records from small journals sometimes carry no abstract, which affected the later stages (Section 3.5). Twenty-eight search strings (Table 2) were run against the title and abstract fields with the terms of each string combined by AND, the publication year restricted to before 2020 and no language or document-type filter at search time. The strings covered the vocabulary of the lifecycle model (quality by design, analytical target profile, method operable design region, design space, lifecycle, life cycle, risk-based, risk assessment, control strategy, failure mode, Ishikawa), the design-of-experiments and robustness vocabulary of chromatographic development, the validation vocabulary beyond the ICH checklist (accuracy profile, total error), transfer, verification and performance verification, and one string aimed at generic active pharmaceutical ingredients. Each string returned at most 50 records per page; every page was retrieved for strings with up to 400 hits, and the first 400

records by relevance for the two strings that exceeded that number. Two planned strings returned an unfiltered response from the index on repeated attempts (the whole index rather than the query's hits); they were replaced by shorter variants, and the replacements are recorded in Table 2. Reference lists of included reviews were not searched, and no other database was queried; both are limitations (Section 6.4).

Table 2: Search strings run against the OpenAlex title and abstract fields (publication year before 2020), with hits, records retrieved, unique records contributed and included studies retrieved by each string

String	Terms (title and abstract, AND)	Hits	Retrieved	Unique	Included	Note
Q01	"quality by design" chromatography	261	261	258	102	
Q02	"quality by design" HPLC	200	200	197	116	
Q03	"quality by design" "liquid chromatography"	157	157	155	79	
Q04	"quality by design" "analytical method"	225	225	219	83	
Q05	"analytical quality by design"	113	113	110	54	
Q06	"analytical target profile"	54	54	54	24	
Q07	"method operable design region"	23	23	23	13	
Q08	"design space" "analytical method"	171	171	163	38	
Q09	"design space" HPLC	101	101	100	52	
Q10	"analytical method" lifecycle	116	116	110	10	
Q11	"analytical procedure" lifecycle	22	22	22	3	
Q12	"analytical method" "life cycle"	451	400	378	14	first 400 of 451 retrieved
Q13	"risk assessment" "method development" HPLC	26	26	25	8	
Q14	"risk assessment" "method validation" HPLC	14	14	14	2	planned string with "chromatography" returned an unfiltered result; HPLC variant run
Q15	"risk-based" "analytical method"	155	155	148	8	
Q16	"experimental design" robustness HPLC	123	123	122	73	
Q17	"design of experiments" HPLC "method development"	42	42	41	24	
Q18	"method transfer" chromatography	106	106	106	11	
Q19	"analytical method transfer"	39	39	38	12	
Q20	"performance verification" "analytical procedure"	8	8	8	1	
Q21	"failure mode" "analytical method"	428	400	394	3	first 400 of 428 retrieved
Q22	Ishikawa HPLC method	16	16	16	3	
Q23	"accuracy profile" chromatography validation	115	115	113	15	
Q24	"total error" "method validation"	44	44	44	10	
Q25	"control strategy" "analytical method"	318	318	309	14	

String	Terms (title and abstract, AND)	Hits	Retrieved	Unique	Included	Note
Q26	"active pharmaceutical ingredient" generic HPLC	22	22	22	0	planned five-term string returned an unfiltered result; three-term variant run
Q27	"stability-indicating" HPLC "quality by design"	48	48	48	45	
Q28	"robustness" "quality by design" chromatographic	114	114	109	79	

Eligibility criteria

Table 3 lists the inclusion and exclusion criteria. A record was eligible if it was a journal article or review published between 1990 and 2019, concerned a chromatographic procedure for the quality of a small-molecule drug substance or drug product (or was a methodological, statistical or regulatory contribution addressed to such procedures), and reported, applied or critically discussed at least one lifecycle or risk-based element. Classical development-and-validation reports that apply the ICH Q2(R1) characteristics after one-factor-at-a-time development, with no risk assessment, designed experiment or lifecycle element, were excluded, as were bioprocess and biologic applications, bioanalytical methods in biological matrices, non-pharmaceutical matrices, techniques without chromatography (electrophoresis alone, spectroscopy, titration) and records that are not journal publications. Herbal medicines were kept when the abstract framed the method as pharmaceutical quality control of a regulated product. Because almost every string contains a lifecycle term, the abstracts of the retrieved records contain that term by construction; the abstract stage therefore decided whether the term denotes an element of the procedure's lifecycle (eligible) or something else (a product design space, a bioprocess, a failure mode of a structure).

Table 3: Eligibility criteria and the screening stage at which each was applied

Criterion	Definition	Stage applied
I1 Record type and period	Journal article or review (conference papers published in journals count); publication year 1990 to 2019	Automated (type), title, abstract
I2 Subject	A chromatographic analytical procedure (HPLC, UHPLC, LC-MS, GC, HPTLC or TLC densitometry, SFC, ion chromatography) for the quality of a small-molecule drug substance or product (assay, impurities, degradation products, residual solvents, dissolution, content uniformity, cleaning), or a methodological, statistical or regulatory contribution addressed to such procedures	Title, abstract
I3 Lifecycle or risk-based element	At least one of: analytical target profile or explicit performance requirement; risk assessment or quality-risk-management tool; design of experiments or chromatographic modelling; design space, MODR or knowledge space; validation beyond the ICH Q2(R1) checklist (total error, accuracy profile, tolerance interval, uncertainty, decision rules); transfer, verification or equivalence; continued performance verification, control charts or system-suitability strategy; change management or lifecycle concepts	Abstract
I4 Language	English	Abstract
E1 Bioprocess or biologic	Preparative or process chromatography, purification, proteins, peptides as products, vaccines, oligonucleotides, biosimilars, cell culture	Automated (keywords), title, abstract

Criterion	Definition	Stage applied
E2 Bioanalytical	Methods in biological matrices (plasma, serum, urine, tissue, blood) and pharmacokinetic applications	Automated (keywords), title, abstract
E3 Non-pharmaceutical or non-chromatographic	Food, environmental, forensic, cosmetic, agrochemical and materials applications; herbal products not framed as medicines; techniques without chromatography (spectroscopy, electrophoresis alone, titration)	Automated (keywords), title, abstract
E4 Record type or language	Dissertations, books and chapters, conference abstracts, editorials, errata, patents, paratext; non-English records	Automated (type), title, abstract
E5 Classical development and validation only	One-factor-at-a-time development with ICH Q2(R1) validation and no element of I3 (a one-at-a-time robustness check is not a lifecycle element; a designed robustness experiment is)	Abstract
OOS Out of scope	Product, process or formulation quality by design; unrelated fields retrieved by the generic terms of the strings (life cycle, failure mode, control strategy, design space)	Title, abstract

Screening

Records were de-duplicated by digital object identifier and then by normalised title, and passed through four stages (Figure 2). Stage 0 was automated: records of excluded types (dissertations, books and chapters, paratext, errata, editorials, reports, preprints) and records whose titles matched keyword rules for bioprocess and biologic work, non-pharmaceutical matrices and bioanalytical applications were removed, and every automated exclusion was logged with its rule (merge28.py in the supplementary material). Stage 1 was a title screen by the author, assisted by a rule set that flagged titles with lifecycle, chromatographic and pharmaceutical vocabulary so that likely eligible titles were read with particular care; every title was read, and each excluded title received a reason code. Titles that named a pharmaceutical chromatographic method without any lifecycle element passed to the abstract stage, because the element may appear only in the abstract. Stage 2 was the abstract screen: abstracts were retrieved for each record from OpenAlex (reconstructed from its inverted index), from Europe PMC (https://europepmc.org) or from Semantic Scholar (https://www.semanticscholar.org), and screened against the criteria of Table 3 with the help of language-model agents that applied a written brief (extract_brief.md in the supplementary material) record by record, fetching one abstract at a time and recording the source of each abstract. Stage 3 was a full-text check for the few records whose abstract was ambiguous and whose full text was openly accessible. Abstract retrieval was the weak point of the process: the sources rate-limited the shared network address once several agents queried them, so the abstract stage was run in three passes (a first pass over all records, then two slower passes over the records without an abstract, routed to the source most likely to hold the abstract for each publisher), and records for which no source returned an abstract after the three passes were decided on the title alone and flagged. The share of such records is reported with the results; their decisions are the weakest in the review and their extraction fields are counted as not reported, which biases every count downward. As a consistency check, a 10% random sample of the abstract-stage records (52 records, seed 28) was screened and extracted a second time by an independent agent pass that had not seen the first decisions, with the same brief; agreement on the inclusion decision and on the extraction fields is reported in Section 4.1, and the author resolved the disagreements by reading the abstracts concerned.

Data extraction and appraisal

A structured form (Table 4) was completed for every included record from its abstract or, where opened, its full text. The form records the bibliographic data, the analytical context (technique, purpose, material, whether a generic, abbreviated new drug application, multisource or pharmacopoeial-adaptation context is mentioned) and, for each of the six lifecycle stages of Figure 1, whether the element is reported and which tool, design, software or acceptance approach is named. Fields not addressed in the abstract were coded as not reported, which makes every count a lower bound of the

practice in the full texts. Ten reporting-quality items (Table 5), one or two per lifecycle stage, were scored 1 when the record explicitly reports the item and 0 otherwise; the sum gives a reporting score between 0 and 10. The score describes what the abstract reports and is not a judgement of the study's validity, since no validated risk-of-bias instrument exists for method-development studies; it is also conservative, because abstracts omit design details, diagnostics and limitations that the full papers may contain. Decisions and extraction records for every record, including the automated and title-stage exclusions, are provided as the screening file of the supplementary material.

Table 4: Data extraction form completed for each included record (fields and categories)

Field group	Fields and categories
Bibliographic	Record identifier, DOI, year, journal or source, record type (original research; review; commentary or regulatory perspective; methodological or statistical)
Analytical context	Technique (HPLC-UV, UHPLC, LC-MS, GC, HPTLC, SFC, IC, CE, multiple, not applicable); purpose (assay; impurities or related substances; stability-indicating or forced degradation; residual solvents; dissolution; cleaning; multiple; not applicable); material (drug substance, drug product, both, not applicable); generic, ANDA, multisource or pharmacopoeial-adaptation context mentioned (yes, no)
Stage 1: target profile	Analytical target profile or explicit performance requirement stated before development (yes, no, not reported)
Stage 2: risk assessment	Risk assessment performed (yes, no, not reported); tool (Ishikawa, FMEA, risk ranking, CNX, other, multiple, none)
Stage 3: method design	Screening design (Plackett-Burman, fractional factorial, definitive screening, other, none); optimisation design (full factorial, central composite, Box-Behnken, D-optimal, mixture, other, none); software (DryLab, Fusion QbD, Design-Expert, MODDE, JMP, Minitab, ACD/LC, other, multiple, none); design space or MODR reported (yes, no); robustness confirmed at the edges of the region (yes, no, not reported)
Stage 4: validation	Validation study performed (yes, no, not reported); acceptance-criterion approach (classical limits; total error or accuracy profile; tolerance interval; measurement uncertainty; equivalence test; multiple; not reported); control strategy or system suitability derived from development data (yes, no, not reported)
Stages 5 and 6: transfer and verification	Transfer, verification or equivalence study (yes, no); continued performance verification, control charts or trending (yes, no); change management or lifecycle discussion (yes, no); knowledge or data management (yes, no)
Outcome and appraisal	Main reported outcome (one line); limitations stated (yes, no); ten reporting-quality items (Table 5); basis of the record (abstract, title only, full text); abstract source (Semantic Scholar, Europe PMC, OpenAlex, none)

Table 5: Ten-item reporting-quality score, with the stage of the lifecycle that each item describes

Item	Scored 1 when the record reports	Lifecycle stage
1 Objective or ATP explicit	The intended purpose and performance requirement of the procedure (reportable value, range, precision or uncertainty target) stated before development or validation	1
2 Risk tool named	A named quality-risk-management tool (Ishikawa, FMEA, risk ranking, CNX) with its output	2
3 Factors and ranges justified	The method parameters studied and their ranges, with the reason for choosing them (prior knowledge, risk ranking, scouting)	2, 3
4 Statistical model and diagnostics	The model fitted to the designed experiment (effects, response surface, retention model) with a measure of fit or diagnostics	3

Item	Scored 1 when the record reports	Lifecycle stage
5 Region verified experimentally	The design space, MODR or robust region confirmed by experiments at or near its edges	3
6 Validation with stated acceptance criteria	Validation characteristics evaluated against acceptance criteria stated in advance (classical limits, accuracy profile, tolerance interval, uncertainty)	4
7 Control strategy or system suitability specified	System-suitability criteria or a control strategy derived from the development data	3, 4
8 Lifecycle, transfer or monitoring addressed	Transfer, verification, continued performance verification, trending or change management reported or discussed	5, 6
9 Data or supplementary material available	Raw data, chromatograms, design matrices or supplementary material stated to be available	all
10 Limitations stated	Limitations of the study or of the approach acknowledged	all

Synthesis

The synthesis is descriptive. For RQ1, records were counted by year, source, record type, technique, purpose and material, and the yield of each search string was computed. For RQ2 and RQ3, the lifecycle elements, risk tools, experimental designs, software, acceptance approaches, transfer and monitoring studies were counted overall, by record type (original research against reviews, perspectives and methodological papers) and by period (1990 to 2012 against 2013 to 2019, the second period starting with the first USP stimuli article on the lifecycle), and the co-occurrence of elements within studies was tabulated to show which parts of the lifecycle are implemented together. An evidence gap map crosses the elements with the record types. For RQ4, the reporting items were counted and the score distribution summarised. No meta-analysis was attempted: the studies share neither outcomes nor designs. The framework of Section 5 was then derived from the elements that the evidence supports, with its gaps marked, and mapped to the sections of ICH Q14 and Q2(R2) and to the pharmacopoeial and metrological anchors (Section 5.1). All counts were computed by script from the extraction files (synth28.py), and the charts of Figures 3 to 9 were drawn from the same file.

