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Review Paper

A Review of The Analytical Methods Established for FDA Approved Drugs In 2022

[1*]Tejaswi Gilakamsetti

[1*]*Department of Pharmaceutical Analysis, Vishnu Institute of Pharmaceutical Education and Research, Narsapur, Telangana- 502313*

**Corresponding Author(s):gilakamsettitejaswi@gmail.com*

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Abstract: In response to the rising number of diseases, numerous new medications have been developed and approved by the FDA to treat various disorders. Before these drugs can enter the market, they must undergo extensive validation and analytical processes to ensure their purity and reliability. These approaches use a variety of analytical methods to gather information regarding the drugs. This overview covers a variety of analytical procedures, including UV spectrophotometry & chromatography approaches (including HPTLC, HPLC, and Gas Chromatography). Additionally, it discusses hyphenated techniques like LC-MS used in the development of newly approved drugs in 2022. In 2022, significant advancements were made in the refinement of these analytical methods, introducing more precise, rapid, and sensitive techniques for drug evaluation. A notable trend was the increased integration of automation and artificial intelligence in analytical processes, enhancing the accuracy of results and streamlining workflows, thereby facilitating quicker approval timelines for emerging pharmaceuticals.

Keywords: FDA approved drugs, HPLC, LC-MS/MS, Analytical methods

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1. Introduction

Developing an analytical technique and validating it are essential steps in the process of finding, creating, and producing medicinal compounds. Given the growing volume of medications introduced to the market annually, method development may involve verifying that an analytical technique is appropriate for determining the amount of an API in a highly potent dosage form. This medication may be a brand-new formulation or a structural modification of the primary medication. In these circumstances, the pharmacopoeias may not include the analytical techniques and standard processes for the newest drugs [1]. Therefore, the creation of analysis techniques is required for these newly authorised medications. To verify the identification, purity, and effectiveness of pharmaceutical products—including their performance—internal control laboratories employ established testing protocols. A variety of techniques, including UV Spectrophotometric, Ultra Performance liquid chromatography, High-Performance thin-layer chromatography, Stability-indicating High-Performance liquid chromatography, LC-MS, Spectro-fluorimetry, GC-MS, and others, can be used to analyse the analyte [2]. Spectrometry as well as chromatography are two analytical techniques used in the pharmaceutical business for the qualitative & quantitative assessment of medication, API, raw materials, and biological samples. These techniques were used to identify, purify, strengthen, and function of medication [3]. The establishment of analytical techniques is primarily responsible for the growth in pharmaceutical manufacturing.

One of the United States national government's specialised agencies is the Food and Drug Administration (FDA). As the Department of Health and Human Services, it was founded in 1906.

The primary duties of this organisation include overseeing and controlling the safety of food, nutritional supplements, prescription drugs, vaccines, biological medicinal items, and medical equipment including radiation-emitting devices, blood products, veterinary supplies & cosmetics [4].

