Chapter 1: Introduction

1.1 Background

Since a low-income population dominates Indonesia and prefers low-cost medicine, most pharmaceutical industries in Indonesia are focusing on producing generic drugs. According to data from **IQVIA,** the market for generic drugs has expanded in the last ten years with an estimated value of around **5 billion USD** in 2024, and it will reach around **9.9 billion by 2033**, reflecting a compound annual growth rate (CAGR) of about 7.8% in the next 5 years. (IQVIA, 2024) One of the key drivers of this growth is the implementation of JKN (JAMINAN KESEHATAN NASIONAL), or the Indonesian health insurance system, also known as **BPJS Kesehatan**. In Southeast Asia, **Indonesia is the largest pharma market**, with an estimated value of around 10.11 billion USD in 2021 (i3l, 2022).

In pharmaceutical manufacturing, quality control laboratories play a crucial role in ensuring drugs that have been produced are safe and efficacious for patients, so accurate and efficient drug analyses in QC labs are critical. One of the techniques to determine drug compounds to ensure drug quality and meet regulatory requirements is using **high-performance liquid chromatography (HPLC**). (USP, 2022).

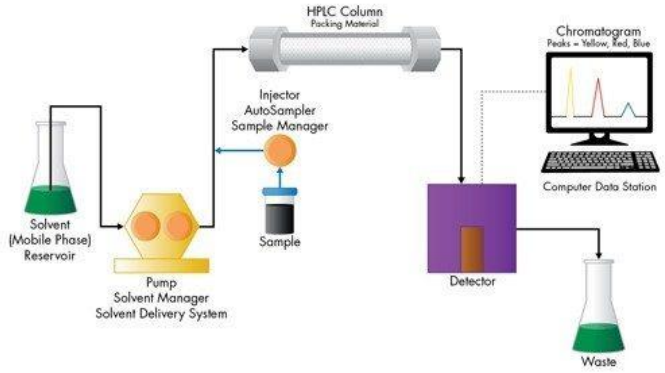


Figure 1. Schematic of HPLC systems, from solvent, pump, column, detector, and chromatogram (Skoog et al., 2014)

One of the challenges of the generic pharmaceutical industry is rapid product release. HPLC, a primary method for drug analysis in QC labs, sometimes requires longer run times per sample. This extended analysis duration could delay product batch release and result in **increased inventory holding costs** and lost opportunities due to **late go-to-market** since the products are unable to be delivered to the market immediately because of waiting for release

approval from QC. (Reddy et al., 2021; Rao & Nanda, 2022). Delaying releases like this is one of the critical factors in the generic drug business as **a low-margin, high-volume product**, and it could directly impact profitability. (IQVIA, 2024)

Another option for longer run times in HPLC analysis is to switch **to Ultra Performance Liquid Chromatography (UPLC)**, which allows for quicker analysis and uses less solvent, helping to save money and reduce chemical waste. However, transferring a method from HPLC to UPLC is not straightforward because the **pharmaceutical industry is highly regulated,** requiring that the UPLC method be scientifically validated and compliant with regulations, which incurs additional costs for method development and validation. There is also a cost barrier, especially for mid- to low-sized pharma producers, since upgrading HPLC to UPLC requires **a high initial investment** for the instrument. (Swartz, 2005).