Results

Search results and screening

The 28 strings returned 3,433 records, of which 2,405 were unique after de-duplication by digital object identifier and normalised title (Figure 2). Automated pre-screening removed 621 records (record type 417; non-pharmaceutical matrix keywords 99; bioanalytical keywords 84; bioprocess or biologic keywords 49; a record can match more than one rule), leaving 1,784 titles for the manual screen, of which 1,269 were excluded on title (out of scope 1013; non-pharmaceutical matrix or non-chromatographic technique 130; bioprocess or biologic 76; bioanalytical 31; record type or language 19) and 515 passed to the abstract stage. At the abstract stage 134 records were excluded (E4 record type or language 43; out of scope 42; E3 non-pharmaceutical or non-chromatographic 25; E5 classical validation only 22; E1 bioprocess or biologic 1; E2 bioanalytical 1), the open full text was consulted for 3 records whose abstracts were ambiguous (none was excluded), and 381 studies were included in the synthesis. An abstract could be retrieved for 247 of the included studies (65%); the remaining 134 were included on the title alone because none of the four abstract sources returned an abstract for them in three passes, and their extraction fields are coded as not reported. The independent second pass on the 10% sample (52 records) agreed with the first inclusion decision in 48 cases and disagreed in 4; across the 720 extraction fields compared for the records that both passes included, 60 differed (8%), mostly between "no" and "not reported" or between neighbouring design categories. The disagreements on inclusion all concerned the record-type criterion (three repository records of conference contributions that the second pass would have included) and one record whose version of record is dated 2020 although the index lists 2019; the author resolved them by applying criteria E4 and I1 as written, and the registry check of the cited studies, which revealed the 2020 case, is the reason the index year is treated as a limitation (Section 6.4).

Table 2 shows the yield of the strings. The quality-by-design strings (Q01 to Q05) and the design-space strings (Q08, Q09) contributed most of the included studies, the transfer strings (Q18, Q19) a distinct cluster of statistical and practical transfer papers, and the accuracy-profile and total-error strings (Q23, Q24) the validation-methodology cluster; the lifecycle, risk-based, failure-mode and control-strategy strings (Q10 to Q15, Q21, Q25) returned mostly records from other fields, which is why the automated and title stages removed so many. A single string found 166 of the 381 included studies, so the strings were complementary rather than redundant.

Volume, growth and distribution (RQ1)

Figure 3 and Table 6 describe the included studies. The literature is recent: 97 studies were published between 1990 and 2012 and 284 between 2013 and 2019, and the annual count rises after the quality-by-design papers of 2007 to 2012 and the first USP stimuli article of 2013. Original research accounts for 290 studies (76%), most of them method-development studies for one product; 47 are methodological or statistical contributions, 34 are reviews and 10 are commentaries or regulatory perspectives. HPLC with ultraviolet detection dominates the original studies (224 studies), followed by UHPLC (27), HPTLC (14), LC-MS (9) and supercritical fluid chromatography (9). Assay and impurity methods are the most frequent purposes, and stability-indicating methods form a distinct group; drug products outnumber drug substances. A generic, abbreviated new drug application, multisource or pharmacopoeial-adaptation context is mentioned in 12 abstracts (3%), which is itself a finding: the literature on lifecycle methods rarely states the regulatory status of the product.

Figure 3: Included studies by publication year, record type and technique, with the title-screened records for comparison

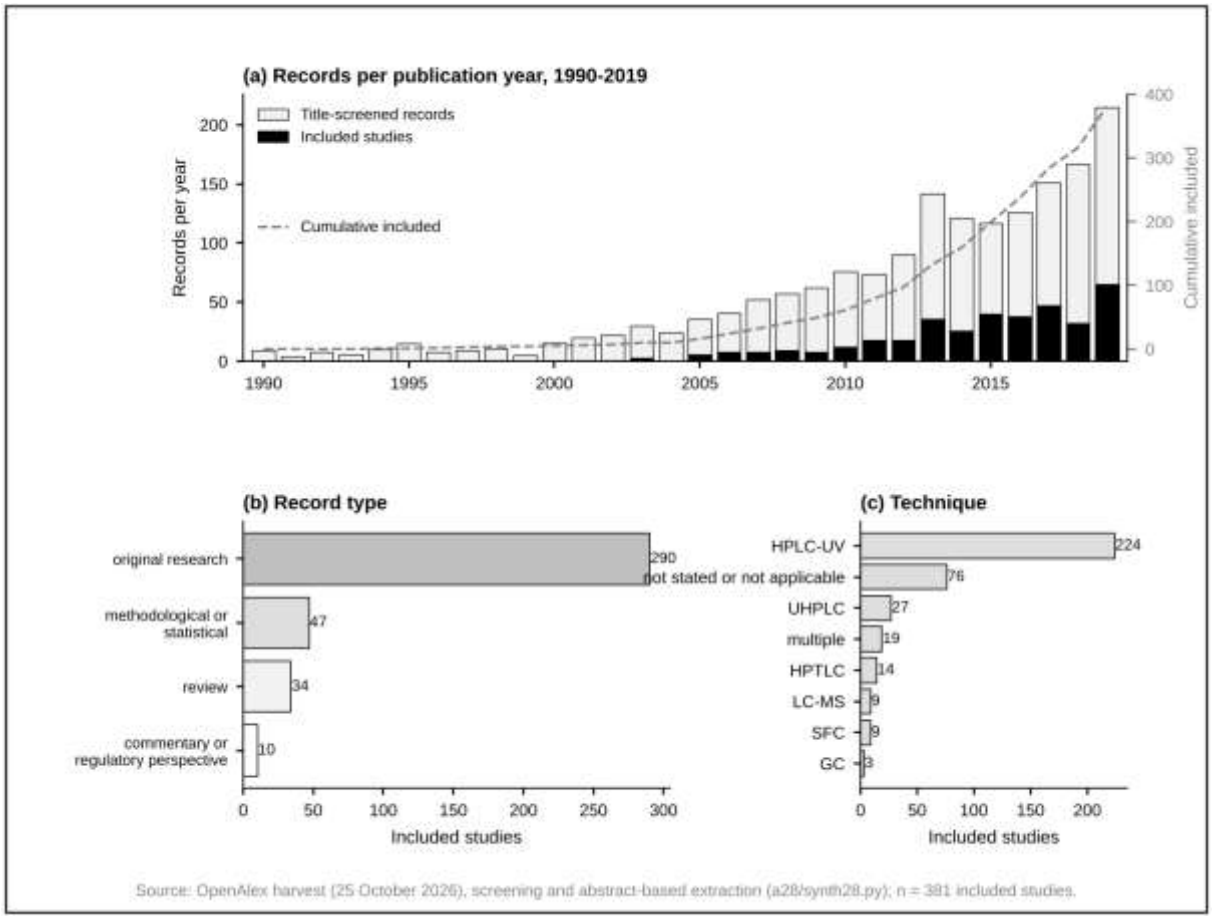


Table 6: Characteristics of the included studies: period, record type, technique, purpose, material, generic context, decision basis and abstract source

Characteristic	Category	Studies	Share
Year band	1990-2012	97	25%
Year band	2013-2019	284	75%
Record type	original research	290	76%
Record type	methodological or statistical	47	12%
Record type	review	34	9%
Record type	commentary or regulatory perspective	10	3%
Technique	HPLC-UV	224	59%
Technique	not stated or not applicable	76	20%
Technique	UHPLC	27	7%
Technique	multiple	19	5%
Technique	HPTLC	14	4%
Technique	LC-MS	9	2%
Technique	SFC	9	2%
Technique	GC	3	1%
Analytical purpose	assay	115	30%
Analytical purpose	not stated or not applicable	105	28%
Analytical purpose	stability-indicating or forced degradation	67	18%
Analytical purpose	impurities or related substances	51	13%
Analytical purpose	multiple	38	10%
Analytical purpose	dissolution	5	1%
Material	not stated or not applicable	161	42%
Material	drug product	116	30%
Material	both	65	17%
Material	drug substance	39	10%
Generic, ANDA or pharmacopoeial context	yes	12	3%
Generic, ANDA or pharmacopoeial context	no	369	97%
Decision basis	abstract	244	64%
Decision basis	title	134	35%
Decision basis	fulltext	3	1%
Abstract source	openalex	204	54%
Abstract source	none	137	36%
Abstract source	europepmc	18	5%
Abstract source	semanticscholar	16	4%
Abstract source	crossref	6	2%

Figure 4 and Table 7 give the sources. Journal of Pharmaceutical and Biomedical Analysis is the leading venue with 58 included studies, followed by Journal of Chromatography A (21) and Journal of Liquid Chromatography & Related Technologies (19); the remainder is spread across chromatography, separation-science, pharmaceutical-analysis and regional pharmacy journals, with a tail of institutional repositories whose records are theses, conference contributions and preprints of journal papers. The concentration in two or three journals means that a reader of those journals sees most of the methodological development, while the applied studies in regional journals, which are numerous, are

the ones with the lowest reporting scores (Section 4.7).

Figure 4: Sources with the most included studies and the yield of the search strings

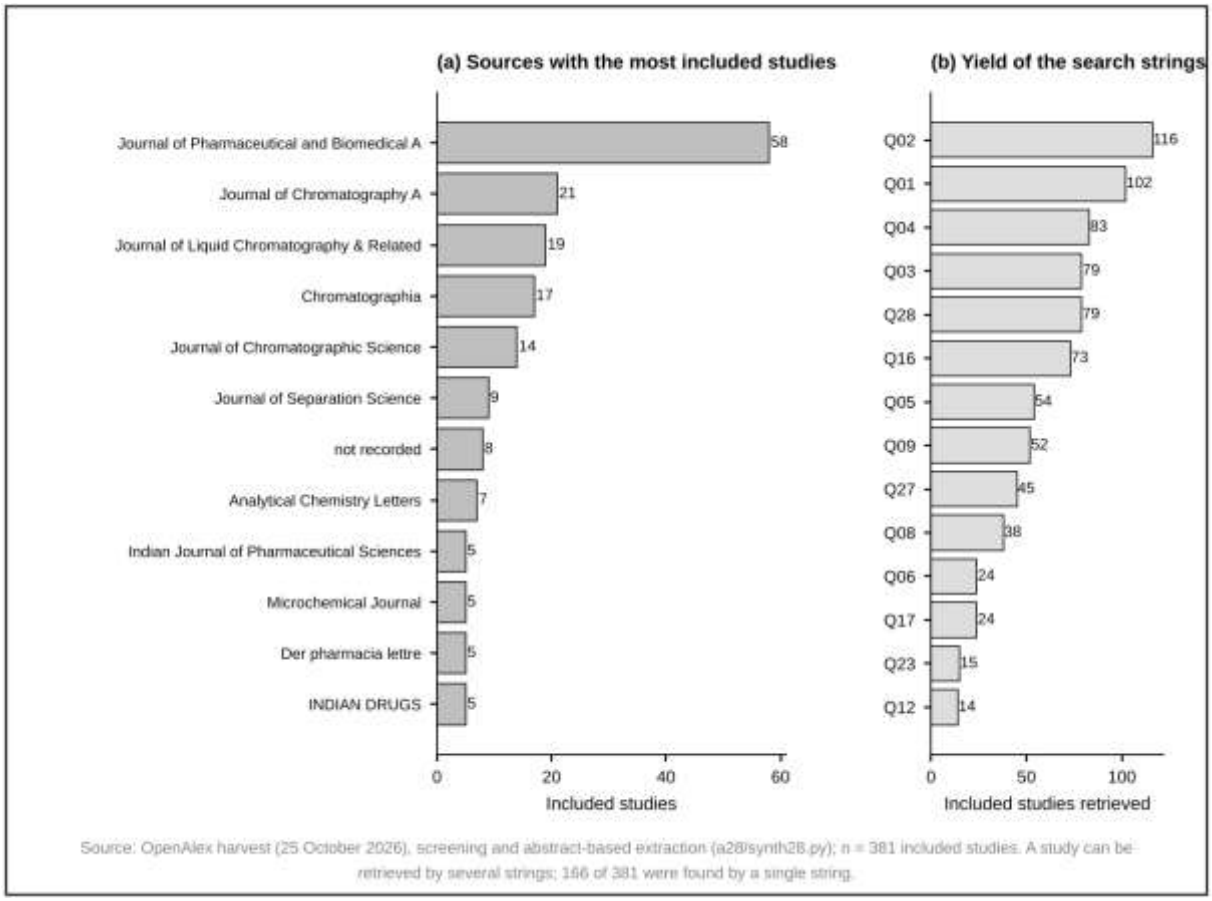


Table 7: Sources with the most included studies, with the number of title-screened records from the same source and the years covered