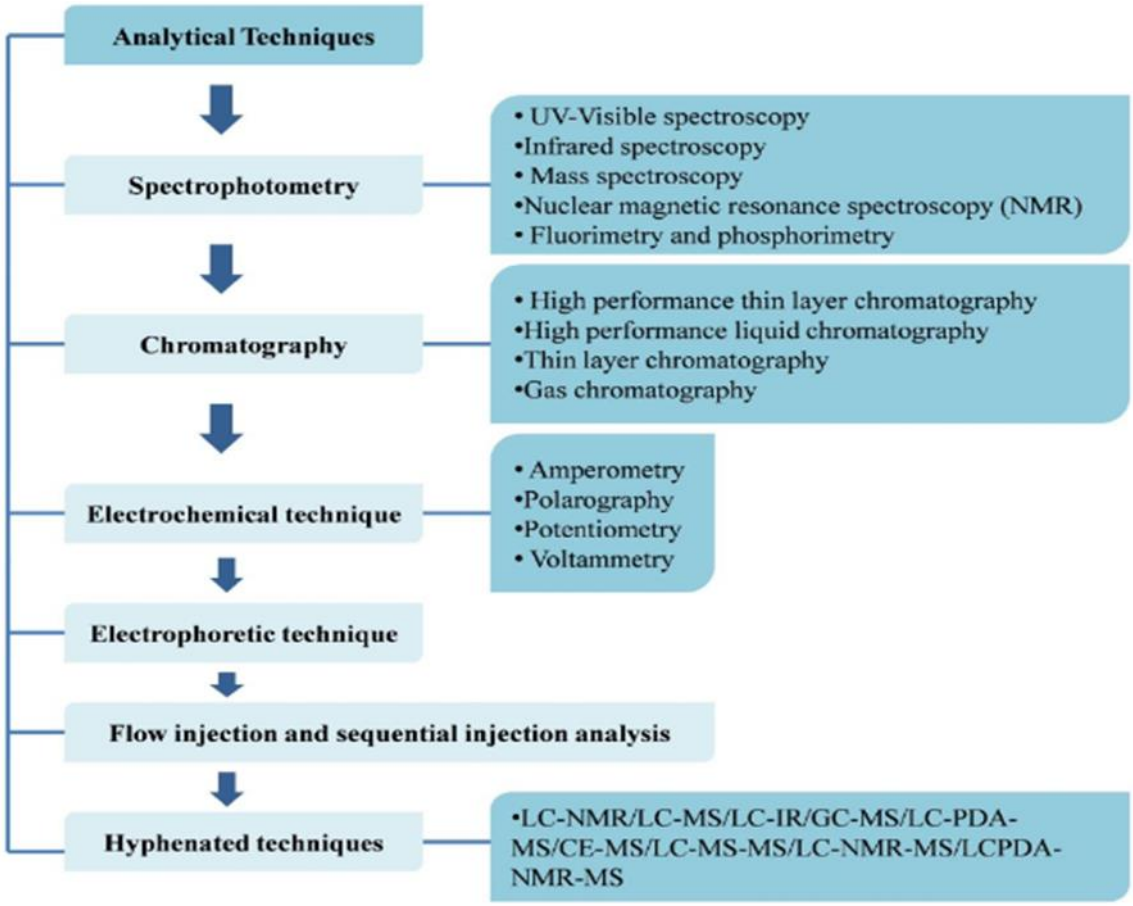

Figure 1: Flow chart of Analytical techniques [5]

Table 1: Various analytical techniques for recently approved medications in 2022

S. No.	Drug Name	API	Analytical method	Method Details	Reference
1	Lytgobi	futibatinib	UPLC-MS/MS	**System:** Acquity UPLC system **Column:** C_{18} column **MP:** 0.1% formic acid in H_2O & ACN **RT:** 1.49 min **Linearity:** 0.003 - 3 µM **LLOQ:** 0.003 µM **Mass Spectrometric Detection:** Positive electrospray ionization in conjunction with MRM mode (m/z 419.2 → 296.0)	[6]
			UPLC-MS/MS (Beagle dogs)	**System:** Waters ACQUITY UPLC instrument, XEVO TQD triple	[7]

				quadrupoles mass spectrometer ESI **Column:** UPLC BEH C_{18} column (2.1 mm × 50 mm, 1.7 µm) **MP:** ACN & 0.1% formic acid **Flow rate:** 0.3 ml/min **RT:** 1.50 min **LLOQ:** 0.5 ng/ml **Linearity:** 0.5 to 100 ng/ml **Mass spectrometric detection:** ESI+ source, multi reaction detection (m/z 418.99 ⟶ 295.97)	
2.	Krazati	Adagrasib	HPLC-MS/MS (Mouse plasma)	**System:** Binary UPLC from Shimadzu Nexera X2/Turbo Ion V™ Turbo Ion Spray **Column:** BEH C_{18} column (30 × 2.1 mm, 1.7 µm) **MP:** ACN & H_2O modified with 0.5% (v/v) ammonium hydroxide & 0.02% (v/v) acetic acid **Flow rate:** 0.6 ml/min **Injection Volume:** 1 µl **Linearity:** 2-2,000 ng/ml **Mass spectrometric detection:** Electrospray ionization in positive mode (m/z 98.0 → 70.0)	[8]
			LC-MS/MS (Rat Plasma)	**System:** Waters 2695 LC-MS/MS system **Column:** Waters X-bridge phenyl C_{18} column **MP:** ACN: 0.1 % TFA in H_2O (50: 50 v/v)	[9]

				Flow rate: 1.0 ml/min **Run time:** 5 min **Linearity:** 40–800 ng/ml **Mass Spectrometric detection:** multiple reaction monitoring in positive mode (m/z 605.12 → 201.62)	
			LC-MS/MS (Human plasma)	**System:** Acquity UPLC (H-class+) using a XEVO TQ-S micro tandem mass-spectrometer **Column:** HSS C18 UPLC column (2.1 × 150 mm, 1.8 µM) **MP: A**mmonium formate 0.1 % v/v in H_2O and ACN **Flow rate:** 400 µl/min **RT:** 3.75 min **Linearity:** 80–4000 ng/ml	[10]
3.	Relyvrio	Sodium phenylbutyrate/taurusodiol	UPLC	**System:** Acquity UPLC system from waters **Column:** waters C_{18} column (150×4.6 mm, 2 µm) **MP:** Phosphate buffer pH 2.5: CH_3OH (45: 65 v/v) **Detector:** PDA at 285 nm **Flow rate:** 1 ml/min **RTs:** SPB- 1.483 min TRS- 2.492 min **Injection volume:** 10 µl **Linearity:** 567–1701 µg/ml for SPB 89–567 µg/ml for TRS **LOD & LOQ:**	[11]