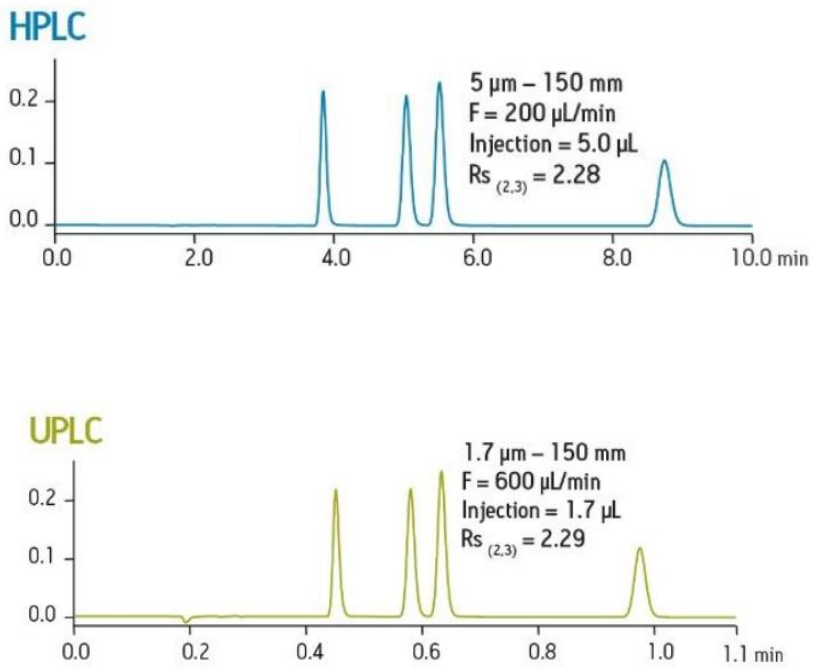


Figure 1.2 Chromatogram example of generic drug analysis, where UPLC takes less than a minute and HPLC takes more than eight minutes (Waters, 2022).

UPLC is becoming a trend in pharmaceutical industries in developed regions such as Europe and the USA or in Asia, like Japan, China, India, and Korea. Ugale et al. reported in his study in 2022 that UPLC is becoming more common in pharma QC labs because it gives **better speed and accuracy** compared with traditional HPLC. Furthermore, Suleiman et al. (2022), in his publication, mention in the Multidisciplinary Digital Publishing Institute journal

that UPLC is now widely used for drug identification and potency testing, especially in analyzing complex drug substances.

In Indonesia, a developing country that produces many types of generic products, the **implementation of UPLC remains relatively low**. This is because many QC lab practitioners are not confident in transferring their HPLC method because they are afraid it will **fail during validation** or it could make **production costs go up** since it needs investment in a new UPLC instrument, which costs almost double or even more compared with an HPLC instrument.

In addition, analysis with UPLC, besides needing skilled personnel, also requires a smaller particle size column with a 1.7-2-micron column, which is more expensive and has a shorter lifetime compared to a 5-micron HPLC column.

1.2 Problem Statement

Even demand for generic drugs in Indonesia is increasing, but the quality control (QC) process is still slow and inefficient, especially for active ingredient analysis by using HPLC. Some of the fast-moving products, such as piroxicam, amlodipine, ranitidine, and ceftriaxone, have been reported to have longer analysis times, which causes delays in product batch release. These kinds of delays often become bottlenecks in production.

On the other hand, ultra-performance liquid chromatography (UPLC) offers solutions with its advantageous technology to speed up the process, but in Indonesia, implementation remains limited due to several challenges below:

- The initial cost of the UPLC instrument is very high, and there **is no evidence data** to show that this **initial investment will pay off**.
- It is still **uncertain** whether UPLC with faster analysis really could **reduce the total costs of QC labs.**
- There is limited regulatory guidance on **how to do the transfer method** from HPLC to UPLC.
- There is **less study** on if UPLC is **economically feasible** for generic drug producers who produce high-volume, low-margin pharmaceuticals.

These problems have made it hard for the Indonesian pharmaceutical industry to fully figure out if UPLC will bring long-term benefits or just more financial problems.

1.3 Research Questions

1. How does the transfer method from HPLC to **UPLC comply with the rules in USP <1225> and ICH Q2(R1)?**
2. How do HPLC and UPLC differ in terms of run times, **cost per test, and waste generation** when analyzing selected APIs such as piroxicam (example of NSAID anti-inflammatory), amlodipine (example of antihypertensive drug), ranitidine (example of antihistamine drug), and ceftriaxone (example of antibiotic drug)?
3. What are **cost comparisons** in HPLC and UPLC processes when calculated using **activity-based costing (ABC**)?
4. How can using **UPLC reduce operations and make production more efficient** for generic drug companies in Indonesia?
5. How **feasible is upgrading to the UPLC method** in quality control (QC) labs in Indonesia, both from a business and regulatory perspective?