Journal or source (top sources)	Included studies	Share of included	Title-screened records	Years
Journal of Pharmaceutical and Biomedical Analysis	58	15%	97	1996-2019
Journal of Chromatography A	21	6%	74	2006-2019
Journal of Liquid Chromatography & Related Technologies	19	5%	21	1997-2019
Chromatographia	17	4%	23	2006-2019
Journal of Chromatographic Science	14	4%	16	2011-2019
Journal of Separation Science	9	2%	16	2013-2019
not recorded	8	2%	139	2010-2019
Analytical Chemistry Letters	7	2%	7	2014-2019

Journal or source (top sources)	Included studies	Share of included	Title-screened records	Years
Indian Journal of Pharmaceutical Sciences	5	1%	5	2015-2019
Microchemical Journal	5	1%	5	2018-2019
Der pharmacia lettre	5	1%	5	2011-2016
INDIAN DRUGS	5	1%	5	2015-2019
Current Pharmaceutical Analysis	4	1%	8	2014-2018
International Journal of Pharmaceutical Sciences and Drug Research	4	1%	4	2014-2019
Other sources (124)	200	52%		

Lifecycle stages and risk tools (RQ2)

Table 8 and Figure 5 give the coverage of the lifecycle elements. Stage 3 dominates: an optimisation design is reported by 168 (44%) of the included studies, a screening design by 72 (19%), named software by 36 (9%) and a design space or MODR by 81 (21%). Stage 4 follows with a validation study in 202 (53%). The stages at the two ends of the lifecycle are sparse: an analytical target profile or explicit performance requirement in 28 (7%), a risk assessment in 38 (10%), a control strategy or system suitability derived from the development data in 16 (4%), transfer or verification in 23 (6%), continued performance verification in 4 (1%), a lifecycle or change-management discussion in 27 (7%) and knowledge management in 3 (1%). Original research reports the design elements more often than the reviews and perspectives, which in turn discuss the lifecycle, transfer and monitoring more often than they are practised. The period comparison shows the shift that the stimuli articles produced: the target profile, risk assessment and design-space elements are all more frequent in 2013 to 2019 than before, while transfer and validation-methodology work is concentrated in the earlier period, when the Liège and Ermer groups published their statistical series.

Table 8: Lifecycle elements reported by the included studies, overall, by record type and by period

Lifecycle element (yes)	All included	Original research	Reviews, perspectives, methods	1990-2012	2013-2019
Analytical target profile or explicit performance requirement	28 (7%)	16 (6%)	12 (13%)	4 (4%)	24 (8%)
Risk assessment	38 (10%)	23 (8%)	15 (16%)	6 (6%)	32 (11%)
Screening design	72 (19%)	67 (23%)	5 (5%)	18 (19%)	54 (19%)
Optimisation design	168 (44%)	159 (55%)	9 (10%)	23 (24%)	145 (51%)
Chromatographic or statistical software named	36 (9%)	32 (11%)	4 (4%)	5 (5%)	31 (11%)
Design space or MODR reported	81 (21%)	57 (20%)	24 (26%)	16 (16%)	65 (23%)
Region verified at the edges	5 (1%)	5 (2%)	0 (0%)	0 (0%)	5 (2%)
Validation study	202 (53%)	192 (66%)	10 (11%)	37 (38%)	165 (58%)
Control strategy or system suitability from development data	16 (4%)	10 (3%)	6 (7%)	6 (6%)	10 (4%)
Transfer, verification or equivalence study	23 (6%)	10 (3%)	13 (14%)	16 (16%)	7 (2%)

Lifecycle element (yes)	All included	Original research	Reviews, perspectives, methods	1990-2012	2013-2019
Continued performance verification or control charts	4 (1%)	1 (0%)	3 (3%)	0 (0%)	4 (1%)
Change management or lifecycle discussion	27 (7%)	9 (3%)	18 (20%)	5 (5%)	22 (8%)
Knowledge or data management	3 (1%)	1 (0%)	2 (2%)	2 (2%)	1 (0%)

Figure 5: Share of included studies reporting each lifecycle element, by record type and by period

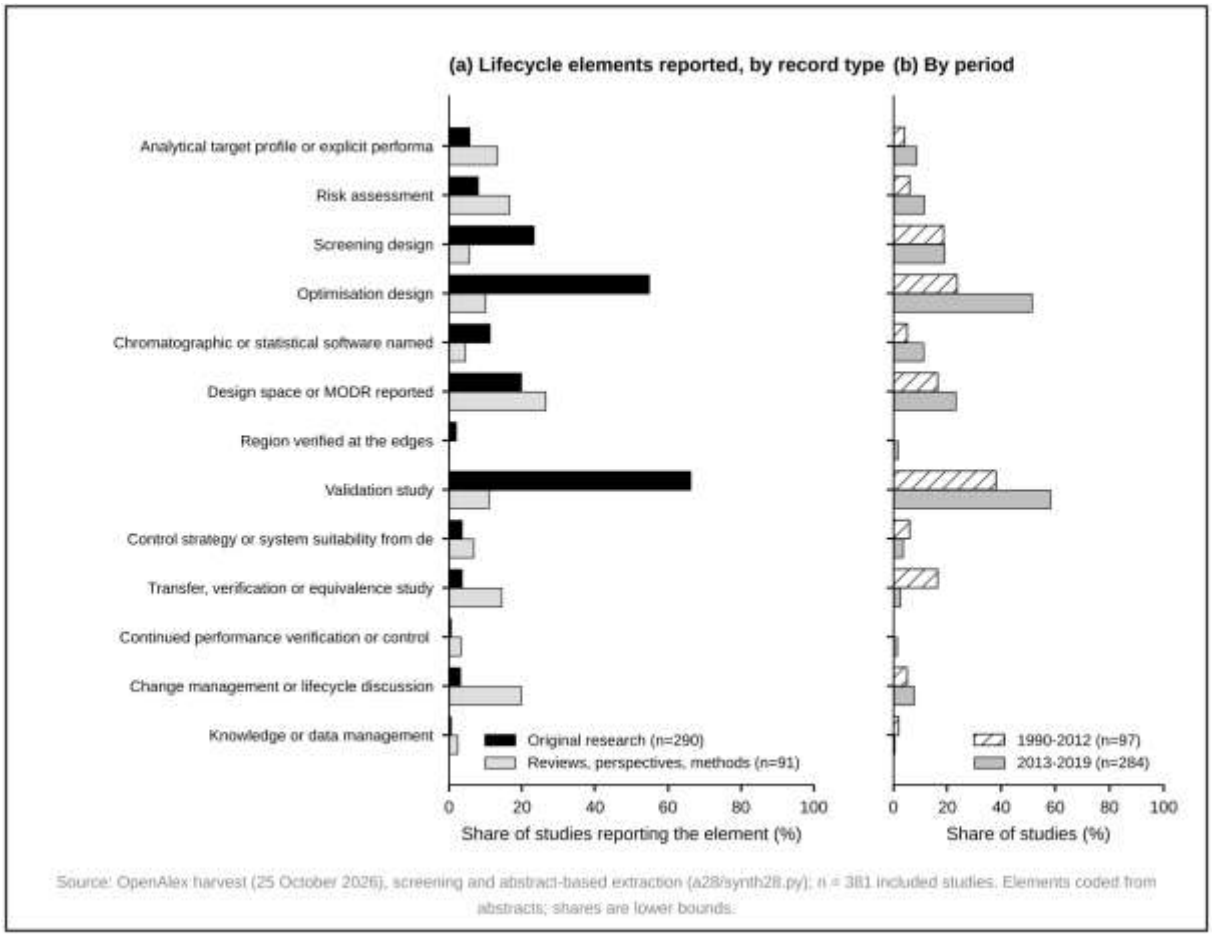


Figure 6 and Table 9 show how the elements combine. The co-occurrence matrix has one dense block, the design elements (screening, optimisation, design space) with validation, and sparse margins: the target profile co-occurs with a risk assessment in 14 studies and with a design space in 12, and transfer and monitoring co-occur with the design elements in a handful of studies. Counting ten elements per study, 172 studies report none or one, 176 two or three, 26 four or five and 7 six or more; 9 studies report the development chain of target profile, risk assessment and designed experiment, and 6 the full chain through design space and validation. A risk tool is recorded for 28 studies: Ishikawa diagrams in 2, FMEA in 2, more than one named tool in 3 and a risk assessment whose tool the abstract does not name or names only as a ranking or scoring in 21; the remaining studies report no risk assessment at all.

Figure 6: Co-occurrence of lifecycle elements across the included studies and the number of elements reported per study

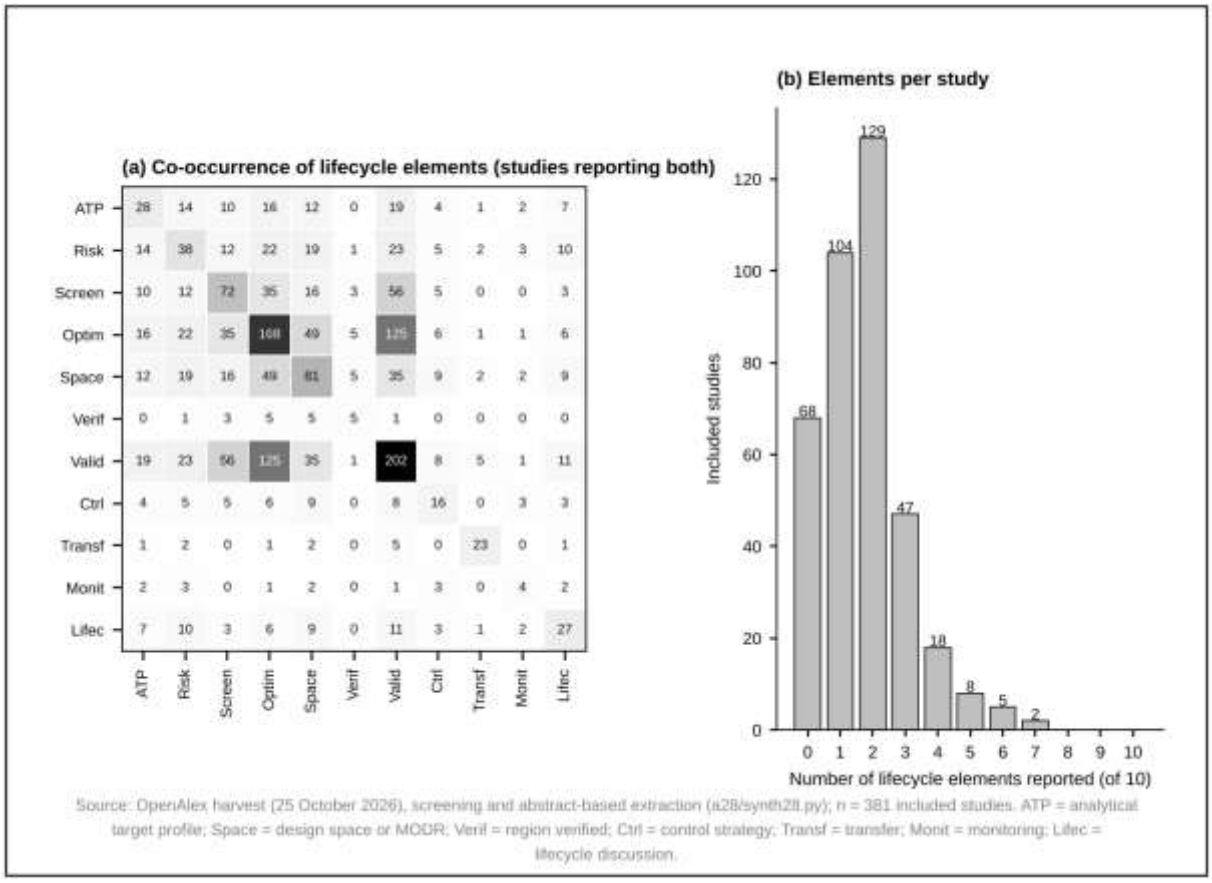


Table 9: Risk tools named and number of lifecycle elements reported per study, overall and by period

