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Edited by Paulo Pereira and Sandra Xavier

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Meet the editors

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Her areas of specialization are quality control in nursing and blood banks; nursing in palliative care, community nursing, and public health; emotional labor of nursing practice in community health; emotions in health and emotional education; and emotional competencies in nursing.

Contents

Preface

Quality management (QM) ensures the reliability and consistency of products or services in a sustainable organization. Consistent quality of products or services is the target of any manufacturer to satisfy the interested parties. "Quality" is defined by ISO 9000:2015 as the "degree to which a set of inherent characteristics of an object fulfills requirements." Typically, QM is composed of four main components: quality planning, quality assurance, quality control (QC), and quality improvement. ISO interprets QC as "a part of quality management focused on fulfilling quality requirements," and it is a process by which entities review the quality of all factors involved in production. Therefore, QM effectiveness is dependent on QC strategy.

QM practices are the basis for the successful implementation and maintenance of any QM system. They should assure the compliance of the seven ISO 9000:2015 principles: customer focus, leadership, engagement of people, process approach, improvement, evidence-based decision-making, and relationship management. In addition, total quality management (TQM) is a strategy that requires not only a QM cycle but also the satisfaction of other basics such as technical requirements. "Total" is understood as the full involvement of all parts of the organization in the continuous satisfaction of interested parties. Compared to a QM strategy based merely on the plan-do-check-act cycle, as referred to in ISO 9001:2015, TQM requires a more detailed QC policy. ISO/IEC 17025:2017 is an example of a global standard based on a TQM policy for the standardization and accreditation of the competence of testing and calibration laboratories. The application of management practices or TQM represents a challenge principally in emerging and developing economies.

QC strategy and practices vary according to the type of organization. At the debut stage, the essential parameters for QC are defined. They vary according to the manufacturing or analytical process. Sampling and traceability types are part of these. Sample traceability is critical to assuring that the reported results are consistent with the sample. A corrective-action/preventive-action (CAPA) viewpoint shows that most of the adverse events reported in laboratories are in the pre-examination phase. This phase is closely related to the source of nonconforming sample traceability. Therefore, a control policy is critical to the reliability of the reports. At the validation stage, the use of experimental lab data distinguishes analytical method validation from the previous selection and verification steps. It is the primary stage using mainly intra-laboratory data. Method validation using appropriate statistical tools should verify the uncertainty of the results in conditions that cannot be entirely controlled by an internal QC design. Obviously, QC cannot be debated just in a testing and calibration laboratory perspective. Control during the manufacturing stage is generally associated with a statistical process control methodology based on the observation of the entire production or on sampling.

This book is focused on new trends and developments in QM and QC in several types of industries from a worldwide perspective. Its content has been organized into two sections and seven chapters written by well-recognized researchers worldwide. The QM section includes a viewpoint of TQM in Nigeria and a discussion of

QM practices in Indian small and medium enterprises. On the other hand, the QC section debates the importance of sample traceability in toxicology and the role of analytical method validation as a first step in drug QC, and presents a case study of quality in testing in a Spanish fuel laboratory. The significance of determination of essential parameters for QC in the production of piezoelectric micropumps is also presented, such as a debate on a class of exponential regression-type estimators of the population mean in two-phase sampling. The determination of impurities in pharmaceuticals is also introduced.

Last but not least, we have to thank the valuable contributions of the researchers. Without them, the publication of this book would not have been possible. In addition, thanks go to our families for all the time taken on the edition of this book.

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Section 1

Quality Management

Chapter 1

Quality Management Practices in Indian SMEs

Ayon Chakraborty

Abstract

The purpose of this chapter is to provide an insight on the status of quality management practices in small and medium-sized enterprises (SMEs) of South India. A survey-based approach was adopted to understand the established quality management practices in the SMEs. A short survey instrument was designed by reviewing the literature on quality management initiatives in SMEs. Sample of 270 manufacturing SMEs across Southern India was selected through stratified random sampling technique. Projects with small teams, management commitment and involvement, communication, and culture change have high influence as success factors in implementing quality initiatives. Overall equipment effectiveness, root cause analysis, bottleneck analysis, and PDCA are often used tools and techniques by the organizations. High cost of training and limited knowledge were the reasons cited for not implementing quality initiatives. The study is an attempt to understand the quality management practices application in SMEs from a specific geographic location. The strength lies in bringing a different perspective from the present studies, whereas specific context of the study limits its generalizability. The findings of this chapter will help the industry to identify current quality management practices in SMEs to focus on improving their performance.

Keywords: quality management, SMEs, tools and techniques, survey, India

1. Introduction

Quality initiatives have long been part of organization strategy. Conventional way of quality initiatives such as ISO series, quality assurance, statistical quality control, zero defects, and total quality management has been the key initiatives for many years. The objective is to overcome challenges and survive in global competitive market [1]. The ability of business to adapt to new customer requirements in a globalized market is of vital importance for long-term success.

Literature suggests that quality management practices are critical for small and medium-sized enterprises (SMEs) to gain a competitive advantage. Intriguingly, the systematic application of quality management practices in SMEs, despite the wide-ranging effort that has been invested and the long-term benefits that may be achieved, remains mostly uncommon [2]. Some possible causes which may account for the low usage of quality initiatives in SMEs have been publicized in previous studies. According to quality management literature [3, 4], the reasons vary from difficulty in differentiating between different initiatives such as International Organization for Standardization (ISO), Total Quality Management (TQM), Six Sigma, and Lean to lack of clarity about the advantages of one initiative over other. SMEs also feel that

ISO as an initiative is sufficient enough to meet their business needs. However, most of the studies have focused on factors related to cultural, organizational, and project differences [5, 6]. A few have examined the influence of those factors pertinent to the tool itself such as worth and user friendliness. The comparative importance of these factors on the application of quality management practices has never been discussed. In addition, these studies tend to examine only the diffusion of quality management tools and techniques in industrial countries such as the US, Britain, and Japan [7], with no prior study in developing economies such as India.

According to Small and Medium Business Development Chamber of India:

> *"SMEs play a vital role in the growth of Indian economy by contributing 45% of the industrial output, 40% of exports, 42 million in employment, create one million jobs every year and produces more than 8000 quality products for the Indian and international markets."*

Further Indian industries such as Manufacturing, Precision Engineering, Food Processing, Pharmaceuticals, Textile and Garments, Retail, IT, Agro, and Service sectors are growing rapidly, there are increasing opportunities for SMEs to enhance their business activities. This phenomenon is not unique to India but has been observed worldwide [8].

Literature also suggests that SMEs should view quality improvement as a journey and not as a destination. The SMEs should learn from large organizations and continuously strive for performance excellence by implementing initiatives such as Lean and Six Sigma [7]. Irrespective of growing importance of SMEs in India, there are limited studies (such as [9, 10]) about the extent of quality initiatives implementation in SMEs. To address this issue, the chapter analyses the context of Indian SMEs and provides empirical evidences related to quality initiatives. The main aim of this chapter is to empirically investigate the current state and extent of quality initiatives implementation in Indian SMEs.

The research contributes significantly to academia and practice. First, the chapter explores through literature the current state of quality initiatives implementation in SMEs throughout the world. Second, it provides empirical evidence of quality practices in Indian SMEs. As the quality practices in Indian SMEs is still at nascent stages (except in automobile or electronic sectors, [9]), this type of study could enhance the thinking of government policy makers and top management to adopt quality initiatives for better management style and preparing SMEs for both local and global competition [1].

2. Theoretical background

The application of QM practices in SMEs has attracted significant interest among practitioners and researchers in quality and process improvement [11, 12]. Since late 1990s, Lean and Six Sigma have been the most widely accepted methodologies for operations improvement and quality management [11–14]. Recently, several practitioners have reported appreciable cost savings, profit maximization, and waste reduction [15, 16]. Lean is a collection of tools aimed at reducing cost while improving the operational speed of businesses processes by eliminating seven types of wastes. This is achieved through company-wide involvement, applying tools such as continuous flow, Kaizen, root cause analysis, value stream mapping, Just-in-Time (JIT), Total Productive Maintenance (TPM), Kanban, and bottleneck analysis [17, 18]. On the contrary, Six Sigma is centered on the application of a well-structured data-driven problem-solving methodology defined by the acronym

DMAIC, that is, Define, Measure, Analyze, Improve, and Control. The methodology has a strong focus on meeting customer needs and reducing variation in the process performance [15].

Understanding the critical success factors (CSFs) and the barriers to QM implementation is crucial for significant and sustainable benefits [8]. Among others, customer focus, particularly the voice of the customer, is the most crucial QM principle [11]. While conducting a survey of manufacturing SMEs in the UK, [4] found that, among 11 critical success factors (CSFs), the most important factors for the successful implementation of Six Sigma are management involvement and participation, linking Six Sigma to customers and linking Six Sigma to the business strategy of the organization.