1.4 Research Objectives

1. **Develop a transfer method** from HPLC to UPLC that meets the regulatory guidelines of USP <1225> and ICH Q2(R1).
2. Comparison between **HPLC and UPLC in terms of SST parameters** (retention times, tailing factor, resolutions, limit of detection, RSD, and theoretical plate) for analyzing the selected APIs: piroxicam, amlodipine, ranitidine, and ceftriaxone.
3. Identify the **main cost driver** during the process in HPLC and UPLC by using the **Activity-Based Costing (ABC) method**.
4. Analyze how long the **payback period and break-even point (BEP**) of the UPLC instrument investment are if UPLC is really able to reduce the cost per test.
5. Assess the **feasibility of UPLC for use in quality control** (QC) laboratories in Indonesia from both a business and regulatory perspective.

1.5 Scope and Limitation

1.5.1 Scope

In this case study, we are focusing on doing an evaluation and feasibility study of transferring analytical methods from classical HPLC to UPLC technology by analyzing 4 selected APIs as fast-moving generic drugs in Indonesia, where each API represents a drug group like anti-inflammatory (Piroxicam), anti-hypertension (Amlodipine), antihistamine (Ranitidine), and antibiotic (Ceftriaxone).

1. There are main areas covered in this case study that include
2. Evaluation of regulatory requirements based on USP and ICH guidelines
3. Technical Performance between HPLC and UPLC
4. A cost analysis will be conducted using the Activity-Based Costing (ABC) method.
5. Payback period and BEP of UPLC instrument investment

1.5.2 Limitations

1. This case study only focuses on the quality control (QC) process and does not cover other testing, such as clinical testing, stability testing, or bioequivalent testing.
2. Our findings are limited to four specific selected APIs, so they may not apply to other types of drugs even in the same therapy group.
3. Cost data used in this study is based on available data on the current market price and may vary depending on the procurement process in different laboratories.
4. The validation method is according to international standards (USP and ICH), and data that is generated by this study could not be used as a data reference for drug registration in the Indonesian Drug Agency, or BPOM.

Chapter 2: Literature Review

2.1 HPLC vs. UPLC: Technology Background

High-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC) are widely used analytical methods that are being used in pharmaceutical manufacturing globally. HPLC as a traditional technique uses a column with a particle size from 5 to 3 µm, and UPLC as the latest technology uses a column with a smaller particle size of less than 2 µm, which helps analysis be faster, more accurate, and more sensitive (Swartz, 2012; Novakova & Vlčková, 2020). Deta

Description	**HPLC**	**UPLC**
Column Particle Size	3–5 µm	< 2 µm
Maximum Pressure	Up to 6,000 psi	Up to 15,000 psi
Analysis Speed	Slower	Faster
Solvent Consumption	Higher	Lower

Table 2.1. Basic comparison of HPLC vs UPLC

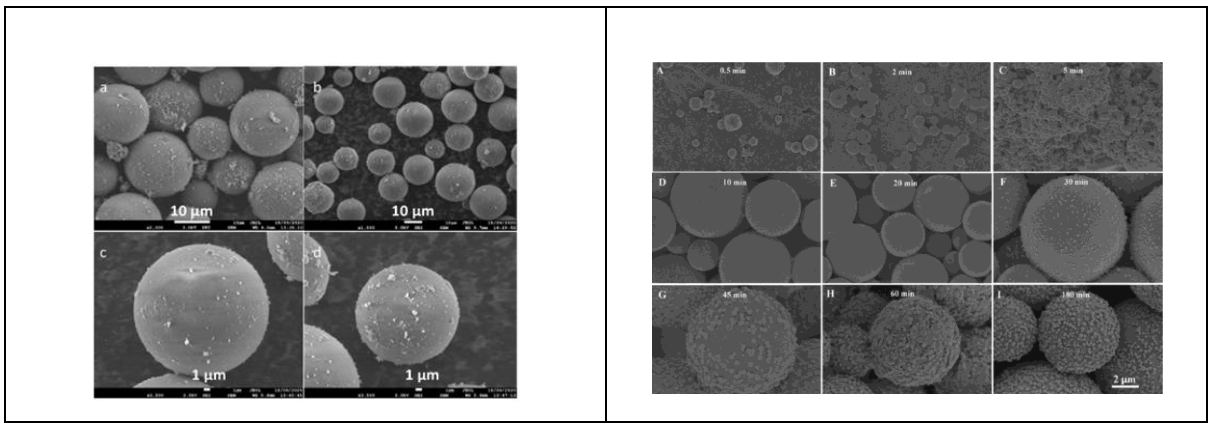


Figure 2.1: HPLC Column Particle (Verma et al., 2018) vs. UPLC Column Particle (Chen et al., 2018)