Risk tool or element count	Studies	Share	1990-2012	2013-2019
none	353	93%	92	261
other	21	6%	3	18
multiple	3	1%	0	3
Ishikawa	2	1%	0	2
FMEA	2	1%	2	0
Number of lifecycle elements reported: 0 or 1	172	45%	57	115
Number of lifecycle elements reported: 2 or 3	176	46%	39	137
Number of lifecycle elements reported: 4 or 5	26	7%	1	25
Number of lifecycle elements reported: 6 or more	7	2%	0	7

Experimental designs, modelling and software

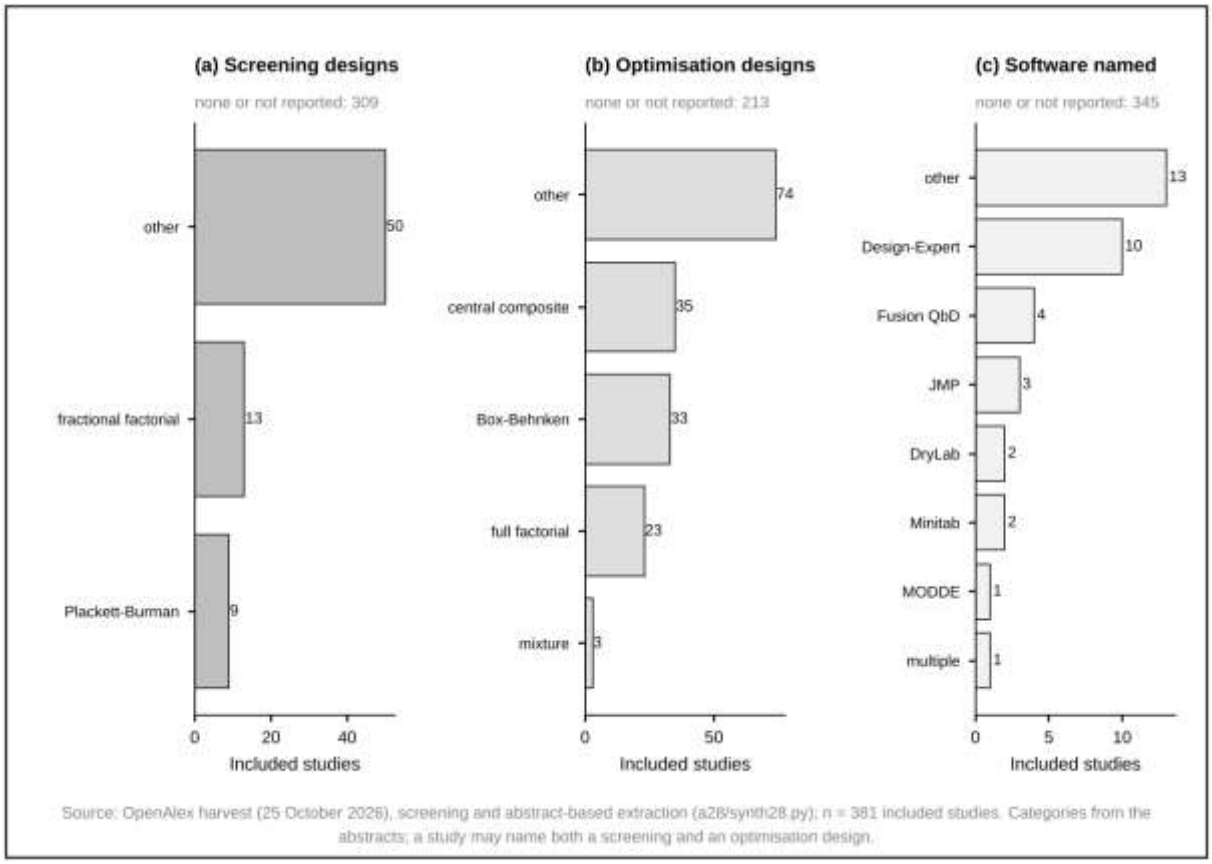
Table 10 and Figure 7 give the designs and tools. Among the screening designs named in abstracts, fractional factorial (13), Plackett-Burman (9) designs are the most frequent, and 50 abstracts mention a screening step without naming the design; among optimisation designs, central composite (35), Box-Behnken (33), full factorial (23), mixture (3) designs account for most of the named designs, with 74 abstracts naming a response-surface or other design without its type. Software is named in 36 (9%) of the abstracts, most often a general design-of-experiments package (Design-Expert (10), Fusion QbD (4), JMP (3), DryLab (2), Minitab (2), MODDE (1); the rest unnamed or other), with DryLab for chromatographic modelling and Fusion QbD for integrated workflows named less often than their

place in the methodological literature would suggest. The studies that model retention from a few runs (DryLab and related approaches) are those that report design-space mapping, column interchangeability and in-silico robustness testing; the studies that use general-purpose designed experiments report response-surface optimisation and desirability functions. Verification of the design space or MODR at its edges is reported by 5 (1%) of the studies, so the regulatory promise of the MODR, movement within it without revalidation, rests on a verified region in a minority of cases.

Table 10: Screening designs, optimisation designs and software named in the included studies

Design or tool	Studies	Share of included
Screening design: none	309	81%
Screening design: other	50	13%
Screening design: fractional factorial	13	3%
Screening design: Plackett-Burman	9	2%
Optimisation design: none	213	56%
Optimisation design: other	74	19%
Optimisation design: central composite	35	9%
Optimisation design: Box-Behnken	33	9%
Optimisation design: full factorial	23	6%
Optimisation design: mixture	3	1%
Software: none	345	91%
Software: other	13	3%
Software: Design-Expert	10	3%
Software: Fusion QbD	4	1%
Software: JMP	3	1%
Software: DryLab	2	1%
Software: Minitab	2	1%
Software: MODDE	1	0%
Software: multiple	1	0%

Figure 7: Screening designs, optimisation designs and software named in the included studies



The methodological core

The counts hide a structure that the reading of the abstracts makes plain: the methodological content of the field was produced by a small number of groups whose papers the applied studies cite and imitate, and the lifecycle elements that each group contributed are the ones the field reports. The Liège group supplied the statistical definition of the design space of an analytical method (the region of parameter settings within which the probability of meeting the performance requirement exceeds a stated level, estimated from predictive models with their uncertainty), the independent-component and multi-criteria extensions, and the screening strategies for antimalarial, antiretroviral and counterfeit-medicine applications; the same group, with its statistical collaborators, supplied the accuracy-profile validation, the total-error transfer criterion and the uncertainty-from-validation argument (Lebrun et al., 2008; Debrus et al., 2011; Rozet et al., 2013; Hubert et al., 2004; Hubert et al., 2007; Dewé et al., 2007; Rozet et al., 2011; Rozet et al., 2012). The Molnár laboratory and its partners supplied the retention-modelling route to the design space, the multidimensional exploration of gradient time, temperature and ternary composition, column-interchangeability workflows and in-silico robustness testing, which are the tools that the applied studies name when they name software (Molnár, 2002; Molnár et al., 2010; Monks et al., 2012). The Brussels group supplied the robustness methodology (which factors, which designs, how to analyse the effects and set system-suitability limits) and the reviews of experimental design in separation science that most applied studies cite for their designs (Vander Heyden et al., 2001; Dejaegher & Vander Heyden, 2007; Dejaegher & Vander Heyden, 2011; Hibbert, 2012). Ermer and colleagues supplied the precision structure (repeatability, intermediate precision from stability data, acceptance criteria derived from the specification) and, with the German transfer group, the equivalence-test concept for transfers and its sample-size argument (Ermer, 2001; Ermer & Ploss, 2005; Ermer et al., 2005; Kaminski et al., 2010); the statistical transfer literature in the Journal of Biopharmaceutical Statistics and the risk-based multi-product transfer of the industrial groups complete that strand (Schwenke and O'Connor (2008); Zhong et al. (2008); Raska et al. (2010); Agut et al. (2011)). The industry and USP papers supplied the lifecycle vocabulary itself, the analytical target

profile and the three-stage model (Borman et al., 2007; Schweitzer et al., 2010; Nethercote & Ermer, 2012; Martin et al., 2013; Barnett et al., 2016).

Two features of this structure matter for the framework. First, the groups rarely overlap: the design-space papers seldom report ATP-based validation, the validation-methodology papers seldom report design spaces, and the transfer papers report neither, so that the co-occurrence matrix of Figure 6 is sparse not because the elements are incompatible but because different communities own them. Second, the applied studies, which are three quarters of the evidence, borrow the development tools (designs, software, response surfaces) far more readily than the statistical decision tools (tolerance intervals, equivalence tests, uncertainty), which require a statistician or a trained analyst; the ratio of classical to total-error acceptance approaches in Table 11 is the measure of that asymmetry, and the framework's explicit statistics lane is the response to it.

Validation, acceptance criteria, transfer and monitoring (RQ3)

Table 11 and Figure 8 describe the validation practice. A validation study is reported by 202 (53%) of the included studies, but the acceptance approach is stated in only 159: classical limits in 125, total error or accuracy profile in 20, tolerance intervals in 2, measurement uncertainty in 3, equivalence tests in 5 and more than one approach in 4. The total-error and tolerance-interval approaches are concentrated in the methodological papers and in the applied studies of the groups that developed them; the applied studies in regional journals apply the ICH Q2(R1) characteristics with classical limits after a designed optimisation, which is the pattern that the lifecycle literature calls quality by design in development followed by quality by testing in validation. The period comparison (Figure 8a) shows the classical approach persisting in 2013 to 2019 while the accuracy-profile approach stays a minority, and the cumulative curves (Figure 8b) show the transfer and monitoring literature growing slowly compared with the design-space literature.

Table 11: Acceptance-criterion approaches, validation studies, design-space reporting and verification at the edges, overall, by record type and by period

Acceptance approach or validation element	Studies	Share	Original research	1990-2012	2013-2019
not reported	222	58%	148	62	160
classical limits	125	33%	125	16	109
total error or accuracy profile	20	5%	16	9	11
equivalence test	5	1%	0	5	0
multiple	4	1%	1	2	2
measurement uncertainty	3	1%	0	1	2
tolerance interval	2	1%	0	2	0
Validation performed: yes	202	53%	192	37	165
Validation performed: not reported	168	44%	94	57	111
Validation performed: no	7	2%	0	3	4
Design space or MODR reported: no	300	79%	233	81	219
Design space or MODR reported: yes	81	21%	57	16	65
Region verified at the edges: not reported	375	98%	285	96	279
Region verified at the edges: yes	5	1%	5	0	5
Region verified at the edges: no	1	0%	0	1	0

Figure 8: Acceptance-criterion approach by period and cumulative number of studies reporting transfer, continued verification, a design space and an analytical target profile