Related empirical studies exist in the literature. Kumar [7] conducted a comparative study of Six Sigma implementation in the UK manufacturing SMEs and found that lack of knowledge and limited resource availability are the main reasons for not implementing quality initiatives in the companies. Recent investigations by [19] show that TQM practices have significant positive effects on competitive advantage and organizational performance. On the other hand, [20] investigated the effect of QM practices on the performance of banks in Jordan. Nulty [21] studied the impact of Lean Six Sigma tools on the profitability of SMEs in Nigeria.

Given the widespread awareness of the importance of SMEs in the world economy, it is necessary to reinvestigate the level of implementation of known quality initiatives in SMEs. These practices have been known to assist SMEs in achieving incremental process and product innovation [22, 23]. A significant number of studies have been done in the developed world, including the UK [5, 22], Australia [7, 11, 24, 25], and other industrialized nations such as USA and Japan [7, 11].

Past research tends to focus on investigating only the diffusion of quality initiatives in industrial countries. Very limited studies have paid attention on developing economies, for instance, from the African and Asian regions [21, 26]. Prajogo [26] studied the critical success factors of QM practices among SMEs in the food processing industry in Malaysia. Shafer and Moeller [27] investigated quality management and the performance of SMEs in the Indian industries. Majumdar and Manohar [2] carried a survey of quality initiatives among manufacturing SMEs in Pakistan. Nulty [21] investigated the effects of Lean Six Sigma methodologies on the profitability of SMEs in the Nigerian context. Preliminary studies on the application of quality management tools in the Namibian context have shown that most SMEs are not aware of high-level quality initiatives such as Six Sigma and Lean [28]. However, a considerable number of SMEs in the country have realized the need for responding to the voice of the customer.

Addressing this gap, this study attempts to investigate the adoption of quality management tools and the barriers behind their implementation in Indian SMEs. It is hoped that the study will provide a number of insights and strategies for effective implementation of quality initiatives for SMEs, enabling the SMEs to realize benefits from the use of the quality initiatives (basic and advanced). Further, the study may help to reveal the interesting common and contrasting characteristics between SMEs and to draw important lessons for incremental process innovation and SME performance.

3. Research methodology

3.1 Questionnaire survey

An exploratory survey of small and medium enterprises in and around Tiruchirappalli (Southern part of India) was conducted. The purpose was to

understand the extent of implementation of quality management practices in these enterprises. According to [29], this kind of exploratory survey provides preliminary evidence of association among concepts as well as exploring valid boundary of a theory. According to [30], survey research is about collecting data from a population or some samples drawn from a population with a focus "to assess the relative incidence, distribution and interrelationships of naturally occurring phenomena" [7]. The researchers in quality management area focus more on data collection through survey to validate hypotheses and research questions [7].

3.2 Structure of the questionnaire

The questionnaire had five parts. The first part of the questionnaire was intended to get some general information of the respondent organization, such as

- size and type of organization (local, multinational, or joint venture),
- whether they have quality department,
- there is a proper quality system in place,
- whether they have implemented quality initiatives.

It is also designed as a filter to segregate the data based on organizations that have or have not implemented quality initiatives.

The second part of the questionnaire attempted to identify the critical success factors that are important while implementing quality initiatives in organizations. The third part consisted of two questions. First question was directed at identifying business performance indicators that are to be improved through quality initiatives. Second question explored the tools and techniques used in implementation of quality initiatives. The fourth part was for those SMEs that have not implemented quality initiatives. There was one question in this part to explore about the reasons behind not implementing quality management practices. The last part was designed to obtain background information on respondents including their name, job title, company, mailing address, phone/fax number, and e-mail.

3.3 Questionnaire design

One of the main concerns while designing questionnaire is to have a proper response format. This helps in safeguarding against alteration in the type and wording of the question, as well as the type of analysis researcher wants to perform [31]. We used a closed-ended questionnaire format to collect quantifiable data, in order to perform statistical analysis. Further, this kind of format makes it easy to complete, facilitates faster data entry, and thus enabling better data analysis and summarizing the findings [32]. The questionnaire included questions on critical success factors, business performance indicators, and quality initiatives grounded in literature. A 5-point Likert-type scale was used to measure critical success factors and quality initiatives (Critical success factors: 1 = no influence, 5 = very high influence; Quality initiatives: 1 = never, 5 = always). Mutingi [33] suggests the use of Likert-type scale as it provides precise measure in comparison to a yes/no or true/false items and is also faster and easier to complete. The rating type scale facilitates researcher's understanding about critical issues or factors as the format allows respondents to indicate relative importance of choices [31].

3.4 Response variables

The dependent variables for this research are:

i. Critical success factors (CSFs)

The literature on quality management discusses about CSFs important for implementing quality initiatives in SMEs. These CSFs are mentioned without any rigorous proof [34, 35]. The CSFs specific to SMEs are mentioned in a few literatures, with support coming from surveys [7, 11]. In our questionnaire design, we follow these previous studies and included CSFs that are important from quality management point of view.

ii. Business performance indicators

The business performance indicators are not much explored in the literature, and there is no specific study exploring it specifically for SMEs. In our survey, we included business performance indicators from previous limited studies [7] and explored further. The survey helped us in preparing a list of business performance indicators related to SMEs, which we want to explore further.

iii. Tools and techniques

There is much literature mentioning tools and techniques used in different organizational process improvement initiatives. Literature focusing on tools and techniques specific to quality initiatives such as Six Sigma in SMEs is limited barring a few studies [31]. Through the survey, we explored the importance placed by SMEs on tools and techniques.

iv. Reasons

The literature focused on SMEs, in describing the difficulties or reasons behind limited use of quality initiatives. The studies though lack academic rigor, they are mainly theoretical in nature. The survey questionnaire included differences and reasons based on previous studies.

The independent variables are:

i. Demographic information

- Type of organization—multinational, local, and joint venture

ii. Type of SME

iii. Size of SME

- Employee size—size or range of full-time employees in the organization

iv. Whether the organization has implemented quality management practices or not

- Yes
  - How long has your company been using the quality initiative
  - Percentage of your business process that you are applying quality initiatives
  - Your skills in quality initiatives

- No
  - Reasons behind not implementing quality initiatives

3.5 Targeted population

The survey was conducted in and around Tiruchirappalli or Trichy based in South India. The city is around 320 km south of Chennai. It is famous for its temples, educational institutes, and public sector units such as Bharat Heavy Electricals Limited (BHEL) and Ordinance Factory. BHEL came into existence in 1960s and has initiated development of industrial estates. This lead to rapid growth in SMEs that increased from 36 to more than 300 in a short span of time.

In recent times, introduction of new products such as windmills, rice husk boilers, and improved government funding in power sector; turnover for SMEs has grown in rapid proportions. The total reported turnover of SMEs was around US$ 500 million, out of which medium scale enterprises contributed around US$ 375 million, while the balance is contributed by small-scale enterprises [36].

The enterprises are also the major employers, employing around 20,000 workers. Though the major buyer is BHEL that accounts for almost 70% of the total production, recent emergence of new clients such as GE, Suzlon, Caterpillar, etc. has increased the competitiveness and array of products among SMEs [36].

There are mostly fabrication enterprises, followed by machine shops, and lastly small units. These small units are engaged in the activities such as shot blasting, galvanizing, drilling, etc., while some of them are manufacturers of electrodes, grinding wheels, paints, etc. In total, there are 250 fabricators, 75 machine shops, and less than 75 small units [36].

Given our proximity to such a large cluster of SMEs, the survey was directed toward this population. This helped us sometime in visiting the organizations, in case they were nonresponsive to our surveys.

3.6 Study sample

For the purpose of this survey, the sample units to be surveyed were divided into two categories on the basis of their turnover (refer **Table 1**). They are:

A total of 16 medium-scale units and 36 out of 250 small-scale units responded to our survey. Responses from 13 units (medium- and small-scale) were incomplete and were excluded, thus leaving 52 usable questionnaires and a response rate of 19.52%.

S. No.	Description	Annual turnover (in Rs million)	Total number of units	Sample number of units
1	Medium scale units	50 or higher	20	16
2	Small scale units	5–50	250	36
Incomplete (not usable)				13
Total sample				65

Table 1.
Overview of the sample.

3.7 Survey implementation

The survey was conducted by mailing the questionnaire along with a cover letter on the institute letterhead to all the SMEs in the targeted population. The purpose of the letter is to make the enterprises familiarize with our research by clearly stating the objectives and benefits of this exercise. Following [7], we designed the survey in a manner to improve the response rate. Therefore, a follow-up letter reminding to send the responses was mailed to those who have not replied. This is done simultaneously with multiple visits to those enterprises by the researchers and research assistants that are in proximity to the institute. Follow-up letter and visits helped in increased response rate (around 30%) from small units. The respondents were offered no incentives except a summary of research findings if they have shown interest by checking the box provided in the questionnaire.