To make sure methods are correct, both UPLC and HPLC must follow ICH Q2(R1) rules. These include accuracy, precision, linearity, and detection limits (ICH, 2005). USP <1225> gives guidance on how to transfer methods. In Indonesia, BPOM follows international standards and asks for proper method validation when registering medicines (BPOM, 2022).

Below benefits comparison between HPLC and UPLC technology

Description	HPLC – Advantages	HPLC – Disadvantages
Cost of Instrument	Lower initial investment	NA
Flow Rate	NA	Longer run times (15–60 min/sample)
Resolution & Sensitivity	Adequate for most QC testing	Limited by 3–5 µm particles
Solvent Consumption	NA	High (1–2 mL/min) → higher cost & waste
Water & Waste	NA	High water and waste disposal cost
Maintenance	Easier handling, robust system	Frequent column replacement, higher solvent filter use
Regulatory Aspect	Mature, widely accepted by USP/EP/WHO	NA
Method Availability	Large database of validated pharmacopoeia methods	NA
Sustainability (ESG)	NA	High waste, solvent, energy use
Training/Skill	Widely known, simple training	NA

Table 2.2 : HPLC advantages vs HPLC Disadvantages

Description	UPLC – Advantages	UPLC – Disadvantages
Cost of Instrument	NA	Higher initial investment (2–3× HPLC)
Flow Rate	Faster analysis (2–10 min/sample), >100,000 samples/year	NA
Resolution & Sensitivity	High resolution with sub-2 µm particles	Columns fragile, clogging risk
Solvent Consumption	Low (0.2–0.5 mL/min), up to 90% solvent savings	NA
Water & Waste	Lower water usage, less waste generation	NA
Maintenance	Lower solvent impact, longer instrument life	Sensitive to contamination, requires clean samples
Regulatory Aspect	Increasing acceptance with method validation (ICH Q2)	Some methods require re-validation or optimization
Method Availability	Growing number of UPLC methods available	Fewer compendial methods compared to HPLC
Sustainability (ESG)	Lower carbon footprint, supports SDG 6 & 12 goals	NA
Training/Skill	Higher technical skill required for operation & troubleshooting	NA

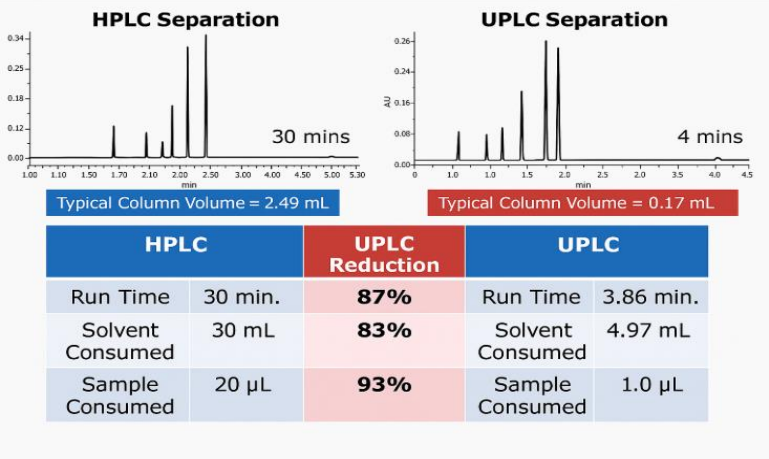
Table 2.3 : UPLC advantages vs UPLC Disadvantages

2.2 UPLC in Pharmaceutical Quality Control

UPLC is now widely used in pharmaceutical quality control because it gives faster and more accurate results. This is helpful for generic drug companies that test many samples.