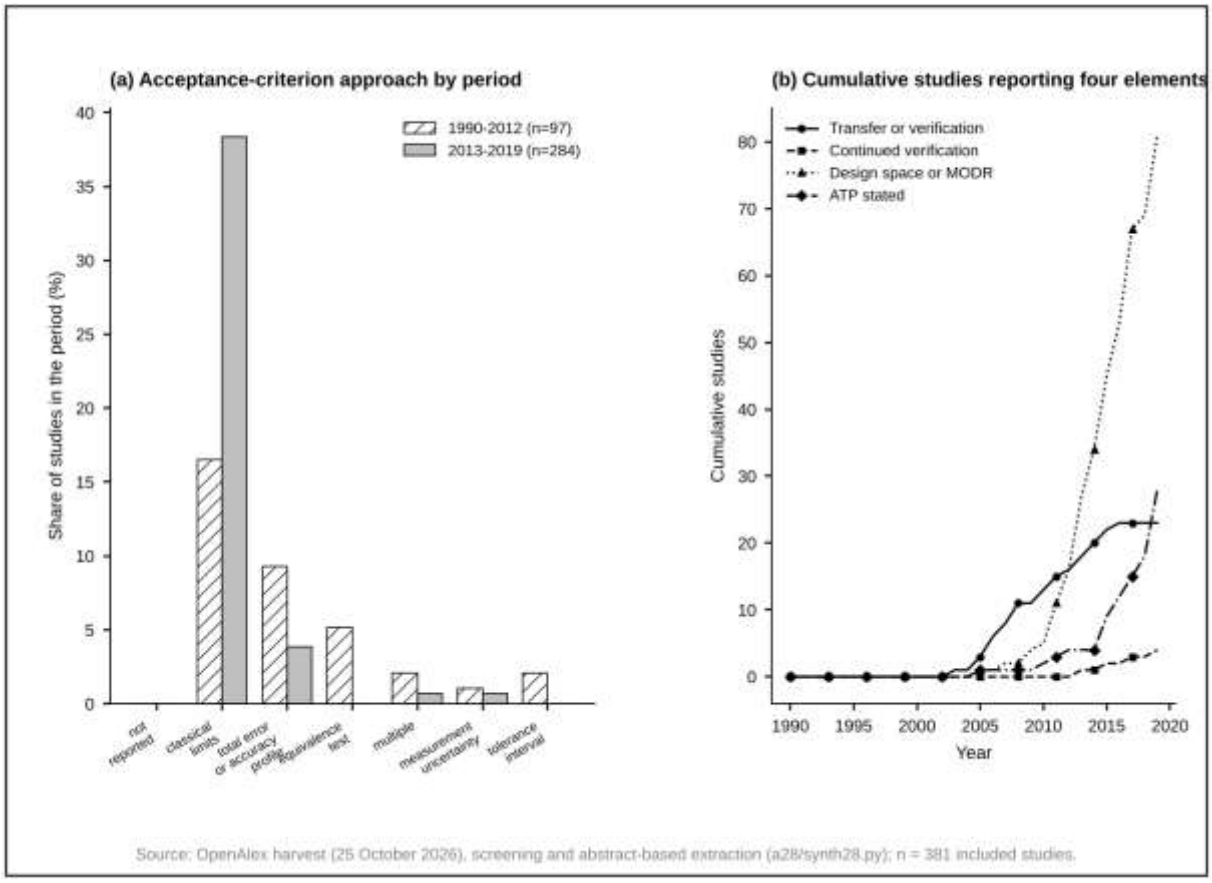


Table 12 lists the 27 studies that report transfer, verification or continued performance verification. The transfer studies form two groups: statistical work on acceptance criteria (equivalence tests, total-error criteria, ratio-based and risk-based approaches, sample-size planning) and practical work on moving methods between column formats and instrument generations (HPLC to UHPLC and narrow-bore columns, with frictional heating and gradient scaling as the technical issues). The monitoring studies are few and recent: capability indices and control charts applied to the analytical method control strategy (Oliva and Llabres Martinez (2017)), an AQbD development that carries its control strategy into routine monitoring, and two risk-based development-and-validation approaches that mention routine monitoring as a stage; the one dedicated continued-performance-monitoring programme that the search found proved to have a 2020 version of record and was excluded under criterion I1. No included study reports a change-management case under a documented MODR, which is the evidence gap at the end of the lifecycle.

Table 12: Included studies reporting transfer, verification or continued performance verification, with the approach and outcome recorded from the abstract

Study	Year	Topic	Approach and outcome (from the abstract)
van Nederkassel et al. (2003)	2003	transfer or verification	Six conventional-column HPLC methods (alkylbenzenes, drug-impurity separations for nimesulide, tetracycline, phenoxymethylpenicillin, erythromycin, and a green tea extract) were transferred to monolithic silica columns;
Schepers and Wätzig (2005)	2005	transfer or verification	NR (no abstract available; title only)
Schepers and Wätzig (2006)	2006	transfer or verification	NR (no abstract available; title only)

Study	Year	Topic	Approach and outcome (from the abstract)
Guillarme et al. (2007)	2007	transfer or verification	Equations for transferring isocratic LC methods to short 20-50 mm columns with 3.5 and 1.7 micrometre particles (UPLC) in pharmaceutical analysis, reducing analysis time up to twelve-fold without loss of separation quali
Dewé et al. (2007)	2007	transfer or verification	NR (title: total error used as decision criterion in analytical method transfer).
Rozet et al. (2006)	2006	transfer or verification	NR (no abstract available; title only)
de Fontenay (2008)	2008	transfer or verification	NR (no abstract; title: analytical method transfer, new descriptive approach for acceptance criteria definition)
Guillarme et al. (2008)	2008	transfer or verification	Gradient method-transfer rules from conventional HPLC to short small-particle columns and UPLC for impurity profiling (a drug and eight related impurities; 12-compound mixture), with up to ten-fold or fifteen-fold shorte
Schwenke and O'Connor (2008)	2008	transfer or verification	Method transfer studies framed under QbD principles; primary objective is to demonstrate equivalence of laboratory mean responses; three representative study designs discussed and one example presented.
Zhong et al. (2008)	2008	transfer or verification	Title only: statistical assessment of analytical method transfer; abstract not recovered
Rozet et al. (2009)	2009	transfer or verification	NR (no abstract available; title only)
Raska et al. (2010)	2010	transfer or verification	Risk-based transfer approach in which activities are set by a risk assessment of the methods and receiving-unit experience; transfer testing can be streamlined or eliminated based on method capability, receiving unit fam
Kaminski et al. (2010)	2010	transfer or verification	NR (no abstract available; title only)
AL-Kamarany et al. (2012)	2012	transfer or verification	Gauge R&R with multivariate statistics showed the receiving laboratory mastered the diclofenac sodium dissolution test (HPLC) validated by accuracy profile (total error) at the sending laboratory, so transfer succeeded w
Agut et al. (2011)	2011	transfer or verification	NR (no abstract; title: panel of transfer strategies selected for risk management, emphasis on integrated equivalence-based comparative testing)
Frömke et al. (2013)	2013	transfer or verification	NR (no abstract available; title only)
R0212	2013	transfer or verification	Title only: robust method optimisation strategy as a tool for method transfer, SFC case; abstract not recovered
Mookhaerjea (2013)	2013	continued verification or control charts	Presents a generic science- and risk-based approach to method development and validation (standardization, qualification, verification and validation as a continuum) with QbD and PAT concepts, SQC and control charts, cas
Ermer et al. (2013)	2013	transfer or verification	NR (no abstract available; title only)
Terzic et al. (2014)	2014	transfer or verification	Review of DryLab software in liquid chromatography for method development, optimisation and robustness testing; supports QbD, 3D design space visualisation and method transfer

Study	Year	Topic	Approach and outcome (from the abstract)
Karmarkar et al. (2014)	2014	transfer or verification	QbD optimisation (Fusion AE) of the USP amiodarone impurities method within USP <621> allowable changes gave a design space and operating space, removed column lot-to-lot variability, and the method was validated and sho
Peraman et al. (2015b)	2015	transfer or verification	AQbD RP-HPLC (PDA) assay of etofenamate in dosage form: QTPP, ATP and risk assessment first, DoE with quadratic model in Sigma Tech software, predictions checked against actual data, validated for targeted performance, r
Raman et al. (2015)	2015	continued verification or control charts	Review of QbD and AQbD for API synthetic processes and analytical method development; AQbD tools listed as ATP, CQAs with risk assessment, DoE, MODR, control strategy, method validation and continuous method monitoring;
Patel et al. (2015)	2015	transfer or verification	Stability-indicating UPLC-PDA method for deflazacort developed and validated per ICH (all parameters met acceptance criteria) and compared with an HPLC-UV method on a conventional column; stress studies done and the majo
Makwana et al. (2016)	2016	transfer or verification	RP-HPLC-UV method for camylofin, diclofenac and paracetamol transferred to UPLC-PDA and validated per ICH for a camylofin-diclofenac tablet, including forced degradation for specificity; run time under 3.5 min.
Oliva and Llabres Martinez (2017)	2017	continued verification or control charts	X-chart and moving range chart over 2 years showed the method in control and stable, but with Cpm and Cpk it did not meet the minimum method capability requirements or the analytical method target requirements
R0315	2019	continued verification or control charts	AQbD RP-HPLC/UV method for cannabidiol and delta-9-THC in cannabis olive oil extracts prepared by pharmacists: critical resolution and run time as CMAs, Doehlert design with Monte Carlo risk-of-failure maps defining the

The generic API context and the evidence gap map

Table 13 crosses the lifecycle elements with the record types. Original research supplies the design and validation evidence; methodological papers supply the transfer and acceptance-criterion evidence; reviews and perspectives supply the lifecycle and change-management discussion; and no record type supplies more than a few monitoring studies. The 12 studies with an explicit generic, multisource or pharmacopoeial context are mostly impurity and assay methods (impurities or related substances 5, assay 3, NA 2, dissolution 1), consistent with the route-dependent impurity profile being the generic manufacturer's main analytical problem; 5 of them report a design space, 2 a transfer or verification element and 2 a monitoring element, so the generic-specific evidence is thin at every stage and thinnest after development.

Table 13: Evidence gap map: number of included studies reporting each lifecycle element, by record type

Lifecycle element	Original research (n=290)	Reviews (n=34)	Commentary or regulatory (n=10)	Methodological or statistical (n=47)
Analytical target profile or explicit performance requirement	16	5	1	6
Risk assessment	23	7	1	7
Screening design	67	3	0	2
Optimisation design	159	2	0	7
Chromatographic or statistical software named	32	1	0	3
Design space or MODR reported	57	11	0	13
Region verified at the edges	5	0	0	0
Validation study	192	0	0	10
Control strategy or system suitability from development data	10	3	0	3
Transfer, verification or equivalence study	10	2	0	11
Continued performance verification or control charts	1	1	1	1
Change management or lifecycle discussion	9	8	4	6
Knowledge or data management	1	0	0	2

Reporting quality (RQ4)

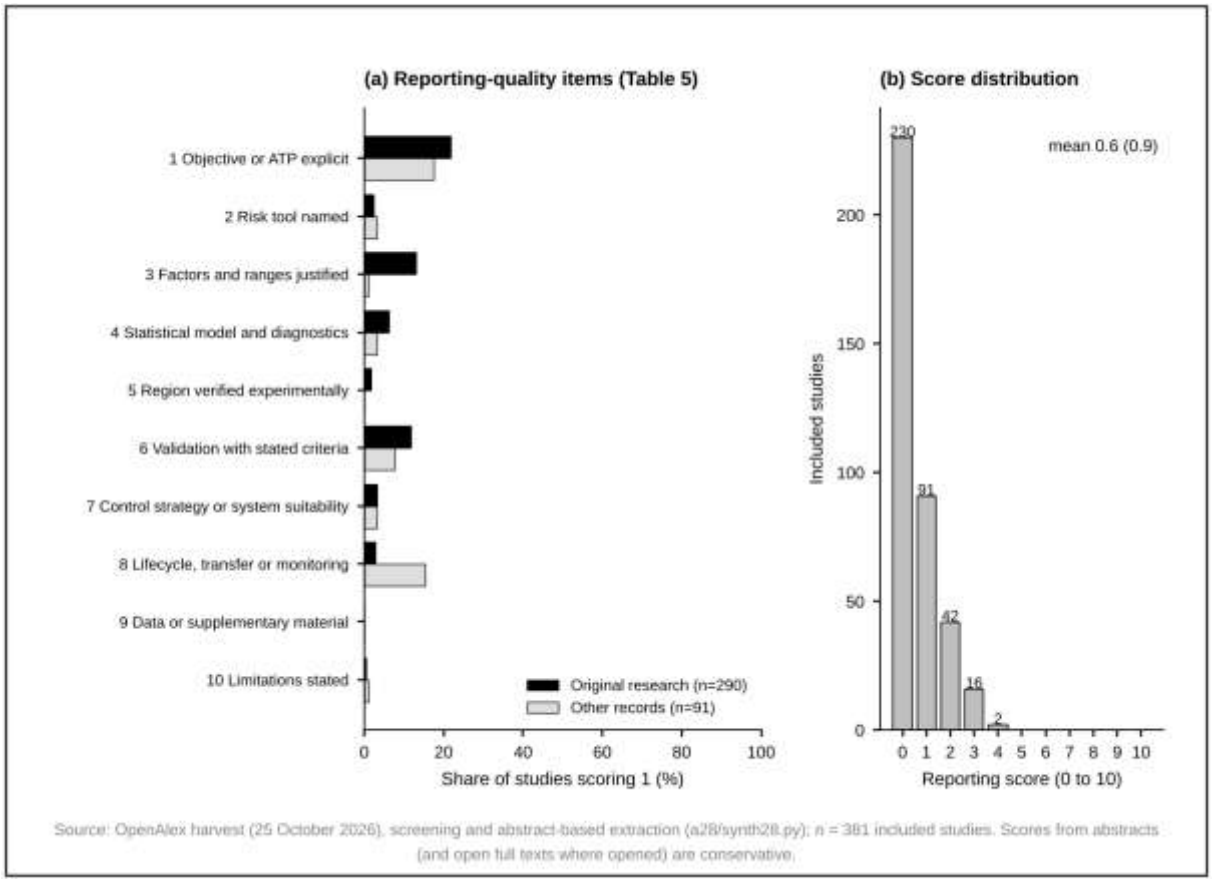
Table 14 and Figure 9 give the reporting-quality scores. The mean score is 0.6 (0.9) of 10 (original research 0.6 (0.9); 1990 to 2012 0.5 (0.8); 2013 to 2019 0.6 (0.9)), and 363 studies score 0 to 2. The items most often reported are objective or ATP explicit (79), validation with stated criteria (41), factors and ranges justified (39); the items least often reported are region verified experimentally (5), limitations stated (2), data or supplementary material (0). Limitations are stated in 2 abstracts. These figures are what the abstracts (and the few open full texts) report, and they understate the full papers; their value is comparative. The applied studies that describe a designed optimisation score on the factors item but rarely on the model, verification, control-strategy and lifecycle items, which is the reporting gap that the checklist proposed in Section 5.4 is meant to close.