4. Findings

4.1 Preliminary analysis

4.1.1 Number of responses

The questionnaire was posted to 270 SMEs who were in the mailing list (refer **Table 2**). The mailing list was based on the information provided by the District Industries Center (DIC) of Trichy. DICs keep database of Micro, Small, and Medium Enterprises and formulate schemes for the development of the sector. A total of 52 were completed, 30 undelivered due to incorrect address, and 10 enterprises declined to participate. Based on the completed responses received, we observed that around 60% of the organizations have some form of quality initiatives, while 25% have not implemented any quality initiatives; remaining enterprises still need to be educated about different quality initiatives. As we focus on both types of enterprises which have or have not implemented quality initiatives, the usable responses for our study are 52. This is similar to the previous studies conducted elsewhere in the world (for e.g. [8]).

There are various reasons for low response rate in our study. One is no clear indication of the SMEs that have implemented quality initiatives. The second limitation is inaccuracy in the list in terms of name and position of the respondents, or targeted organizations' mailing address is not properly updated. The list also failed to highlight the enterprises that have closed down. Given the limitations and reviewing the literature on similar studies, we found the response rate for our study acceptable to make meaningful conclusions [7, 11].

Status	Number	Response rate (out of all organizations) (%)
Total sent	270	
Undelivered	30	11
Declined invitation	10	4
Returned (usable)	52	19.52

Table 2.
Overview of the sample.

Concerns about bias emerging from low response rate are frequently expressed in survey research literature. A study of the literature about survey response rate in quality management shows that the variation is from 11.5 to 25.2% (refer **Table 3**).

Thus there is a growing body of knowledge which seems to suggest that low response rate does not necessarily means that there is a high nonresponse bias (please see [37, 38]).

> *"Assembly of [survey-related] methodological studies whose designs permit estimation of nonresponse bias shows that empirically there is no simple relationship between nonresponse rates and nonresponse biases. That is, research results comport with the assertion that covariance between survey variables and response propensities are highly variable across items within a survey, survey conditions, and populations. Hence, there is little empirical support for the notion that low response rate surveys de facto produce estimates with high nonresponse bias (pg. 670)". (As observed from [36])*

Another factor which connects with low response rates is representativeness. But studies such as those in **Table 3** and also by [7] suggest that as long as the samples include different types of companies in the region, representativeness of the respondent balance the bias due to low response rate. Accordingly, this study is able to gather information from SMEs having diverse businesses and thus is representative of the population within the given region.

In summary, the current literature suggests shift in view about nonresponse bias and representativeness arising from low response rates in surveys. New research seems to suggest that the influence of low response rate on bias and representativeness is less straightforward in contrary to the assumption among researchers [36].

4.1.2 Organization profile

The types of SMEs which participated in the survey include manufacturers of boiler parts and boiler components, cement plant equipment, steel plant equipment, fuel firing equipment such as burners, valve, and valve manufacturing, camshafts manufacturing, automotive parts manufacturers, and others. Others involve furniture

Sl. No.	Authors	Management system	Country	Sample targeted	Organizations responded	Response (%)
1	Beaumont and Sohal [39]	ISO 9001	Australia	252	59	23
2	Antony [40]	Six Sigma	UK	200	28	14
3	Bhuiyan and Alam [41]	ISO 9001	Canada	138	30	22
4	Chan [42]	ISO 9001	Hong Kong	330	83	25.2
5	Kumar and Antony [43]	IMS	UK	500	64	12.8
6	Bernardo et al., [44]	IMS	Spain	1615	435	27
7	Kumar et al., [45]	IMS	UK and Australia	500 and 800	64 and 92	12.4 and 11.5

Table 3.
Questionnaire surveys and response rates (adapted from Khanna et al. [46]).

manufacturers, waste and wastewater treatment product manufacturers, and some service providers such as computer-aided design services to product development companies. It is observed that the core manufacturing companies such as boiler components, cement and steel plant equipment, and automotive components manufacturers mainly use quality initiatives, and they have turnover of more than 50 million. On the other hand, smaller enterprises such as furniture manufacturers or wastewater treatment plant component manufacturers do not use any quality initiatives.

As the present study is to explore about quality initiatives implementation in small and medium enterprises, we did not explore further behind to understand why small enterprises are not implementing quality initiatives. But we like to understand the reasons further through qualitative study of these organizations and develop a framework to spread implementation of quality initiatives implementation in Indian SMEs.

4.2 Descriptive analysis

4.2.1 Critical success factors (CSFs)

Success factors as concept was introduced by [38] and later popularized by [47]. Prajogo [47], extending ideas from [38], defines CSFs as "the limited number of areas in which results, if they are satisfactory, will ensure successful competitive performance for the organization."

The above definition proposes to "identify an ideal match between environmental conditions and business characteristics for a particular company" [48].

The CSFs (along with their average scores) identified from this study are shown in **Table 4**.

The study included 18 CSFs after going through the literature. These CSFs were identified from studies that focused on quality initiatives in SMEs in general or from studies on specific practices such as Lean and Six Sigma implemented in the enterprises. All the CSFs have been rated from medium to high influence. CSFs such as Projects with small teams and Management involvement and commitment were rated as high influence. This is understandable given SMEs have less number of employees, and this prevents forming large teams for quality initiatives. Also for any quality management practices to be initiated and implemented need continuous support from top management, which in most cases also involves the owner of the enterprise [7].

CSFs	Average score
Projects with small team	4.25
Management involvement and commitment	4.00
Communication	3.94
Cultural change	3.94
Team members with great motivation	3.89
Project management skills	3.81
Frequent feedback and measurement	3.75
Organizational infrastructure and culture	3.69
Projects with multiple independent team	3.64
Right amount of documentation	3.61

Table 4.
Critical success factors.

Our study further identified other CSFs having near high influence include communication and culture change. These are very important given the context of our study. As BHEL (Bharat Heavy Electricals Limited) is the major customer for most of the surveyed SMEs, it requires major shift in the culture of these SMEs to focus on quality initiatives and not being complacent to satisfy a single customer.

4.2.2 Business performance indicators

Literature suggests business performance indicators as customer requirements translated by organizations from Voice of Customer (VoC) [34]. Prior studies have not much focused on business performance indicators from an SME perspective. We identified 10 business performance indicators relevant to SMEs and found from the responses that all of them fall into the category of moderate to high relevance. Business performance indicators such as proximity to consumer and warranty returns are rated to have high relevance (refer **Table 5**). This can again be understood based on the context. BHEL and Ordinance Factory (both Public Sector Units (PSUs)) being major customers for most of the SMEs make the above-mentioned business performance indicators very relevant. As discussed in earlier section, the PSUs contribute toward 70% sales of the products for the SMEs in and around Tiruchirappalli.

This argument can further be strengthened as the other relevant business performance indicators highlighted by the respondents include special order lead time, on-time delivery, and price satisfaction all pointing toward the importance of PSUs as customers for these SMEs.

4.2.3 Tools and techniques

Prior studies on SMEs have focused on the application of various tools and techniques. Examples include studies carried out by [4, 8, 11]. Based on the literature, we have identified tools and techniques which are commonly used in SMEs for our study. The responses showed (refer **Table 6**) that most of these tools and techniques are used occasionally by the SMEs.

This can be attributed to availability of major customers for these SMEs, providing them steady order and thus keeping them in business. It also highlights the need for education to these SMEs about various quality initiatives along with tools and techniques that can be beneficial in improving their bottom line.

CTQs	Average score
Proximity to customer	4.49
Warranty returns	4.29
Relationship management	4.18
Correct invoice	4.12
Percentage of customer order	4.11
New product development	4.06
Price satisfaction	4.03
Brand image	3.96
On-time delivery	3.35
Special order lead time	2.92

Table 5.
Business performance indicators.

Tools	Average
Overall Equipment Effectiveness	4.00
Root Cause Analysis	4.00
Bottleneck Analysis	3.86
PDCA (Plan, Do, Check, Act)	3.79
Single Minute Exchange of Die (SMED)	3.79
Poka – Yoke (Error proofing)	3.43
Inspection	3.36
Value Stream Mapping	3.00

Table 6.
Frequency of usage of quality management practices by SMEs.

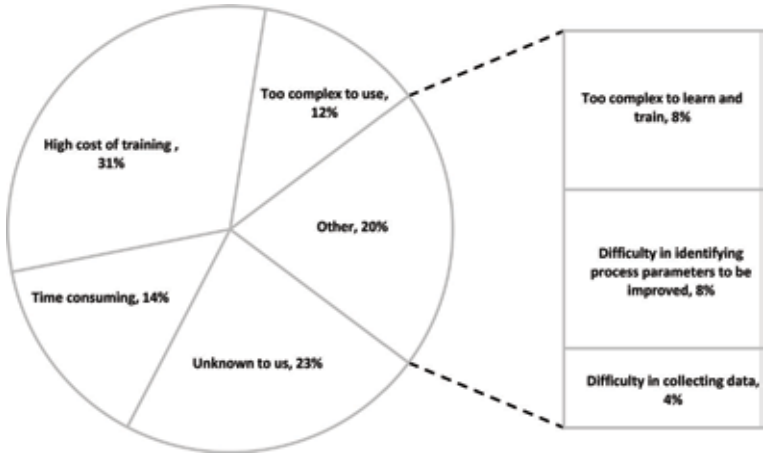

Figure 1.
Reasons for not implementing quality initiatives.