				SPB = 1.56 and 5.19 µg/ml TRS = 1.48 and 4.95 µg/ml	
4.	Sotyktu	Deucravacitinib	HPLC-MS/MS (Human Plasma)	**System:** A mass spectrometer SCIEX API 4000 with Shimadzu prominence LC **Column:** ACE-C_{18} column (4.6 × 100 mm, 5 µm) **MP:** CH_3OH: 2 mM ammonium formate (80:20 v/v) **Flow rate:** 0.9 ml/min **Injection volume:** 5 µl **Linearity:** 0.500 - 601.050 ng/ml **Mass spectrometric detection:** electron spray ionization source in multiple reaction monitoring mode (m/z 426.3 → 358.2)	[12]
			LC-MS	**System:** Acquity UPLC system **Column:** Phenomenex Gemini, C_{18} (250 × 4.6 mm, 5µ) **MP:** Ammonium acetate (pH 4.75) buffer & ACN **Injection volume:** 10 µl **Flow rate:** 1.0 ml/min **Detection wavelength:** 254 nm **Linearity:** 5 - 150 µg/ml **Mass spectrometric detection:** protonated molecular ion peak with electrospray	[13]

				ionization positive mode (m/z 358.1805)	
5.	Vtama	Tapinarof	HPLC	**System:** HPLC system **Column:** Kromosil C_{18} (250 × 4.6 mm, 5µ) **MP:** Phosphate buffer: methanol (100:900 (v/v)) **Flow rate:** 1.0 ml/min **Injection volume:** 10 µl **Run time:** 6 min **Detection wavelength:** 313 nm **RT:** 2.88 min **Linearity:** 5-30 µg/mL	[14]
6.	Mounjaro	Tirzepatide	Spectrofluorometer	**System:** Shimadzu RF-6000 spectrofluorometer TIR exhibit intense native fluorescence in ethanol at λem = 303 nm after excitation at λex = 225 nm	[15]
7.	Voquezna	Vonoprazan, amoxicillin, and clarithromycin	RP-UPLC	**System:** Acquity UPLC system **Column:** Hibar Bis phosphonate C_{18} column (100 × 2.1 mm, 2 µm) **MP:** 0.1 N monobasic potassium phosphate buffer (pH 3.8): ACN (60:40) **Flow rate:** 0.2 ml/min **Run time:** 3 min **Detection:** Tunable ultra-violet at 210 nm **Linearity:** CLA 25–150 µg/ml AMO 25–150 µg/ml VON 1–6 µg/ml	[16]

			RP-UPLC	**System:** Acquity UPLC system **Column:** Hibar C_{18} (100 x 2.1 mm, 2 µm) **MP:** Ammonium Acetate & ACN in equal volumes **Flow rate:** 0.3 mL/min **Injection volume:** 1.0 µl **RTs:** CLA 1.24 min AMO 0.97 min VON 1.66 min **Linearity:** CLA 25 - 150 µg/ml AMO 25 - 150 µg/ml VON 1 - 6 µg/ml **LOD and LOQ:** CLA 0.07 µg/ml & 0.22 µg/ml AMO 0.81 µg/ml & 2.45 µg/ml VON 0.03 µg/ml & 0.09 µg/ml	[17]
8.	Vonjo	Pacritinib	LC-MS/MS	**System:** Shimadzu LC-20AT UPLC System **Column:** Shim-pack velox C_{18} (2.1× 50 mm, 2.7 µm) **MP:** 0.1% formic acid in H_2O: 0.1% formic acid in CH_3OH **Flow rate:** 0.3 ml/min **Linearity:** 1-1500 ng/ml **LLOQ:** 1 ng/ml **Mass spectrometric detection:** Multiple reaction monitoring (MRM) mode with positive ions detection (m/z 473.25→ 97.15)	[18]
9.	Cibinqo	Abrocitinib	RP-HPLC	**System:** HPLC system consisted of	[19]