Table 14: Reporting-quality items and score distribution, overall, for original research and by period

Reporting item or score	All included	Original research	1990-2012	2013-2019
1 Objective or ATP explicit	79 (21%)	63 (22%)	25	54
2 Risk tool named	10 (3%)	7 (2%)	0	10
3 Factors and ranges justified	39 (10%)	38 (13%)	0	39
4 Statistical model and diagnostics	21 (6%)	18 (6%)	3	18
5 Region verified experimentally	5 (1%)	5 (2%)	0	5
6 Validation with stated criteria	41 (11%)	34 (12%)	12	29
7 Control strategy or system suitability	12 (3%)	9 (3%)	4	8
8 Lifecycle, transfer or monitoring	22 (6%)	8 (3%)	4	18
9 Data or supplementary material	0 (0%)	0 (0%)	0	0

Reporting item or score	All included	Original research	1990-2012	2013-2019
10 Limitations stated	2 (1%)	1 (0%)	0	2
Score 0 to 2	363	275	95	268
Score 3 to 4	18	15	2	16
Score 5 to 6	0	0	0	0
Score 7 to 10	0	0	0	0
Mean score (SD)	0.6 (0.9)	0.6 (0.9)	0.5 (0.8)	0.6 (0.9)

Figure 9: Reporting-quality items scored from the abstracts and the distribution of the ten-item score



A risk-based lifecycle framework for chromatographic methods in generic API quality

From the evidence to the framework

The framework in Figure 1 was introduced in Section 2 as the coding structure of the review; this section states what the evidence of Section 4 supports in each of its six stages, what it does not, and how the stages map to ICH Q14 and Q2(R2) (Table 15). Three findings shape the design. First, the literature is strongest at stage 3: a designed experiment is reported by 205 (54%) of the included studies and a design space or MODR by 81 (21%), with the Liège and Molnár groups supplying the statistical and software foundations (Lebrun et al., 2008; Debrus et al., 2011; Rozet et al., 2013; Molnár et al., 2010; Monks et al., 2012). Second, the stages that precede and follow development are thin: an explicit target profile is reported by 28 (7%) of the studies, a named risk assessment by 38 (10%), verification of the region at its edges by 5 (1%), transfer or verification studies by 23 (6%) and continued performance verification by 4 (1%). Third, only 6 studies report the chain from target profile through risk assessment and design space to validation, so the lifecycle as a whole is described far more often than it is practised. The framework therefore treats stages 1, 2, 5 and 6 as the elements that a generic API organisation must

build deliberately, because the published practice will not supply them by imitation, and stage 3 as the element for which methods and software are mature.

Table 15: Framework elements mapped to the sections of ICH Q14 and Q2(R2), to pharmacopoeial and metrological anchors, and to the evidence of the review

Framework element (Figure 1)	ICH Q14 section or concept	ICH Q2(R2) section or concept	Other anchors	Evidence from the review (Section 4)
1 Analytical target profile with target measurement uncertainty and decision rule	Analytical target profile (Q14 Section 3); minimal versus enhanced approaches (Section 2.1); the analytical procedure lifecycle (Section 2.2)	Validation study designed from the intended purpose; reportable range (Q2(R2) Sections 2.1 and 2.3)	USP <1210>; Eurachem guides (Magnusson & Örnemark, 2014; Ellison & Williams, 2012)	ATP or explicit performance requirement in 28 (7%) of the studies; with a risk assessment in 14, with a design space in 12
2 Risk assessment and knowledge management	Knowledge management and risk management (Q14 Sections 4.1 and 4.2); identification of parameters and attributes	Not addressed directly	ICH Q9 tools; Q10 knowledge management	Risk assessment in 38 (10%); a named tool (Ishikawa, FMEA) in 7; knowledge management in 3
3 Method design with designed experiments, modelling and MODR	Robustness and analytical procedure parameter ranges, including proven acceptable ranges and the MODR (Q14 Sections 5.1 and 5.2)	Robustness (Q2(R2) Section 3.4) may be evaluated during development	DoE and chromatographic modelling literature (Dejaegher & Vander Heyden, 2007; Molnár et al., 2010)	Designed experiment in 205 (54%); design space or MODR in 81 (21%); software named in 36 (9%); region verified at its edges in 5
4 Validation as performance qualification against the ATP	Analytical procedure control strategy and established conditions (Q14 Sections 6 and 6.1)	Validation tests, methodology and evaluation (Q2(R2) Section 3); combined approaches for accuracy and precision (Section 3.3.3); validation of lower range limits by accuracy and precision (Section 3.2.3.4)	SFSTP accuracy profile (Hubert et al., 2007); USP <1225>, <1210>	Validation study in 202 (53%); classical limits in 125 against total error, accuracy profile or tolerance interval in 22
5 Transfer and verification by equivalence	Lifecycle management and post-approval changes (Q14 Section 7)	Validation during the lifecycle: partial or full revalidation after changes (Q2(R2) Section 2.2)	USP <1224> and <1226>; ISPE guide; equivalence tests (Kaminski et al., 2010; Limentani et al., 2005)	Transfer, verification or equivalence study in 23 (6%), 16 of them before 2013; equivalence-test acceptance in 5

Framework element (Figure 1)	ICH Q14 section or concept	ICH Q2(R2) section or concept	Other anchors	Evidence from the review (Section 4)
6 Continued performance verification and change management within established conditions	Established conditions (Q14 Section 6.1); lifecycle management and post-approval changes (Section 7; ICH Q12)	Validation during the lifecycle (Q2(R2) Section 2.2)	Control-chart tradition (Shewhart, 1931; Westgard et al., 1981); USP stimuli articles (Barnett et al., 2016)	Continued performance verification or control charts in 4; lifecycle or change-management discussion in 27; no change-management case under a documented MODR
Governance core: control strategy, established conditions, quality system	Control strategy (Q14 Section 6); submission of analytical procedure related information, including documentation for the enhanced approach (Sections 10.1 and 10.2)	Recommended data for each validation test (Q2(R2) Section 3)	ICH Q10 and Q12; FDA guidance (U.S. Food and Drug Administration, 2015)	Control strategy or system suitability derived from development data in 16 (4%); knowledge or data management in 3; full chain from ATP to validation in 6

Stage 1, the analytical target profile, is defined in the framework as a document that states, for each reportable value, the range, the target measurement uncertainty (or the maximum combined bias and precision) and the decision rule that the result will serve, derived from the specification and the risk level of the attribute. The ATP concept entered the literature through the industry and USP papers (Borman et al., 2007; Schweitzer et al., 2010; Martin et al., 2013; Barnett et al., 2016) and was given an operational form by the uncertainty-profile and tolerance-interval methods that translate a target uncertainty into validation acceptance limits (Hubert et al., 2007; Rozet et al., 2012; Ermer & Ploss, 2005). ICH Q14 Section 3 now requires the ATP for the enhanced approach and recommends it for the minimal one; ICH Q2(R2) Sections 2.1 and 2.3 tie the validation study and the reportable range to the intended purpose. For a generic API the ATP has a particular use: the same ATP can be met by a pharmacopoeial method, an innovator method or an in-house method, so the ATP rather than the method becomes the regulatory object, which is the premise of the lifecycle model's flexibility.

Stage 2, risk assessment and knowledge management, is the stage at which the review finds the largest gap between prescription and practice. Where a tool is named in the abstract it is an Ishikawa diagram or an FMEA (2 and 2 studies, with 21 more naming a ranking, scoring or unspecified tool), the tools of ICH Q9 (International Council for Harmonisation, 2005b; Stamatis, 2003; Ishikawa, 1985), and the two methodological studies of FMEA in analytical validation show that the tool's output depends on the team and the scales used and must be calibrated against prior data to be consistent (van Leeuwen et al., 2009; Oldenhof et al., 2011). The framework therefore specifies a risk register per method type (assay, related substances, residual solvents, dissolution) that is seeded from prior knowledge (column databases, retention models, forced-degradation results, transfer history) and updated as data accumulate, in line with ICH Q14 Sections 4.1 and 4.2 and the knowledge-management expectation of ICH Q10 (International Council for Harmonisation, 2008; International Council for Harmonisation, 2020b).

Stage 3, method design, is the mature stage. The framework adopts the two-step design logic that

dominates the evidence (a screening design on the ranked parameters, then an optimisation design or a retention model on the influential ones), with the design space defined as the region where the probability of meeting the ATP exceeds a stated level, estimated with model uncertainty rather than from the mean response surface (Lebrun et al., 2008; Debrus et al., 2011; Rozet et al., 2013; Dejaegher & Vander Heyden, 2007; Dejaegher & Vander Heyden, 2011; Hibbert, 2012; Sahu et al., 2018). Chromatographic modelling software shortens the experimental burden and makes column interchangeability and in-silico robustness testing possible (Molnár, 2002; Molnár et al., 2010; Monks et al., 2012; Snyder et al., 2004; Euerby & Petersson, 2003). The framework adds what the evidence lacks: experimental verification at the edges of the region, reported by 5 (1%) of the studies, is made a gate condition (G3 in Figure 1), because ICH Q14 Section 5.2 allows movement within a MODR without regulatory notification only when the region has been demonstrated.

Stage 4, validation as performance qualification against the ATP, follows the accuracy-profile and tolerance-interval literature (Hubert et al., 2004; Hubert et al., 2007; Feinberg, 2007; Hoffman & Kringle, 2005; Hoffman & Kringle, 2007; Rozet et al., 2011; Rozet et al., 2012), which ICH Q2(R2) Section 3.3.3 now admits as a combined approach for accuracy and precision and Section 3.2.3.4 as a route to the lower range limit. The evidence shows that the classical checklist still dominates reporting: of the studies with a stated acceptance approach, 125 report classical limits and 22 a total-error, accuracy-profile or tolerance-interval approach. The framework specifies ATP-derived acceptance criteria written into the validation protocol, the accuracy profile as the primary decision, intermediate precision estimated from a nested design with the number of series set from the required width of the tolerance interval (Ermer & Ploss, 2005; Hahn & Meeker, 1991; Burdick & Graybill, 1992; United States Pharmacopeial Convention, 2018d), and detection and quantitation limits defined from the accuracy profile rather than from signal-to-noise alone (Currie, 1968; Currie, 1999; Armbruster & Pry, 2008).

Stage 5, transfer and verification, rests on a small but coherent body of statistical work: equivalence tests with acceptance limits derived from the ATP replace significance tests of mean differences, and the total-error criterion extends the accuracy profile to the receiving laboratory (Dewé et al., 2007; Kaminski et al., 2010; Limentani et al., 2005; Chambers et al., 2005; Schuirmann, 1987). The pharmacopoeial chapters on transfer and verification and the ISPE guide supply the designs (United States Pharmacopeial Convention, 2018c; United States Pharmacopeial Convention, 2018b; International Society for Pharmaceutical Engineering, 2003). The framework makes transfer and compendial verification the same procedure: a comparative study whose acceptance limits come from the ATP, with sample sizes computed from the intermediate precision of the sending laboratory. For a generic organisation with several sites and contract laboratories this is the stage at which the ATP pays for itself, because one set of limits serves every transfer.

Stage 6, continued performance verification and change management, is the least evidenced stage (4 (1%) of the studies). The framework imports the control-chart tradition (Shewhart, 1931; Roberts, 1959; Page, 1954; Lucas & Saccucci, 1990; Westgard et al., 1981; Montgomery, 2012) into the procedure's system-suitability and quality-control results, with capability indices and control charts as the monitoring tools proposed by the one methodological study on the subject in the evidence base, and the periodic method review and the change-within-the-MODR rule as the governance tools of ICH Q14 Section 7 and ICH Q12 (International Council for Harmonisation, 2019; International Council for Harmonisation, 2020b). The knowledge base of the governance core stores the ATP, the risk register, the models, the MODR, the validation data and the performance history, so that each change can be assessed against the method's documented knowledge rather than reinvestigated.