4.2.4 Reasons for not implementing quality initiatives

The reasons for not implementing or widely using quality initiatives by the respondents are presented in **Figure 1**. There are two types of respondents in our study. One set of SMEs has some quality initiatives in place, remaining are still to decide on implementing the initiatives. High cost of training emerged as one of the major reasons the SMEs are shying away from quality initiatives. Complexity in learning, time consuming efforts, difficulty in identifying process parameters, and difficulty in data collection further restrict the usage of quality initiatives by the SMEs. High percentage of respondents also mentioned about limited or no knowledge about quality initiatives. This shows the need for better education and exposure on various quality initiatives to these SMEs by academic and practitioner community.

5. Discussion

In this study, we focused on understanding the extent of quality initiatives implementation in Indian SMEs. First objective of the study was to observe the critical success factors (CSFs), which are important for the SMEs. The results show projects with small team as one of the important factors. This factor identified in

our study is different from existing studies (e.g., [1, 7, 11]). Other factors such as management commitment, communication, and cultural change relate to the "softer side" (or "human side") of the quality initiatives implementation [11, 25, 49].

Business performance indicators are important criteria that help the firm to win customer loyalty [7]. The objective here is to understand the importance given to customers by the SMEs in order to gain customer loyalty. Proximity to customer, warranty returns, and relationship management featured highly influential for the units to gain customer loyalty.

Third objective of our study was to identify tools and techniques usage by the SMEs while implementing different quality initiatives. The literature talks about TQM, Six Sigma, and Lean implementation in Australian and UK SMEs [1, 11]. We found most of the SMEs were ISO 9001:2015 [38] certified based on the ISO 9000 [50] principles. These SMEs uses techniques such as overall equipment effectiveness, root cause analysis, and PDCA cycle. High adoption of ISO 9001 by SMEs is in consensus with the literature [51, 52]. High adoption of ISO 9000 by SMEs is in consensus with the literature [51, 52]. Further findings of low adoption of Six Sigma and Lean are also in agreement with literature [11].

Finally, we wanted also to identify the reasons behind SMEs not adopting quality initiatives. High cost of training and unknown to us emerged as major barriers to quality initiatives implementation. SMEs not knowing about quality initiatives are an area which calls for attention. This shows there is limited knowledge about different initiatives irrespective of wide spread success associated with different quality initiatives. This calls for systematic education and training required in these organizations to spread the implementation of quality initiatives. Literature suggests lack of resources and lack of top management commitment as impeding factors in introducing quality initiatives in SMEs [4, 11, 16].

The study showed the importance of team and management commitment as important success factors. Therefore, managers of Indian SMEs need to play an important role in promoting quality initiatives. As most of the SMEs are near to the customer in this study, the managers need to focus on warranty returns and building long-term relationship with the customer. Further, there is a need for managers to understand the importance of education and training of employees in different quality tools and techniques, problem-solving skills, data analysis, and statistical techniques [1]. According to [53], managers need to understand and satisfy the individual employee needs and also improve the quality of life for employees. This will help in successful adoption of quality initiatives. Also, government policy makers can coordinate with senior management in SMEs and focus on developing training programs to enhance employee skill and thus prepare the organizations to adopt quality initiatives such as TQM, Lean, and Six Sigma, which will enable them to compete locally and globally.

Methodological fit is a well-developed field in management research. Edmondson and McManus [54] in their paper have discussed extensively about methodological fit at different phases of study based on the existence of relevant theory. According to their research, they suggest at exploratory stage:

> *"The research questions are more open-ended than those used to further knowledge in mature areas of the literature. In studies where theory is nascent or immature, researchers do not know what issues may emerge from the data and so avoid hypothesizing specific relationships between variables" (p. 1162).*

Further, [32] suggests to use exploratory surveys as basis for developing concepts and methods for future descriptive and explanatory surveys. In short, as suggested by [55], the whole purpose of an exploratory survey is to elicit a wide variety of responses from individuals with varying viewpoints in a loosely structured manner as the basis for design of a more careful survey.

Finally, we like to state that limited sample size has restricted rigorous statistical analysis as well as generalizability. But this can be overcome by using multiple stage study as followed by [56] or progressing through different stages of theory as explained by [54]. Our study response rate is acceptable based on prior similar studies such as by [56] and [2], where the response rate was between 23 and 25%. As discussed by [57], low response rate is acceptable as long as the sample is representative of the population. In our study scenario, we feel the representativeness of our sample and thus we are able to identify the required variables of our study through exploration.

6. Conclusions

The purpose of our study was to explore and understand the extent of quality initiatives usage in SMEs. The study was carried out in Tiruchirappalli, which has a cluster of SMEs catering to the two big PSUs in the region. The findings lead to insights related to quality initiatives in these SMEs. We were able to see the effect of nearness of major customers in the area, as evidenced from the high relevance of business performance indicators such as proximity to customers, relationship management, percentage of customer orders, etc.

Tools and techniques usage by SMEs vary from seldom to occasionally, and it is a cause for concern. The reason can be inferred back to known customers for these SMEs. Further probing into the reasons of not applying quality initiatives reveals high cost of training and no knowledge of tools and techniques as main deterrent for the SMEs. This needs to be further explored through in-depth case studies with some of these SMEs.

Finally, the study is an attempt to understand and evaluate the quality management practices in SMEs from a specific geographic location. This lead to some differences in the preferences from existing studies which is both a strength and limitation of this chapter. The strength lies in bringing a different perspective from the present studies. The study is relevant for the SMEs because they have very limited focus. The findings from this study will help them in looking beyond and extending the customer base. By avoiding the problems highlighted in our study, the SMEs can learn to educate themselves in quality management practices.

As mentioned earlier, sample distribution may be regarded as a limitation of the study, because all respondents were from a single geographic location, limiting the generalizability of the findings to SMEs of a specific region (Southern India). Low response rate is another limitation, which we plan to overcome by conducting multilevel multiple exploratory case studies with SMEs identified from the survey response. The case study research (with cross-case analyses) will help us understanding different quality management practices across SMEs [30]. We also plan to conduct a national level survey of SMEs. Future research can also focus on a global survey and understand the cultural effect on successful implementation of quality initiatives in SMEs.

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Chapter 2

Total Quality Management in a Resource-Starved Nation

Martins Emeje, Kokonne Ekere, Olubunmi Olayemi, Christianah Isimi and Karniyus Gamaniel

Abstract

Total quality management (TQM) is defined as management approach, which empowers employees to adequately satisfy the customer needs. For efficient TQM, management is required to be fully committed, focused and goal-driven. The needs of employees such as tools and resources required for efficiency, self-improvement and corresponding recognition to reward for hard work are paramount in TQM; to achieve this in a resource starved nation such as Nigeria is a huge challenge. In 2016, the National Institute for Pharmaceutical Research and Development (NIPRD) decided that it was adopting TQM in its research and development activities. The challenge, however, was lack of infrastructure and trained personnel in this highly specialized and sensitive area. Respite came when the United States Agency for International Development (USAID) through the United States Pharmacopoeia Convention Promotion of Quality Medicines (USP/PQM) agreed to provide support. Two years later (2018), NIPRD laboratory has been accredited by the American National Accreditation Board (ANAB) as the only academic institution and probably the only academic-based research institute in West Africa. We discuss herein TQM in a resource starved nation like Nigeria and propose that developing countries should collaborate in all areas of TQM with a view to upgrading institutions to international standards.

Keywords: total quality management, ISO 17025, international aids, infrastructures, personnel motivation

1. Introduction

Organizations are set up to either fill a need, solve actual problems and/or satisfy the needs of their customers and very often, this is achieved through adherence to international standards epitomized by total quality management. The quality of the final product or services is assured only if quality was built into the product rather than waiting to check the quality of the outcome. Furthermore, human resources are vital in any laboratory quality management system. Therefore, it is expedient that the organization is able to effectively manage its human resources to bring about successful implementation of the total quality management system [1, 2].