One example of how UPLC is used in generic drug quality control is from a report by Waters Corporation. They used UPLC to test a tablet that contains paracetamol and caffeine. The instrument used was the ACQUITY UPLC system. This method helped reduce the testing time from 10 minutes (with HPLC) to less than 2 minutes (with UPLC). It also gave better results in terms of peak sharpness and separation. The system met important quality standards like resolution above 2.0, tailing factor below 1.5, and more than 10,000 theoretical plates. This shows UPLC is good for testing many samples quickly while saving time and using less solvent (Waters, 2020).

In addition, a scientific study by Novakova and Vlčková (2020) reviewed several global pharmaceutical applications of UPLC in QC laboratories. For instance, multinational companies have used UPLC to analyze antihypertensive drugs, antibiotics, and anti-inflammatory agents in both single and combination formulations. These implementations led to reduced cycle times, lower variability, and better compliance with ICH and FDA standards. The study highlighted how UPLC enabled routine QC labs to process more samples per day while improving robustness and sensitivity—benefits especially important in high-volume operations common in global generics manufacturing.



HPLC		UPLC Reduction	UPLC	
Run Time	30 min.	87%	Run Time	3.86 min.
Solvent Consumed	30 mL	83%	Solvent Consumed	4.97 mL
Sample Consumed	20 µL	93%	Sample Consumed	1.0 µL

Figure 2.2 : HPLC and UPLC comparison in terms of run time, solvent consumption, and sample. Adapted from Bhardwaj et al. (2018)

However, changing from HPLC to UPLC is not always easy. Problems like unclear peaks, high noise, or tailing can happen if not optimized (Havlíková et al., 2019). Some global

studies show success with APIs like Piroxicam, Amlodipine, Ranitidine, and Ceftriaxone (Moin et al., 2020; Shaikh et al., 2018; El-Bagary et al., 2019), but such studies are still rare in Indonesia.

2.3 HPLC vs UPLC Considerations

When deciding whether to move from HPLC (High-Performance Liquid Chromatography) to UPLC (Ultra-Performance Liquid Chromatography), pharmaceutical laboratories must consider several important factors. These include method validation, technical performance, regulatory compliance, and cost-effectiveness (Swartz, 2012; Novakova & Vlčková, 2020).

One of the main challenges is that UPLC operates at much higher pressures—up to 15,000 psi—compared to HPLC, which usually runs below 6,000 psi. This high pressure may damage old or incompatible equipment if not properly upgraded (Waters Corporation, 2004). In addition, method transfer from HPLC to UPLC requires.

- Revalidation of the analytical method following ICH Q2(R1) guidelines for accuracy, precision, linearity, and detection limits (ICH, 2005).
- Software updates or new chromatography data systems (CDS) that can handle UPLC output and resolution (BPOM, 2022).
- Training for laboratory analysts, especially to handle faster run times, higher sensitivity, and pressure-sensitive systems.

These technical and regulatory needs can lead to extra costs, especially during the transition phase. To evaluate the true cost and benefit of switching, Activity-Based Costing (ABC) can be used. This method calculates the real cost per test by including

- Consumables (solvents, columns), Instrument use time,
- Analyst labour
- Waste disposal.

When UPLC increases the number of tests completed per day and reduces resource usage, it improves return on investment (ROI**)**. For generic drug manufacturers with high testing volume, this can lead to significant operational efficiency (Ugale et al., 2022; Suleiman et al., 2022).

2.4 Evaluation Methods

2.4.1 Regulatory Framework

Analytical methods used in pharmaceutical quality control must meet international regulatory standards. The International Council for Harmonisation (ICH) provides the most widely accepted guideline for method validation through ICH Q2(R1). This guideline outlines the key parameters that must be evaluated to ensure the method is reliable and suitable for its intended purpose (ICH, 2005). These parameters include:

- **Accuracy**: How close the results are to the true value
- **Precision**: Reproducibility under the same conditions (repeatability) and different conditions (intermediate precision)
- **Linearity and Range**: The method's ability to produce results directly proportional to the concentration of the analyte
- **Detection Limit (LOD) and Quantitation Limit (LOQ):** The smallest amount of substance that can be detected or quantified
- **Specificity**: The method's ability to test the target compound without interference
- **Robustness**: The method's reliability under small changes in conditions

In addition to ICH, the United States Food and Drug Administration (FDA) also requires that any analytical method used in drug development and manufacturing be properly validated. According to the FDA Analytical Procedures Guidance for Industry (FDA, 2021), changes to methods or instruments (such as replacing HPLC with UPLC) must be justified with scientific data and validation results.