				WATERS Alliance 2695 **Column:** Inertsil C_{18} (250mm×4.6mm, 5µm) **MP:** Phosphate buffer PH 4.8: CH_3OH (55:45% v/v) **Flow rate:** 1 ml/min **Injection volume:** 20 µl **Detection wavelength:** 282 nm **RT:** 4.8 min **Linearity:** 10-130 µgm/ml **LOD and LOQ:** 1.3 and 3.9µgm/ml	
			HPLC-MS/MS	**System:** liquid chromatography system coupled to a triple-stage quadrapole TSQ Quantiva™ mass spectrometer **Column:** C_{18} column Xselect™ HSS T3 (2.5 µm, 2.1x150 mm) **MP:** 0.2% formic acid in H_2O & 0.1% formic acid in ACN **Flow rate:** 0.3 ml/min **Run time:** 10 min **RT:** 3.52 min **Linearity:** 0.5–200 ng/ml **LLOQ:** 0.5 ng/ml **Mass spectrometric detection:** (m/z 324.10 →149.00)	[20]
			spectrophotometric method	**Solvent:** Dimethylsulfoxideas **Absorbance wavelength:** 303 nm **Linearity:** 2-14 µg/ml	[21]

				LOD & LOQ: 1.226 µg/ml & 5.226 µg/ml	
10.	Quviviq	Daridorexant	HPLC	**System:** Waters e2690 alliance HPLC system **Column:** SpursilTM C18 **MP:** Phosphate buffer (pH 3): ACN [30:70 (% v/v)] **Flow rate:** 1.0 ml/min **Detection wavelength:** 270 nm **Linearity:** 2.0-10.0 µg/ ml **LOD & LOQ:** 0.089 µg/ml & 0.271 µg/ml	[22]

Table 2: Newly approved drugs without analytical methods in 2022

S. No	Drug Name	Active Ingredient	Manufacturing Company
1	Nexobrid	anacaulase-bcdb	MediWound LTD
2.	Briumvi	Ublituximab-xiiy	TG Therapeutics
3	Xenoview	hyperpolarized Xe-129	Polarean, Inc.
4	Lunsumio	mosunetuzumab-axgb	Genentech, Inc.
5.	Rezlidhia	Olutasidenib	Rigel and Forma Therapeutics, Inc.
6	Tzield	Teplizumab-mzww	Provention Bio, a Sanofi Company.
7	Elahere	Mirvetuximab soravtansine-gynx	Elahere, ImmunoGen, Inc.
8	Tecvayli	teclistamab-cqyv	Janssen Biotech, Inc.
9	Imjudo	tremelimumab	AstraZeneca
10	Omlonti	oomidenepag isopropyl ophthalmic solution	Santen and UBE.
11	Elucirem	gadopiclenol	Liebel-Flarsheim Company LLC
12	Terlivaz	Terlipressin	Scotmed Care Pvt. Ltd.
13	Rolvedon	eflapegrastim	Hanmi Pharmaceutical
14	Daxxify	daxibotulinumtoixnA-lanm	Revance Therapeutics, Inc
15	Spevigo	spesolimab-sbzo	Boehringer Ingelheim
16	Xenpozyme	Olipudase alfa	Sanofi

17	Amvuttra	vutrisiran	Alnylam Pharmaceuticals, Inc.
18	Camzyos	Mavacamten	Dr.Reddy's Laboratories
19	Vivjoa	oteseconazole	Mycovia Pharmaceuticals
20	Pluvicto	lutetium (177Lu) vipivotide tetraxetan	Advanced Accelerator Applications, part of Novartis.
21	Opdualag	nivolumab and relatlimab-rmbw	Bristol-Myers Squibb Company Princeton
22	Pyrukynd	mitapivat	Agios Pharmaceuticals
23	Enjaymo	sutimlimab-jome	Bioverativ.
24	Vabysmo	faricimab-svoa	Roche Pharma India
25	Sunlenca	Lenacapavir	Gilead Sciences, Inc.

2. Conclusion

The development and validation of analytical methods are crucial steps in the production of medicinal products. An examination of the available research reveals that numerous drugs were approved for market use in 2022. According to the review, Table 1 and Table 2 list drugs that have established methods using spectroscopy and chromatography, both individually and in combination with other drugs. However, for many newly approved drugs, no spectroscopic or other analytical data are currently available. While various validation parameters for specific medications have been published, it is evident that several analytical techniques such as spectrophotometry, HPLC, UPLC, UPLC-MS/MS & LC-MS could be further developed and refined for these new formulations. This represents a significant opportunity to create new analytical procedures for recently approved pharmaceuticals, particularly those that lack well-established methods or are used in combination with other treatments. Additionally, the development of these new techniques could enhance the precision, accuracy, and reliability of drug analysis, ultimately improving the quality and safety of pharmaceutical products available on the market.

List of Abbreviations

MP- Mobile Phase

RT-Retention time

LLOQ-Lower Limit of Quantification

SPB-Sodium phenylbutyrate

TRS-Taurusodiol

CLA-Clarithromycin

AMO-Amoxicillin

VON-Vonoprazan

ACN- Acetonitrile

H2O-Water

CH_3OH-Methanol

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