Quality is an important aspect of delivering goods and/or services. It is a vital feature of any project that wishes to attract, retain and satisfy customers. Total quality management itself is defined as management approach which empowers employees to adequately satisfy the customer needs. These approaches include qualitative

techniques of organizing human resources in such ways that meet the present and future needs of customers. For efficient total quality management, the management is required to be fully committed, focused and goal-driven [2]. Total quality management ensures that products are not just handed to customers but that they are served with relevant information, and given apt responses to questions and needs through appropriate feedback systems. In addition, the needs of the employees such as tools and resources required for efficiency, self-improvement programs, and corresponding recognition to reward for hard work are paramount in total quality management; achieving total quality management in a developing country, especially, a resource-starved one like Nigeria is no mean task; the National Institute for Pharmaceutical Research and Development walk on this path of quality (ISO 17025) *via* total quality management was expectedly a tedious task, but, the support of the United States Agency for International Development (USAID) and the United States Pharmacopeia Convention and Promotion of Quality Medicines (USP/PQM) through training and provision of simple but basic materials helped us attain this feat; In 2015/2016, NIPRD decided it was adopting total quality management in its research and development activities. Two years later (June 2018), NIPRD laboratory has been accredited by the American National Accreditation Board (ANAB) as the only academic institution and probably the only academic based research in West Africa in ISO 17025. We discuss herein our personal experiences of trying to adopt and/or adapt international standards of total quality management in Nigeria, a resource starved nation. We conclude by proposing that developing countries should collaborate in all areas of total quality management with a view to upgrading institutions to international standards [1–4].

2. Documentation, work ethics and professionalism

The customer is always right! This is an adage that has been used as a business culture to guarantee that customers are satisfied. In this millennium, attention is placed on improving ways to achieve customer satisfaction through developing resources. However, without good management, these resources could degrade, break down or become inefficient which ultimately affects the outcome to customers. Nigeria is a country rich in natural resources; oil and gas, coal, limestone, ore and other agricultural resources which serve as innovative starting materials for various industries and the Nigerian Government has over the years established several policies and programs to harness and develop these resources through several means including research and development. The National Institute for Pharmaceutical Research and Development (NIPRD) was established with the mandate to employ research and development as a means to promote economic growth *via* development of indigenous resources [4, 5].

NIPRD is an academic based research institute with many intellectuals; a fertile ground for training students, intern pharmacists and professionals from various institutions around the globe. Our research entails development of methods and skills to fulfill a particular purpose and we do this from the stand point of intellectuality and with utmost care [6]. NIPRD's ISO 17025 certification was made possible with support from International agencies such as USAID and USP (PQM). They taught us several processes leading to the achievement of total quality management and we were guided by several quality systems; one of which is good documentation. Documentation itself is seen as the means by which systems/organizations strive to instill quality into processes and products. It portrays the goals towards achieving quality and cascades to all categories of the organization. Documentation is a correct, complete and concise practice that provides information to meet the customer's requirements, it also ensures that accurate observations are made with regards to the process and the product. It is important that all steps governing a

process be well-written down, reviewed and approved by appropriate authorities; more so, it is easier to remember what has been written down than what is said verbally. Therefore, documentation is a critical aspect of research that involves the supply and collection of information and ensures continuity of ideas. Quality management systems organize documentation into different levels like; policy, procedures, work instructions and records such that changes in any aspect of documentation would not affect other aspects [3].

2.1 Quality policy

This is the very first step in determining the path to total quality management; the policy written in the quality manual defines the organization's goals and principles, stating what is to be done and how to achieve it in simple and plain terms. This document becomes a legal tender for operations involving both the employees/staff and customers alike. The NIPRD quality policy is contained in the quality manual; developed to give information about the management structure and its lines of communication to all levels of staff. This policy also enumerates the role management plays as it relates to accountability and authorization in the Institute and its laboratory. NIPRD quality manual identifies the different scopes of activity and services that can be rendered and the timelines for delivery of results, in addition, the quality manual also contains the processes for feedback and response from customer satisfaction [1].

2.2 Procedure

This describes documentation of techniques and methods that are applicable in accomplishing all that is stated in the quality manual. It defines who is to handle a procedure, the specifics of that procedure or process, where and how this would be executed as well as all information useful for conducting an analysis or rendering service. Our ways of conducting business in NIPRD was refined with the advent of ISO 17025 and this has enabled us assure the quality of results given out to our customers. For example, ISO requires that each analyst have a populated file in the laboratory apart from his/her personnel file which is resident in the Institute's Department of Administration upon employment; this procedure was strange to us because the belief/thought was that since every staff was employed based on his/her expertise, there would not be need to have any of such other documentation that specifies his expertise in the laboratory. However, we learned this type of documentation which includes items like; curriculum vitae, job description relating to the specific analysis that he/she does and the equipment he/she can handle is very crucial to quality management. More so, such details as educational qualifications have also been adopted to be included in the analyst's personnel file; this shows proof of the ability and competence of the analyst to operate an equipment and carry out analysis.

Another scenario in the NIPRD laboratory is that of documentation in the "sample receipt logbooks". When samples are brought in for analysis, they are usually passed through the Business Unit of the institute (Consult Unit) where all the necessary information about the sample received and the analysis to be performed on the sample is documented. Such sample is then given a unique description (ID) in form of numbers or codes and sent to the laboratory for analysis as required. In the laboratory also, all information about this sample; the name, type or form of sample, manufacturing and expiry dates, NAFDAC registration number, the assigned ID etc. are recorded in the sample receipt logbook, showing evidence of receipt. However, for samples procured by individual researchers for research purposes, no entry in the Business Unit or in the laboratory sample receipt logbook was usually made. This is because we did not term such samples as "business samples" even though all

such information about the sample was usually written in the researcher's notebook. Conversely, ISO taught us that all samples to be received into the laboratory had to be received from a central point; the Business Unit and had to be documented. This new approach was difficult but, we welcomed and adjusted to it as an integral part of total quality management to ensure traceability and quality. This is also true for chemicals used in the laboratory; when requests are made to the NIPRD store, all receipt from the store is also entered into the appropriate receipt logbook with suitable information traceable to the suppliers, the store and the laboratory. All these form part of the controls that ensure quality is built into products given to customers [1–3]. Although NIPRD has in time past being offering trainings on various levels to its staff, we did not for once give certificates to participants, because, we thought such "in-house trainings" did not require certificates of participation. However, the walk towards ISO certification showed the necessity of such documentation and we adopted it; issuing and keeping all training attendances and certificates for training received and given. Even minute details like having a register for cleaning of the laboratory have been embraced as part of the process to achieve total quality.

Another culture of ours at NIPRD was for the Head of Laboratory to notify the responsible analyst(s) about any sample request upon its receipt. Then the analyst would report back on the availability and/or sufficiency of materials and equipment needed. Furthermore, in trying to ensure good quality and customer satisfaction, we learned that only analysis requested for should be conducted using appropriate methods as requested by the customer or stated by pharmacopeia standards and/or validated methods. On the other hand, when carrying out research and a method cannot be adopted, we usually substitute with another, but through the process of ISO certification, we realized that such change or substitution in methodology need to be communicated to the customer with adequate information on the reason for change and then an approval for such substitution must be obtained [3]. Even though it is expedient to adhere to stated methods, sometimes in carrying out research, innovations could occur or challenges met on the bench. This actually is what research is all about; where you discover a new thing, an unlikely outcome in the process which could become the heart of that research, leading to a patent! As is with every research in the developing world, adjustments are usually made to the quantities of materials and/or choice of medium or solvent used as a result of unavailability. This process of documentation does not only clarify the methodology to be used but assures that the customer is ultimately satisfied with the process of analysis.

2.3 Work instructions

These are detailed guidelines/directives stated in simple but concise terms on how to actualize the procedures presented above. We discovered that, for utmost effectiveness, such instructions are best written by the process owners i.e. those who would be responsible for carrying out the tasks. This helps to ensure that appropriate steps are taken in carrying out all tasks in addition to creating ownership and professional pride for those involved. These instructions could be; techniques or method of each procedure, the equipment to be used, how and when it should be maintained, the type of environment required for such procedure, the requirements for handling materials to be used and the safety measures for those involved in executing the process. In addition, references of other procedures relating to the analysis to be carried out, the factors to be considered in producing good outcome and the procedure to confirm that the outcome/products meet the requirements are also documented. These instructions are placed physically at the point of use so that they are visible to all. In the NIPRD laboratory, we have these instructions placed just by the equipment to be used so that the very first operation like turning or

switching on the equipment can be performed as required. We also have documents (Standard Operating Procedures; SOPs) drawn up for every procedure, these point out detailed step by step operation or instructions for each process. Even tasks as little as cleaning are not excluded in the documentation, we had "cleaning schedules" which stated the persons charged with keeping the laboratories cleaned. It is essential that every user understands and masters the requirements in these SOPs and that it should speak to the exact steps the user will need to perform. All users are expected to be knowledgeable and trained periodically on these SOPs, and even when proficient users are given other job descriptions, it is compulsory to have them trained on the operations of the new job.