In Indonesia, the National Agency of Drug and Food Control (BPOM) follows both ICH and ASEAN guidelines. BPOM Regulation No. 17/2022 requires validation reports to be included in drug registration files, especially when upgrading or transferring analytical methods (BPOM, 2022).

Evaluation Parameter	Acceptance Criteria	Reference
Accuracy	98–102% recovery	ICH Q2(R1)
Precision (RSD)	≤ 2% (repeatability and intermediate precision)	ICH Q2(R1)
Linearity (R^2)	≥ 0.99	ICH Q2(R1)
LOD/LOQ	Based on signal-to-noise (3:1 for LOD, 10:1 for LOQ)	ICH Q2(R1)
SST: Resolution	> 2.0	USP <621>
SST: Tailing Factor	< 1.5	USP <621>
SST: Theoretical Plates	> 2,000	USP <621>
SST: %RSD RT	< 1.0%	USP <621>
Statistical t-test	p-value < 0.05 (significant difference)	Statistical Criteria
ROI Analysis	Positive ROI within 3–5 years	Company Finance Estimation

Table 2.4: Evaluation parameter for HPLC and UPLC method validation

2.4.2 Benefit-Cost Analysis

Evaluating the transfer from HPLC to UPLC requires more than just technical comparison. It is also important to understand the economic impact, especially for pharmaceutical companies in Indonesia, where cost control is critical. This study uses activity-based costing (ABC) and payback period models to assess whether UPLC is a financially viable option.

1. **Activity-Based Costing (ABC)**

The ABC model is a costing method that assigns costs based on activities performed, not just on volume or usage. It provides a more accurate way to determine the real cost per test by breaking down the process into cost drivers such as

- Solvent and chemical use
- Column and equipment wear
- Instrument run time
- Analyst labor time
- Waste disposal costs

According to Kaplan & Cooper (1998), ABC is especially useful in laboratory environments where overhead costs are high and must be carefully allocated. By applying ABC, this study can compare the cost per analysis for HPLC and UPLC methods, accounting for both direct and indirect costs**.**

Although ABC is widely used in manufacturing and service industries, its application in laboratory environments remains limited in scientific literature. However, select studies demonstrate its feasibility and benefits in this context:

- Hematopathology Lab (India): Gujral et al. (2010) applied ABC to calculate per-test costs in a hospital-based hematopathology laboratory. Their findings revealed that reagents and labor were the most significant cost contributors. The study emphasized that traditional costing methods often distort true costs by failing to allocate indirect overhead properly (Gujral et al., 2010).
- Quality Assurance Laboratory (USA): Chakraborty et al. (2018) demonstrated the utility of ABC in a QA laboratory, showing that indirect costs—such as instrument maintenance and compliance tasks—must be traced through cost drivers like machine-hours or calibration events to obtain accurate test-level costing (Chakraborty et al., 2018).

These examples reinforce the rationale for applying ABC to pharmaceutical quality control settings, where high test volumes and regulatory constraints make cost transparency and efficiency critical.

2. Cost Saving and Payback Period

The time it takes for cumulative net savings to equal the initial investment is calculated as

$$\text{Payback Period} = \frac{\text{Initial Investment}}{\text{Annual Cash Savings}}$$

A shorter payback period is more attractive, as it indicates faster recovery of cash outflows (Ross et al., 2019; Drury, 2013). In the context of switching to UPLC, the investment includes the cost of a new instrument, software upgrades, training, and validation. The return comes from: reduced analysis time (higher sample throughput), lower solvent and waste costs, improved data quality (fewer repeat tests), regulatory and operational efficiency

If the payback period is short such 3-5 years, then switch to UPLC can be considered economically feasible (Novakova & Vlčková, 2020; Suleiman et al., 2022).