Workflow and decision logic

Figure 10 gives the framework as a workflow across six organisational lanes, with the messages that pass between them. The analytical development lane runs stages 2 and 3; the statistics lane designs and analyses the experiments and sets the decision rules and sample sizes; the quality control laboratory writes the validation protocol with ATP-based criteria, executes it and runs the method in routine use with system suitability and control charts; the receiving site runs the equivalence study; the quality and regulatory lane owns the ATP and the change-control decision; and the knowledge management system receives the artefacts of every lane. Two loops define the lifecycle: the loop from a failed fitness-for-purpose decision back to development, and the loop from a change outside the MODR back to

change control and regulatory assessment. The workflow is deliberately explicit about the statistics lane, because the evidence shows that where statisticians are part of the team (the Liège, Ermer and USP groups) the ATP, tolerance intervals and equivalence tests appear, and where they are not, the classical checklist persists.

Figure 10: Risk-based lifecycle workflow for chromatographic methods in BPMN form: six organisational lanes, gateways, message flows and the two learning loops

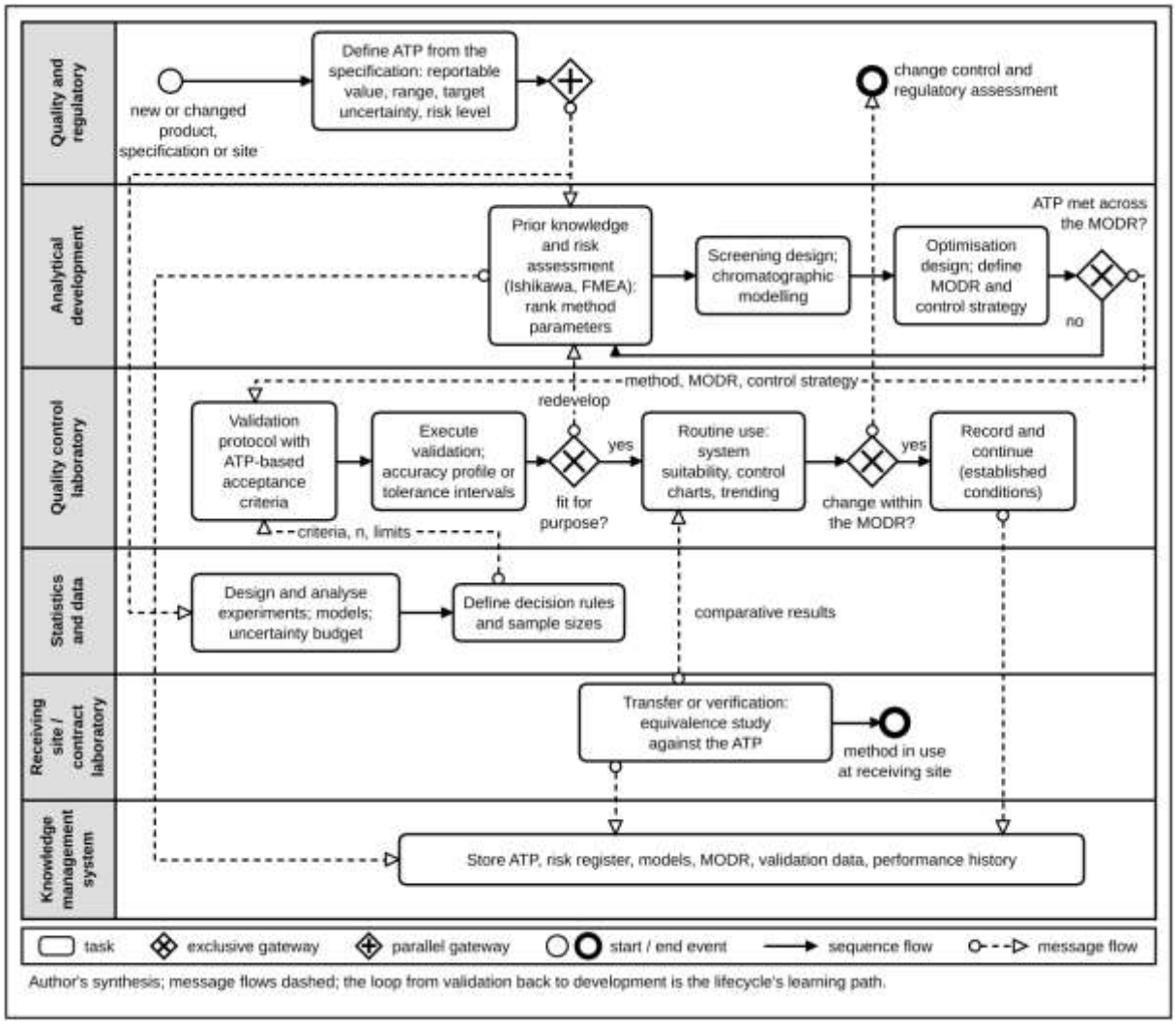
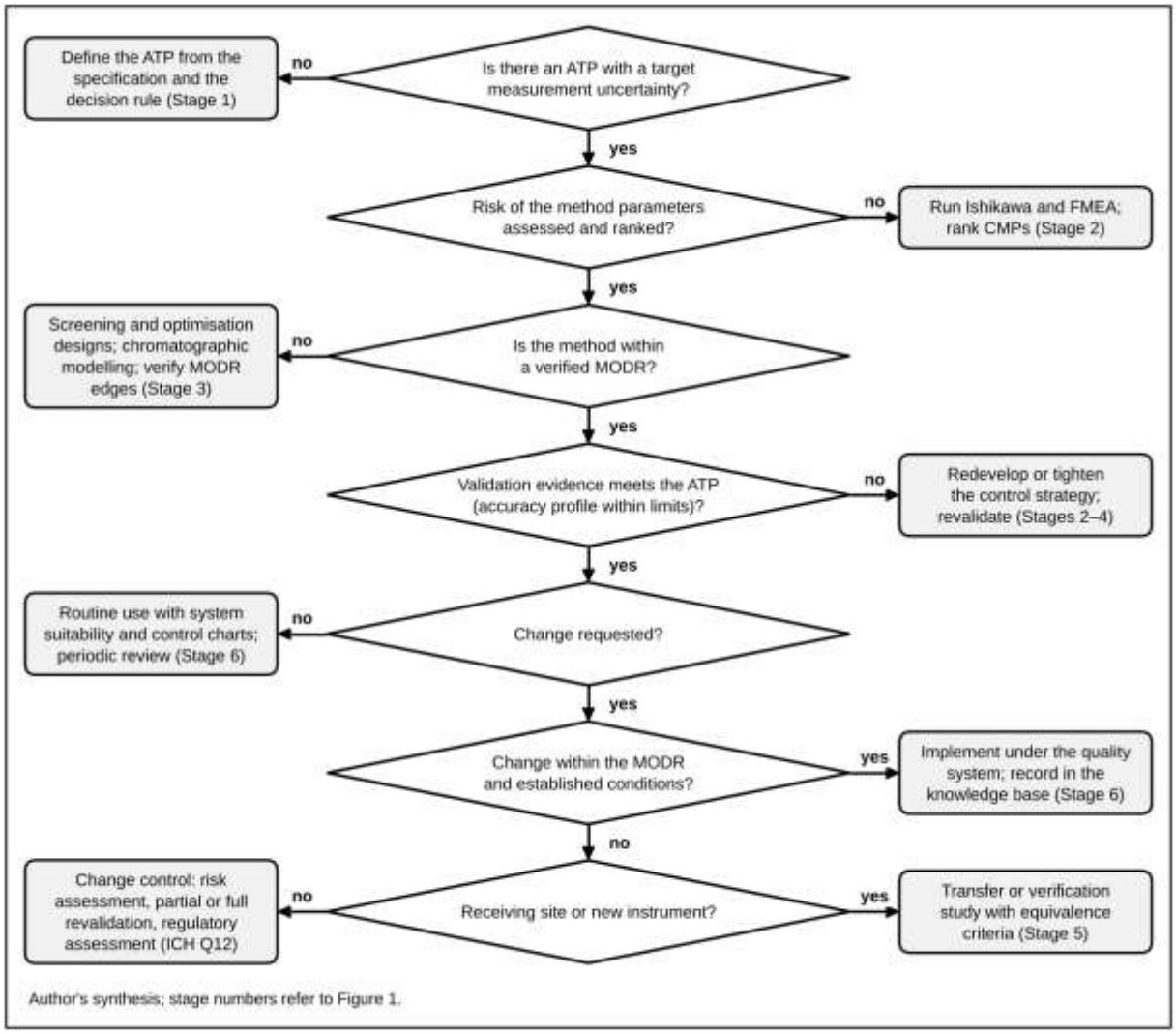


Figure 11 gives the decision logic that a method owner applies to any method, new or legacy, at any point in its life. The questions run in the order of the stages: whether an ATP with a target uncertainty exists; whether the method parameters have been risk-ranked; whether the method lies within a verified MODR; whether the validation evidence meets the ATP; whether a change is requested; whether the change lies within the MODR and the established conditions; and whether the change concerns a receiving site or instrument. Each negative answer names the stage to be completed. For legacy methods, which are the majority in a generic portfolio, the tree gives the retrofit path: define the ATP from the specification, risk-rank the parameters from the method's history, and decide from the recorded performance whether a MODR must be established before the method can be changed under established conditions.

Figure 11: Decision tree for risk-based lifecycle actions on a chromatographic method, new or legacy, with the stage of Figure 1 that each leaf completes



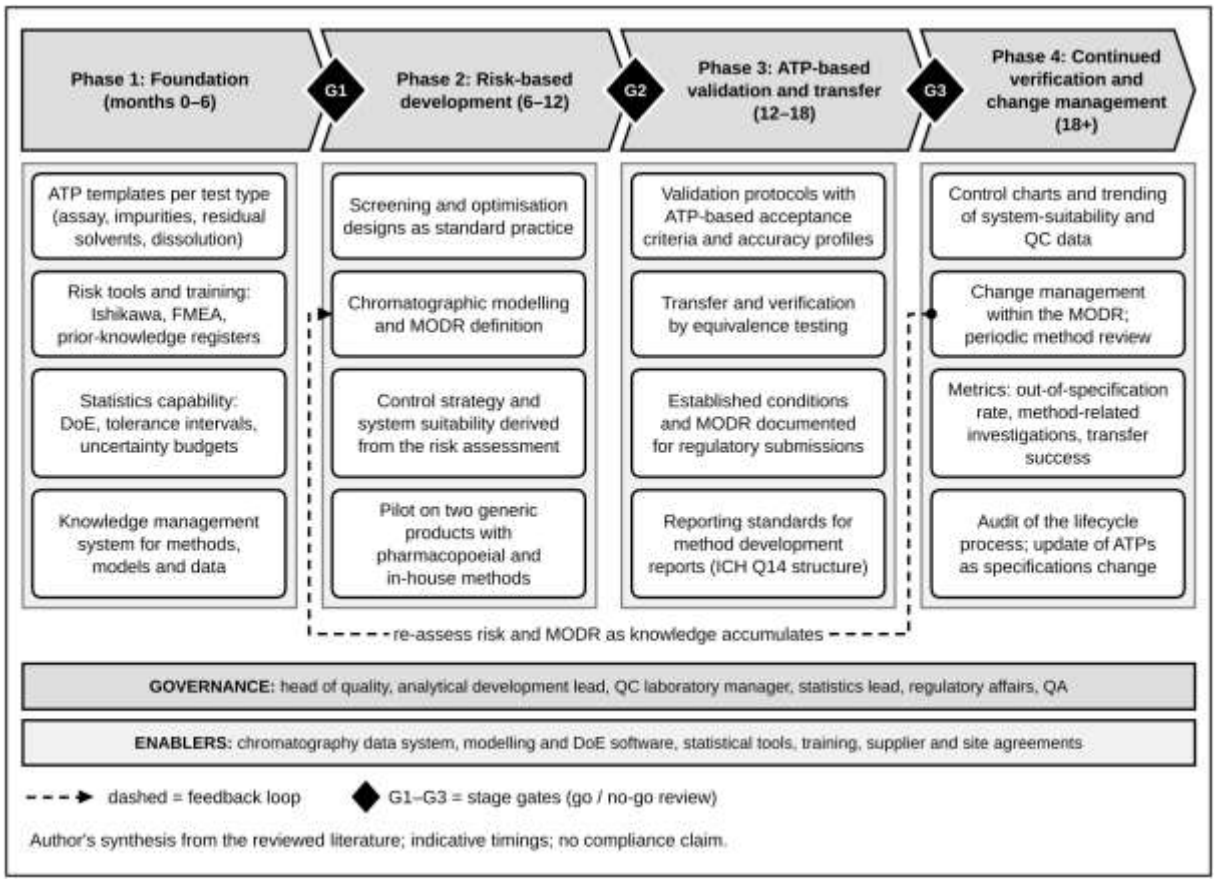
Elements specific to generic API quality