2.4 Records/results

These are the outcome of whatever task or analysis that was performed. They could be given as forms which have been stamped and/or signed showing approval of the process, outcome or product. Other records could be the supplier's documents, records of equipment calibration and maintenance and in addition results of audits conducted. This makes all actions traceable and provides data for correction where necessary. Appropriate documentation of results would also show how the product was verified to have met specifications and the customer's expectation. Part of attaining good quality systems entail that records or results are filled correctly and at the time the process was performed; with pictorials where necessary. In principle, what is not documented was not done! Record keeping or data management is a crucial aspect of ensuring quality in any organization and so must be taken seriously. Data must be stored appropriately and be accessible or retrievable when needed and where new records exist, the old should be kept for a specified period before being discarded. It is important that testing laboratories provide proof that the processes used met defined objectives as stated in their policies and it is the prerogative of each laboratory to define the records and results necessary to achieve this. In the NIPRD laboratory, the proof of following processes or procedure are the data or results generated during the process; these are usually in form of print outs, results from investigations and requisitions or memos. Our filing systems basically include the use of laboratory note books and computers; these are properly signed by the analysts who conducted the analysis and then verified by technical managers. Data stored in the computers are secured by passwords which are only accessible to the analyst (who entered the data), the technical manager (who verified the data) and the Head of Laboratory (who reviewed the process and the results). All the procedures leading to appropriate data storage are succinctly documented in the appropriate SOPs. At the end of every analysis, NIPRD laboratory issues a Certificate of analysis to the customer through the Business unit stating the results of the analysis. Records/results could also include investigations into reasons why processes failed (non-conformance), who or what was responsible for such failure and the corrective/preventive action (CAPA) plans to forestall such occurrences. Other records include calibration reports, reports of internal/external audits and equipment maintenance records. The TQM ensures that documentation defines the series of processing, standards and techniques required to preserve the quality of a system through monitoring and continual improvement to the end in order to ensure that the customer's needs are met [3].

2.5 Work ethics and professionalism

Ethics begat quality and one cannot exist without the other. For an organization to deliver on quality, it must be guided by such behaviors that lead to right-doing. Some

individuals learn these ethics as part of their life-long growth process while others acquire it on the job through training. This means our cultural background and level of exposure play an important part in deciding what is wrong or right and what a wrong or right process is. Therefore, it is quite essential that an organization sets its own code of ethics as a means of control, however, these must not be high-ended but achievable. Good work ethics and professionalism are part of the measures required to attain total quality management. It is actually not sufficient to just set the codes/rules but to provide resources that support these codes. Therefore, management must be committed to ensuring staff have the prerequisites for realizing its goals/policies and this can be attained through training. Training and re-training is an integral part of total quality management and we went through diverse forms of training by USP trainers. The records of these trainings show the competence of each persons involved in the process of analysis and guarantees that he/she has the minimum required to perform such process and in order to build quality into the product [7, 8].

NIPRD, being an academic institution, prides itself in academic growth and excellence, we develop our career through ascension in the academic ladder by undergoing higher degrees, relevant trainings etc. [6]. Total quality management requires that each staff has the requisite knowledge in doing their assigned jobs, carrying out analysis *via* exposure to current techniques and instrumentation necessary for the analysis. All analysis must be conducted with utmost professionalism while also ensuring customer satisfaction. In order to build a strong team, the management must ensure that staff performance is measured and assessed; staff evaluation and recognition is a critical aspect of total quality management which has been the culture in NIPRD. Periodically, staff in NIPRD assess their colleagues and the reward or otherwise is solely a result of that assessment. This gives rise to healthy competition which helps to build a team of competent and goal-driven employees. Although NIPRD is an institution with many departments and units, we have learnt to break down barriers of work space and embrace the concept of working across units. This has led to wholesome and total quality of all evaluations/analysis and also improved customer satisfaction.

In addition to ensuring staff are properly trained, the institute also ensures that the appropriate equipment for each analysis is provided. All equipment are listed in a database resident with the Maintenance Unit and contains the calibration certificates of each equipment, the next due date for calibration, out of specification status (when the equipment has failed to meet the required specifications) and personnel authorized to operate the equipment. All these are geared towards keeping the equipment operational so as to achieve good results. Tropical regions like Nigeria are plagued with high temperature which could affect the process of analysis and ultimately the result. Therefore, monitoring the temperature of the environment becomes very important; simple tools like the thermo-hygrometer which were needed to for this were graciously provided by the sponsors (USAID/USP) and installed in the laboratory. Records from this device are charted to ensure that the temperature of the laboratory is controlled and suitable for both the equipment and the process of analysis; it became apparent that our work culture and attitude had to change once we saw that this was geared towards improving the quality of the system; it was no longer sufficient to just view results as they come but to critically analyze them. For example, the ISO requirement is that a negative result be investigated and not just thrown aside, this we learnt and adopted. Such tools as corrective and preventive actions are raised to make sure that the action is corrected and to forestall its future occurrence. In addition, staff are taught to investigate such results with questions like; why did this result fail to meet specification? How did it fail? At what point during the analysis do you think the sample failed? And who/what was specifically responsible for the said action? It is no longer enough to just identify the problem and move to provide solutions, it is good practice to

thoroughly investigate so that such actions do not recur in future. Ethics and codes are principles which bother on individualism and affects the manner in which each staff responds to these codes. People would usually subscribe to values or beliefs that they are used to and this expresses itself in the way they set out to achieve set goals and policies. It is therefore necessary for management to understand each individual's eccentricity and use it to achieve its goals but this does not preclude the necessary requirements of each employee in fulfilling his or her role in an organization moving towards achieving quality. Integrity, reliability, consistency, good communication, respect for other people's opinion and the sense of responsibility are important ethical codes/values that lead to quality [8–10].

3. Human resources in total quality management

3.1 The importance of human resources in total quality management

Human resources (HR) are a vital part of the quality management system and is one part that cannot go unrecognized. They are the sole most vital asset in any laboratory and they are led by a competent and accountable management whose main responsibility is to ensure the successful implementation of the total quality management. This aspect of total quality management is very critical because its quality determines the productivity of the laboratory and quality of all jobs performed. Without human resources there will be no quality management system. From the start to finish of a laboratory quality system the personnel involved go a long way in ensuring that this is achieved. The human resources comprise of the management team, quality assurance team/unit, analysts, security personnel, cleaners, etc. Each of these group of human resources is essential in the whole process as one cannot function without the other. They each have their contribution and unique role that makes total quality management a reality. For this to occur, team work is very important between the various groups of personnel. Team work between the management, analysts, and support services played a major role towards the success of the accreditation exercise. If this cooperation was not evident the quality management system would have been deficient. In the NIPRD scenario, the analysts were grouped together with a key person appointed as the lead. This was done to build a culture of team work between the personnel. The quality management system (QMS) is a system of interaction, which exists at all levels, i.e. between the management team, quality assurance team, analysts and others. It is this interaction that makes total quality management what it is and makes it successfully implemented in laboratories. Another unique feature of total quality management is that each group of personnel have a range of qualifications and training which is then harnessed together to form a strong team for the execution of the quality management system. Suffice it to say that human resource is the foundation on which total quality management is built [11, 12].

3.2 Function of human resource in total quality management

All personnel involved in the quality management system have specific roles and functions they perform. One of the requirements of the ISO 17025 accreditation is for all personnel in the organogram to have a file and this file contains the job description of each person. The job description entails a brief credential of the personnel, job summary, key areas of responsibilities in ISO 17025, research functions (level of effort), key working relationships, qualifications and experience, on-the-job training, key abilities and personal abilities. The leadership of the laboratory quality management system must have a set vision and goals for the

laboratory which they must ensure its successful implementation. They should have the necessary skills for team building, communication, motivation and resource management. The managerial and technical personnel all perform unique roles. The managerial personnel are shouldered with the responsibility of ensuring all resources needed are provided in terms of infrastructure, human, etc. The technical managers, deputy technical managers and analysts each have unique roles and functions they play. For instance, in the case of NIPRD, these are the various personnel involved in quality management system. Firstly, the Director-General is the contact person/coordinator of quality management system which all the other personnel report to. He/she is responsible for providing resources needed for the successful implementation of the laboratory quality management system. Generally speaking the DG/CEO is also the head of the laboratory because he/she coordinates, manages, and monitors all activities of the laboratory. Consequently, the management review meetings which are to be held regularly are to be chaired by the DG/CEO. In addition, the annual work plan and budget are to be reviewed and approved by the DG/CEO. He/she is also to ensure that the training plan for the laboratory is effectively implemented. Administrative duties and functions are performed by the Director of Administration and Supplies. These administrative duties include personnel appointment, welfare and laboratory store. The quality assurance unit made up of a quality assurance manager and two deputy quality assurance managers. This unit is the major driver of the quality management system because they develop the quality manual which guides and governs the activities of the laboratory. The quality manager is to ensure the correct application of the management system in the laboratory. They manage and maintain the laboratory quality management system and report directly to the Director General. All standard operating procedures generated by the technical scopes are to be approved by the QAU before trainings and implementation. They also schedule internal audits yearly and ensure that the appropriate corrective action plans are implemented. They can also be involved in any other activity as directed by the DG/CEO. The deputy quality assurance managers assist the quality assurance manager to achieve the set goals. They are also required to stand in for the quality assurance manager in time of absence. The deputy in charge of documentation handles all activities related to QA documentations and archiving. The quality assurance team is composed of the quality assurance unit and representatives of the various departments in charge of quality management system. The technical departments in NIPRD each have a head of department (HoD) who are in charge of the general supervision of all activities in the department. The HoD is the first port of call for receipt of samples from the consultancy services unit and is required to ensure the implementation of requirements in the lab quality manual. The HoDs report to the Director General. For each technical scope, a technical manager and deputy technical manager is appointed whose main responsibility is to ensure continuous availability of resources required for efficient and effective analytical testing in each test scope. In addition, they are saddled with the responsibility of ensuring the continuous monitoring of all laboratory operations. The technical manager/deputy technical manager allocates the samples for analysis. They also develop and ensure implementation of an annual work and training plan for the laboratory. All SOPs prepared by the responsible analysts have to be reviewed by the Technical manager before approval by the quality assurance unit. The competence of analysts to perform certain tests is essential therefore the TM develops competence tests for each analyst which each analyst must successfully complete before authorization. The equipment used by the analysts have to be properly maintained by the instrument maintenance unit therefore it is the responsibility of the technical manager to ensure that appropriate maintenance is done regularly. The technical manager reports to the HoD or DG/