2.5 Strategic Adoption and SWOT Analysis

In generic pharmaceutical manufacturing, laboratories must balance cost-efficiency with regulatory accuracy. UPLC provides faster run times, better sensitivity, and lower solvent usage, which aligns with long-term goals like reducing waste, increasing sample throughput, and improving turnaround time (Swartz, 2012; Suleiman et al., 2022).

However, the high initial investment in UPLC instruments, software, and staff training can be a barrier. Therefore, labs must perform cost modeling using ABC and project the financial return using payback period calculations before making the switch. The ABC model allows labs to evaluate cost per test by identifying all relevant cost drivers (Kaplan & Cooper, 1998). For strategic planning, ABC helps answer:

- How much does each test truly cost with HPLC vs. UPLC?
- Which steps consume the most resources?
- What areas offer potential cost savings?

This information helps managers justify funding and prioritize equipment upgrades. payback calculation provides a quantitative measure of financial benefit over time. It allows companies to estimate how quickly the cost of UPLC can be recovered through operational savings. A positive ROI with a payback period of less than 3–5 years is considered acceptable in most pharmaceutical business strategies (Novakova & Vlčková, 2020)

Decision Factor	**Evaluation Approach**	**Tool**
Regulatory Impact	Compliance with ICH, USP, BPOM	Method validation, SST
Operational Cost per Test	Compare direct and indirect lab costs	ABC Model
Investment Payback Period	Estimate over 3–5 years	Cost saving and payback period
Capacity Improvement	Analysis risk and benefit, strength and threat	SWOT Analysis

Table 2.5: Tools for strategy adoption

2.6 Research Gap

Many studies compare HPLC and UPLC, but few combine both aspects: compliance with regulation consideration and Cost with ROI analysis for generic drug factories, for example,

- Moin et al. (2020) developed a UPLC method for piroxicam with better resolution and faster time but didn't include cost data.
- Shaikh et al. (2018) created a UPLC method for ranitidine and cefixime but didn't discuss transfer issues.
- El-Bagary et al. (2019) focused on the sensitivity of Amlodipine but did not analyze cost impact.

This research aims to give a complete evaluation that includes technical performance, cost benefits, and regulatory requirements. The goal is to help quality control (QC) laboratories in Indonesia make better decisions when considering switching from HPLC to UPLC

Chapter 3: Methodology

3.1 Research Design

In this study, we are using **both quantitative and qualitative methodologies** to evaluate the transfer method from regular HPLC, which is being used by many pharmaceutical companies, to the UPLC method, which is quite new technology in Indonesia. The qualitative part is starting with generic pharma industry practitioners (more than 5 years' experience in generic pharma laboratory) interviews about their experience and then continuing with the quantitative part by conducting laboratory experiments. This method will give full pictures and understanding **about technical performance, economic feasibility, and challenges and difficulties of converting methods from HPLC to UPLC in QC lab pharma** (Kaplan & Cooper, 1998; Swartz, 2012). This study will find out the benefit of UPLC implementation over HPLC by analyzing four selected APIs: piroxicam, amlodipine, ranitidine, and cefixime. These APIs are selected due to the below reason.

Those APIs are widely prescribed and part of the top-selling generic drugs in Indonesia and part of BPJS/JKN (Jaminan Kesehatan Nasional) and public health tenders (BPOM, 2022).

Therapeutic indications:

1. **Piroxicam** is an anti-inflammatory drug, part of NSAID drugs, or a non-steroidal anti-inflammatory medicine (NSAID) that is used to treat osteoarthritis and rheumatoid arthritis (Shaikh et al., 2018).
2. **Amlodipine** is a popular antihypertension drug that contains a calcium channel blocker (El-Bagary et al., 2019).
3. **Ranitidine** was an antihistamine that was popular for reducing stomach acid production and treating gastroesophageal reflux disease (GERD) and heartburn. Even though it is quite popular in Indonesia, globally, ranitidine has been banned by several countries due to impurity issues (Moin et al., 2020).
4. **Cefixime** is part of the antibiotic group, which is a third-generation cephalosporin. This drug is often prescribed by doctors to treat severe infections, especially on respiratory and unrainy systems (Suleiman et al., 2022)