Four features of generic API quality are built into the framework. First, the impurity profile of the generic route is the primary input to the ATP of the related-substances method: the process impurities and degradation products to be separated, their thresholds under ICH Q3A and Q3B and the degradation pathways from forced-degradation studies define the specificity requirement, and the framework requires the impurity list to be an explicit part of the ATP and the risk register (International Council for Harmonisation, 2006a; International Council for Harmonisation, 2006b; Bakshi & Singh, 2002; Blessy et al., 2014; Alsante et al., 2007; Singh et al., 2012; Görög, 2018; Baertschi et al., 2011; U.S. Food and Drug Administration, 2009). Second, pharmacopoeial and innovator methods are treated as candidate methods to be assessed against the ATP rather than as fixed procedures: a pharmacopoeial method used as published is verified (stage 5), an adapted one re-enters stage 3 and is validated against the same ATP (United States Pharmacopeial Convention, 2018a; United States Pharmacopeial Convention, 2018b; United States Pharmacopeial Convention, 2018e). Third, the multiplicity of sites, suppliers and contract laboratories is handled by making transfer a standing capability with ATP-derived limits, and by keeping column-interchangeability data in the knowledge base (United States Pharmacopeial Convention, 2018c; Snyder et al., 2004; Euerby & Petersson, 2003). Fourth, the economic case is made explicit through the metrics of stage 6: the out-of-specification rate attributable to methods, the number of method-related investigations, the transfer success rate and the cost of revalidation, which are the quantities that the lifecycle model is expected to reduce and that the evidence base does not yet report (Lionberger et al., 2008; Yu, 2008; Yu et al., 2014).

Implementation roadmap and reporting

Figure 12 gives an implementation roadmap in four phases with three stage gates. Phase 1 builds the foundation: ATP templates per test type, risk tools and training, statistical capability (designed experiments, tolerance intervals, uncertainty budgets) and a knowledge management system. Phase 2 makes screening and optimisation designs, chromatographic modelling and MODR definition standard practice, with a pilot on two products. Phase 3 introduces ATP-based validation protocols, transfer by equivalence testing and the documentation of established conditions and the MODR for submissions in the structure of ICH Q14 Section 10. Phase 4 adds control charts and trending, change management within the MODR, the metrics listed above and a periodic audit of the lifecycle process. The dashed feedback from phase 4 to phase 2 is the learning path: as performance history accumulates, the risk register and the MODR are re-assessed. The timings are indicative and no compliance claim is made.

Figure 12: Implementation roadmap for risk-based lifecycle management of chromatographic methods in a generic API organisation: four phases, three stage gates, governance and enablers



Finally, the review supports a reporting checklist for method-development studies, because the reporting score of Section 4.7 shows that the published evidence rarely states the elements that would make a method reusable: the ten items of Table 5 are proposed as the minimum content of a method-development report or paper (objective and ATP; risk assessment with its tool and output; factors, ranges and their justification; the statistical model and its diagnostics; verification of the region; validation criteria stated in advance; the control strategy and system suitability; lifecycle, transfer or monitoring plans; data availability; and limitations). The checklist mirrors the documentation expected for the enhanced approach in ICH Q14 Section 10.2, so that a study reported against it can be submitted with little reformatting.

Discussion

Answers to the research questions

RQ1. The pre-2020 literature on lifecycle and risk-based approaches to chromatographic methods for

small-molecule quality is small, recent and concentrated: 381 studies met the criteria from 2,405 unique records, 75% of them published in 2013 to 2019, and 79 of them in two journals. Its growth follows the quality-by-design papers of 2007 to 2012 and the USP stimuli articles of 2013 and 2016, which is consistent with the lifecycle model having diffused from a few industry and academic groups into applied method development rather than arising from practice (Borman et al., 2007; Schweitzer et al., 2010; Nethercote & Ermer, 2012; Martin et al., 2013; Barnett et al., 2016). RQ2. The stage that the literature implements is method design: a designed experiment is reported by 54% of the studies (67% of the original research) and a design space or MODR by 21%, while the target profile, the risk assessment with a named tool, verification of the region, transfer, monitoring and change management are reported by minorities, and the full chain by 6 studies. RQ3. Validation is still reported mostly against the classical checklist; the total-error, accuracy-profile and tolerance-interval approaches that ICH Q2(R2) now admits are a minority concentrated in the groups that developed them; transfer has a coherent statistical literature; monitoring and change management under a documented MODR have almost none. RQ4. Reporting is thin: the mean reporting score is 0.6 of 10 from abstracts, and the items that would make a method reusable (model diagnostics, verification of the region, control strategy, data availability, limitations) are the least reported. The framework of Section 5 follows from these answers: it adopts the mature design stage as practised and specifies the under-evidenced stages as deliberate organisational capabilities.

Relation to prior reviews and to ICH Q14 and Q2(R2)

The narrative reviews of analytical quality by design describe the same workflow (ATP, risk assessment, designed experiments, design space, control strategy, validation and lifecycle) and illustrate it with selected studies (Vogt & Kord, 2011; Orlandini et al., 2013; Rozet et al., 2013; Peraman et al., 2015a; Sahu et al., 2018; Deidda et al., 2018; Parr & Schmidt, 2018). This review adds the quantities: how often each element is reported, how the elements combine and how the practice changed over time. The result qualifies the narrative picture in two ways. The reviews present the lifecycle as a sequence; the evidence shows it as a dense centre (design and validation) with sparse ends, so that the published "quality by design" method is typically a designed optimisation followed by a classical validation and no documented lifecycle. And the reviews cite the statistical foundations (tolerance intervals, total error, Bayesian design space, equivalence testing) as if they were adopted; the evidence shows them used by a minority, which is why the framework assigns a statistics lane of its own.

ICH Q14 and Q2(R2) were adopted after the period reviewed, and the review therefore describes the evidence on which they rest rather than their uptake. Read against the guidelines, the evidence supports the minimal and enhanced approaches as described in Q14 Section 2.1 and the parameter-range and MODR concepts of Section 5.2, for which the methods and software are mature; it is thinner for the ATP of Section 3 and the knowledge and risk management of Section 4, where the guideline prescribes more than the pre-2020 literature practised; and it is thinnest for the lifecycle management of Section 7 and the established conditions of Section 6.1, where the guideline relies on ICH Q12 mechanisms that the method literature had not yet exercised. For Q2(R2), the combined accuracy-and-precision approach of Section 3.3.3 and the accuracy-and-precision route to the lower range limit of Section 3.2.3.4 have a strong methodological basis in the accuracy-profile literature (Hubert et al., 2004; Hubert et al., 2007; Feinberg, 2007; Rozet et al., 2012) but little applied uptake before 2020. The guidelines are, in this reading, ahead of the evidence at the ends of the lifecycle, which is where the framework places its implementation effort.

Implications for generic API organisations and for regulators

For a generic API organisation the findings suggest a sequence. The analytical target profile should be written first for the methods that carry the most risk (related substances for the generic route, assay for release, dissolution for the product), because it is the object against which pharmacopoeial, innovator and in-house methods can all be assessed and because it supplies the acceptance limits for validation and transfer alike. Designed experiments and chromatographic modelling can be adopted from the literature as they stand, with the addition of edge verification. Validation protocols should state ATP-derived criteria and use the accuracy profile where the total-error logic fits the decision; this is the change that the evidence shows to be least made and that Q2(R2) now permits. Transfer should be run as an equivalence study with limits from the ATP, which is the one stage where the generic business

model (many sites, many suppliers, many contract laboratories) makes the lifecycle model's economics immediate. Monitoring and change management under a documented MODR should be built as capabilities, with the metrics of Section 5.3, because the literature offers no template. The roadmap of Figure 12 orders these steps; its gates are meant to be reviewed against the metrics rather than the calendar.

For regulators and pharmacopoeias the review points to two needs. The first is a reporting standard for method-development studies, because the evidence base cannot be reused as it is reported; the ten items of Table 5, aligned with ICH Q14 Section 10, are a proposal. The second is published examples of change management under a MODR, because the lifecycle model's regulatory benefit (movement within established conditions without prior approval) rests on a practice that the pre-2020 literature does not document; the Q14 annex examples are a start, and post-2020 case reports would be the natural subject of an update review.

Limitations

Table 16 lists the limitations. The decisive ones are the single index, the single reviewer with keyword- and agent-assisted screening, and the abstract-based extraction: each makes the counts lower bounds and the reporting scores conservative, and none can be remedied without full-text, dual-reviewer work that the design of this review did not include. The scale of the search (over two thousand unique records) and the transparency of the process (every decision, rule and extraction record is in the supplementary material) are the compensating strengths, and the protocol can be re-run against other indices and periods. The 10% independent re-screening gives a measure of consistency, not of validity. The generic-specific findings rest on the 12 abstracts that mention the context and should be read as indicative. The framework is a synthesis and a proposal, not a validated instrument; its mapping to ICH Q14 and Q2(R2) is the author's reading of the guideline texts.

Table 16: Limitations of the review and what would address them

Limitation	Why it matters	What would address it
One bibliographic index (OpenAlex) and 28 strings in title and abstract	Records not indexed in OpenAlex, or whose abstracts do not use the search terms, were missed; two strings had to be shortened; two strings were truncated at 400 records by relevance	Searches of Scopus, Web of Science and PubMed with the same strings; citation chasing from included reviews
Single reviewer with keyword-assisted title screening and agent-assisted abstract screening	Screening errors cannot be estimated from inter-reviewer agreement; the automated keyword rules may have excluded eligible records	Dual independent screening with kappa statistics; a pilot calibration set
Extraction from abstracts for most records	Elements that abstracts omit (software, design type, verification at the edges, limitations) are under-counted; reporting-quality scores are conservative and not comparable with full-text appraisals	Full-text extraction for the included studies, with the form of Table 4
No formal quality or risk-of-bias instrument exists for method-development studies	The ten-item reporting score is a description of reporting, not an assessment of validity	A consensus reporting checklist for analytical procedure development, as proposed in Section 6
Heterogeneous studies without common outcomes	No meta-analysis; counts and shares describe practice, not effect sizes	Standardised outcome reporting (robustness margins, uncertainty, transfer success) in future studies

Limitation	Why it matters	What would address it
Pre-2020 scope and index years	The literature written after the ICH concept paper and the Q14 and Q2(R2) drafts is not covered, so the review describes the evidence base of the guidelines rather than their uptake; the publication year is the index year, which for some records is the online-first date (one cited study proved to have a 2020 version of record and was excluded)	An update review covering 2020 onwards against the same protocol; version-of-record years checked for every included study
Generic API context inferred from abstracts	Few abstracts state whether the method concerns a generic or multisource product; the generic-specific findings rest on a small subset	Surveys of generic manufacturers and regulatory assessment reports
Citation data not collected	Influence of the studies could not be weighed	Bibliometric coupling and citation analysis from the OpenAlex records

Conclusion

This systematic review of the pre-2020 literature on risk-based lifecycle management of chromatographic methods for small-molecule pharmaceutical quality screened 2,405 unique records from a reproducible search of one bibliographic index and synthesised 381 studies. The literature is recent, concentrated in a few journals and groups, and strong at one stage of the lifecycle: a designed experiment is reported by 54% of the studies and a design space or MODR by 21%, with mature statistical and software foundations. It is weak at the stages that make the lifecycle a lifecycle: an explicit target profile, a named risk assessment, verification of the region, ATP-based acceptance criteria, transfer by equivalence, continued performance verification and change management are each reported by minorities, and only 6 studies report the chain from target profile to validation. Reporting is thin at precisely the items that would allow a method to be reused. ICH Q14 and Q2(R2) are therefore ahead of their evidence base at the ends of the lifecycle. The framework derived from the evidence takes the mature design stage as it is practised and specifies the under-evidenced stages as deliberate capabilities for a generic API organisation, with the analytical target profile as the regulatory object, a statistics lane in the workflow, equivalence-based transfer as the stage with the most immediate economic return, and a reporting checklist to make future studies reusable. The companion article applies the validation stage of this framework in a worked, simulation-based account of HPLC method validation under ICH Q2(R2) and Q14.

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