CEO. The laboratory top management communicates with the subordinates through memos, management review meetings and Quality Assurance team meetings. The analysts are the key personnel involved in the operations of quality management system. All personnel are expected to sign an impartiality and confidentiality declaration form stating their commitment to the laboratory. Anyone found involved in dishonest activities would be subjected to the laboratories disciplinary action. They perform tasks by following laid down instructions and procedures and document their results in a specific manner. They report to the technical manager who reviews each work done in the laboratory notebook. The key analyst is in-charge of the technical operations of the equipment while the other analysts act as a support in case of absence. Apart from analysis of samples, analysts are responsible for preparing sample and standard, monthly reports, SOPs and other Quality Assurance documents. When errors occur during analysis, the analyst is expected to report same to the technical manager immediately. Hygiene and safety of the laboratory is very important therefore the analyst is expected to follow safety instructions and maintain the laboratory in a neat and clean manner. They also prepare standard operating procedures for each test scope which is then reviewed by the technical manager and HoD before seeking approval by the quality assurance unit. Before analysts can operate equipment within their test scope, they are expected to receive an authorization letter from the head of department after satisfactory performance on the competency tests. In addition, all laboratory personnel are expected to sign a confidentiality declaration form. The NIPRD consultancy services is also a part of the quality system; it is through this unit that samples are received and stored before allocation to the laboratory and these processes are all documented. They also receive feedback from customers concerning the services rendered so as to know areas that require improvement. In the event of a complaint from a customer, the consultancy services unit is expected to report same to the laboratory which will then investigate and implement corrective actions. The store unit is responsible for keeping of items required by the laboratory in the form of reagents or materials. The instrument maintenance team is a key component of total quality management; they deal with the maintenance of equipment used to perform laboratory tasks. Support services such as the security and cleaning personnel are also critical as the cleanliness and safety of the laboratory is essential. The results obtained from laboratory can be affected if necessary hygiene measures are not put in place [9].

3.3 Qualifications/experience of human resource in total quality management

It is important that all technical personnel involved in total quality management are qualified and experienced in order to perform their various tasks efficiently [3]. The quality assurance manager who drives the whole process should be someone with adequate knowledge and experience in quality management system. For example, in NIPRD quality management system the technical managers responsible for supervision of the technical activities are all highly qualified educationally and professionally, this includes professors and PhD holders. This is due to the supervisory role they perform; therefore, they need to be better equipped and have a thorough understanding of the technical activity so that they can correct or solve any difficulties the analysts may have. Apart from educational qualifications, there may also be some professional qualifications in laboratory quality management system that could also be beneficial. It is important that a personnel file is maintained which contains the curriculum vitae and all certificates to show the educational and professional qualifications of each personnel. The curriculum vitae of each personnel should contain their career objective and educational achievements. This is an essential requirement of ISO 17025 laboratory accreditation. In certain technical

areas the personnel are expected to have some certification. In carrying out some specific tests they are expected to have relevant knowledge of the technology used, required legislation and standards and understand the significance of deviations when they occur during the process.

3.4 Training of HR in TQM, the NIPRD model

Training and retraining of personnel is very essential in total quality management if they are to accomplish the set goals [3]. It is important for human resource to be kept abreast of recent developments in the area of total quality management. All personnel in total quality management need to be trained (technical and non-technical personnel). If training/retraining is not conducted, there is the possibility of knowledge gaps which will eventually obstruct total quality management. One of the management's commitments to the NIPRD quality management system as stated in the quality manual is to enhance the technical capacity of personnel in NIPRD laboratory through trainings. Peradventure the laboratory needs contract staff and additional support personnel, it is recommended that such personnel too are competent, trained and supervised in their respective areas. In the case of NIPRD quality management system various training programs are planned, approved by the management and documented. The initial training is a general orientation organized by the NIPRD administration for all new employees to acquaint them with the aims and objectives of the institute. Laboratory orientation is also done by the head of department for all laboratory staff including trainees. Continuous trainings which is done in-house and external trainings are all part of the process to add, change or reflect knowledge and attitudes. In preparation towards the ISO 17025 accreditation several trainings were conducted by consultants from USP/PQM and these trainings were highly rigorous. It included theory and practical sessions. The trainings were conducted at different levels with some involving only technical personnel while others involved all the personnel. The trainings which started in 2016 were highly structured and in most cases lasted for weeks. The external trainings in 2016 were basically to familiarize personnel with the ISO 17025 standards and guidelines to keep them abreast of what is expected of them. In 2017, a gap assessment program was conducted to assess the "baseline" state of the institute. The first part of the gap assessment was to review the status of the quality manual which is an important documentation. Also, sections 4 and 5 of the ISO 17025 standards was assessed. The second part involved a laboratory inspection which involved the sample receipt area. Practical demonstrations of the various technical scopes were performed. At the end of the gap assessment all deficiencies and opportunities for improvement found during the gap assessment were discussed. Practical trainings which included case studies and subsequent laboratory hands-on were conducted. Training on compendia techniques on the various technical scopes were conducted to make personnel aware of current pharmacopeia standards for each analytical test, this is because the ISO 17025 standards require that only current pharmacopeia methods are used for each test. Another feature of these trainings were the self-assessment tests which were often done before and after each training. These assessments were very interesting as they helped to give an idea of each personnel's state of knowledge in particular areas. Most times these trainings tend to cover all sections of the ISO 17025 standards. In NIPRD, personnel were trained on various aspects such as writing and implementing effective standard operating procedures, good documentation practices, root cause analysis, corrective and preventive action, internal auditing, handling out-of-specification (OOS) test results, etc. The trainings were highly interactive with times for discussions and contributions. They were highly educative as most personnel always learnt one or two new things at each session. In order to

check if these trainings were effective and being implemented by the NIPRD personnel, the USP/PQM consultants conducted external audit of the laboratory QMS at regular intervals to keep staff up to date. After each audit session, a report was done and corrective/preventive action taken. At the end of each training, certificates were presented to staff who performed well in the assessments. Completion of the training attendance form at each training session was mandatory as it was used as an objective evidence for earning certificates. Training evaluation form was used at the end of each training to assess personnel. Personnel training needs assessment form allows personnel to identify proposed training with dates for the year, location of training, description of training need, training duration and trainer. A training record form is to be kept in each personnel file and this contains a list of all trainings undertaken with location and date. According to the ISO 17025 standards, training is important because, before personnel can be authorized to handle an equipment, they must have gone through some competency tests at different levels to test their ability to produce reliable, reproducible and repeatable results.

3.5 Problems with human resource that could arise in total quality management

The importance of human resource in total quality management has already been extensively discussed. Suffice to say that, it is necessary that highly competent and trained personnel are involved in the NIPRD total quality management [2]. However, it is possible that unforeseen circumstances may arise with human resource which may affect the total quality management. Each laboratory should have an efficient method of dealing with such issues as may arise with personnel, so that it does not negatively affect the system. When human resources are not appropriately managed, this can affect the output of the organization. For instance, if personnel are not adequately trained to perform their given tasks, it can lead to fatal errors which may lead to death depending on the tests being performed. This is why training and retraining is a key component of human resource management in any laboratory. In addition, the reward system in each laboratory should be well established to motivate personnel. It is a known fact that if personnel are not motivated there would not have the zeal to perform work and this can also introduce errors in results. Therefore, it is essential that the welfare of personnel is taken seriously to improve their productivity and output. In the NIPRD quality management system model for example, three or four analysts were appointed, trained and authorized for each scope, this is to overcome any challenges that may arise due to absence of an analyst. In the ISO 17025 accreditation process of NIPRD, it was compulsory that at least two analysts be present for each activity at any point in time. No analyst was left alone to carry out tasks in order to avoid any issue of monopoly. This goes back to the subject of team work which brings about success because with team work there is no looser. We strongly believe that not monopolizing knowledge and involving everyone as a team was one of the factors that helped NIPRD. Though there were some attitudinal challenges with some analysts, this did not affect the smooth running of the whole process as there were always trained and competent personnel available.

4. Management in total quality management leadership

4.1 Leadership

The role of leadership in total quality management cannot be over emphasized [11]. Top management Commitment and leadership is a critical factor to the success

of total quality management implementation. Though there are many definitions given to leadership, we prefer to define leadership here, as the ability to inspire followers to share in, and work with the leader to actualize organizational vision. This is the definition that best fits the leadership that bought total quality management into being at NIPRD. The vision to making NIPRD a center of excellence for total quality management started way back in 2010 with the introduction of ISO 9001-2008 quality management system standards. Being a Research institute, the introduction of quality way of doing thing was a difficult task for the leadership as many were not aware of QMS and those who were, did not see the need for quality management system in a research institute. Because it was a priority for the leadership then, conscious effect was made to ensure the engagement of a consultant to lead the organization to being certified. The Institute got ISO 9001-2008 certified in 2015 but still struggles with the funds needed to maintain the certification. It is clear that, lack of sustainability plan is a drawback. NIPRD is a departmental based organization and the different scopes are domiciled in deferent departments unlike a company setting where all activities are centrally controlled under one unit. Based on the facility tour of the team, scopes where selected to be part of the total quality management. Once these scopes were identified, a meeting was held with Top and Unit managers with the aim to generate the gaps in training and infrastructural needs of every scope [6].

As a first step to ensure leadership commitment and participation, the management set up of a Quality Assurance Team who were to be responsible for the coordination of all activities that would lead to total quality management implementation. This team comprised of the Quality Manager, two Deputies on the first level and a representative from all departments/units on the total quality management program of the institute on the second level. The Quality Manager had the responsibility of being the liaison officer between the institute and USP/PQM representative. To ensure that leadership participation and commitment is maintained, management members were requested to be part of every meeting and training. The ISO 17025 model for total quality management implementation has different levels of leadership and all levels have to be responsible and committed to ensure implementation. NIPRD though running a traditional organizational structure that could support the quality management system of 9001 had to create another structure to support the total quality management. In this structure every level of leadership comes with different responsibilities and the success to implementation is dependent of all succeeding.

4.2 NIPRD organogram

NIPRD runs a normal traditional mechanistic institutional management structures which is characterized with a small upper management that make all the decisions. The management that makes all the decisions are DG and Heads of Department [6]. This type of structure management operates a top to bottom hierarchical management. This type of management is not supportive of total quality management implementation as employees tend to strive to pursue personal rather than organizational goals. The NIPRD Organizational structure which had a single line of communication had to be modified to one that has a larger authority and employees work more for organizational goals.

4.2.1 The DG/CEO

He is the overall head of the total quality management team and is saddled with the duty of creating an enabling environment for the successful implementation

of the system. Our experience shows that, the commitment and vision of the DG/CEO was a crucial element in implementing total quality management. Development of the vision statement which is one of the responsibilities of the leadership was done with the employees to ensure staff buy-in. The leadership is responsible for providing organizational framework needed to support the system. The education and continuous development of staff is one of the leader's responsibilities and this was adequately demonstrated by making available, the available resources to training all employees. At NIPRD, like many academic based institutions, departmental barriers exist and very often are obstacles to speedy execution of services. A successful total quality management must break this barrier, and this was achieved with the commitment of both the institute leaders and laboratory managers.

4.2.2 The quality assurance unit

The unit is directly responsible to the DG/CEO and they are in charge of the general implementation of the total quality management. They are responsible for the planning of and coordinating the various training needs of everyone. The Quality Assurance Team, which is made up of the quality assurance unit and the representative from all the departments involved in the total quality management was formed to be a support to the all processes of the total quality management system.

4.2.3 Head of department (HoD)

The second level of leadership under the total quality management organizational structure are the Heads of Departments and together with the Director General they form the Management. The HoD is responsible to the CEO and have all the responsibilities of management. All reports are passed through them to the quality assurance manager. Some of them also function as technical managers on scopes domiciled in their department.

4.2.4 Technical managers

The technical manager of any scope must be familiar with methods and procedures of the scope, he/she must understand the purpose of each test. The technical manager should be vast in in knowledge and well trained in the scope area and there should possess a training records to back his/her competency. The technical manager takes responsibility for the performance of the analyst by ensuring compliance with the ISO 17025. The TM ensures that the analyst follows all standard operating procedure and takes responsibility for any report generated from the test results. The technical manager has total controls on all technical operations and approves results for onward submission to the HoD before submission to the quality assurance manager.

4.2.5 Analysts

These are the process owners and need to have complete knowledge of the processes that they work with as this is critical to the success of the total quality management implementation strategies. Without knowing how to do the job, the analyst will not be able to improve on the process towards improvement. The knowledge of the process is achieved by repeatedly working with that process, and also continuous training. The analyst must be qualified and have training records to back their competencies.

4.2.6 Instrument maintenance unit

The maintenance unit on the NIPRD organizational structure is answerable only to the Director of Administration and all members in that unit belong to the department. This was however modified on the ISO 17035 organogram. The maintenance team was deliberately created to have representation from different department also done in a bid to break down departmental barrier and foster inter-departmental cooperation. The unit was created to manage all equipment in the laboratory, consequently named Internal Maintenance Unit.

5. Physical infrastructure as a challenge to total quality management

One of the major challenges when implementing total quality management in an organization in a resource starved nation like Nigeria is lack of basic infrastructure. Infrastructure could be physical or human. Physical infrastructure includes; environment, material, machine and money.

5.1 Environmental/cultural background

Culture is a series of laydown assumptions that a group of people has developed in learning to cope with problems of external adaptation and internal integration; they have worked well enough to be valid, and are therefore thought to new members as the correct way to perceive, think and feel in relation to these problems. It is hard to analyze an organizational culture because as an outsider, you will only understand how organization behave but rarely can one understand why it behaves the way it does. Cultural values of an institution such as company philosophy, norms and justification are communicative and people of the organization are aware of these.

The National Institute for Pharmaceutical Research and Development is made up of the Director General/Chief Executive Officer, highly intellectual research scientist of diverse field and specialization, Technologist and Administrative staff. NIPRD combines research and administration. Its vision is to build a Centre of Excellent in research and development of phytomedicines, pharmaceutical and biological products, drugs and diagnostics towards improving the health and well-being of mankind. It is therefore made up of 5 core departments [6] namely, Pharmaceutical Technology and Raw Materials Development, Medicinal Chemistry and Quality Control, Medicinal Plant Research and Traditional Medicine, Pharmacology and Toxicology, Microbiology and Biotechnology. However, achieving a uniform environment condition which is very important for total quality management and ISO is usually difficult due to the diversity of activities going on simultaneously in various laboratories. Bring the various departments in one roof where such condition can be achieved was difficult nut to crack for NIPRD due to its cultural background. Before total quality management can work, it is important to understand existing cultural values of the organization. Occupational background can affect the culture of an organization. Relationship between organizational culture and operational management have been established, people's belief influences existing practices and manufacturing performance. For long, underlying value systems influence how people behave and act. Knowledge of the environmental impact of a product, services or process is an important factor in eliminating the harmful parts in a product or service with respect to the environmental health of the society.

5.2 Cost of implementing total quality management

The cost of building quality into any product is capital intensive process at the initial stage, but may be cheaper and yield better result than testing for quality in a product, because, it reduces deviations and costly investigations, and also avoid regulation compliance problems. Money invested by an institution to minimize defect or prevent mistakes is believed to cost the organization little compared to the disastrous expenses that might be incurred by an organization if total quality management is ignored.

5.3 Tools for employee to use

The NIPRD is a parastatal of Federal Republic of Nigeria, and Nigeria being an oil rich nation, ordinarily should not have problems with funding of its public institutions, but this is far from being the case; most of the equipment NIPRD were certified for by ANAB were donated to the institute by USAID, in fact during the pre-assessment audit, the auditors made fun of the institute dissolution test apparatus as been too old and should be transferred to museum. The state of the apparatus was so pathetic that almost all components were not performing efficiently; for example, like all other equipment such as the pH meter, analytical balances, UV–vis spectrophotometers, etc., it had not been calibrated for decades. In such a situation, despite the willingness of staff members to adopt total quality management, it was difficult.

5.4 Epileptic power supply

With the meager resources allocated to the NIPRD, the institute run on generators for at least 6 hours for every working day [13]. A researcher will have to plan his/her experiment within this time frame. This makes it difficult to achieve optimum environmental condition since most reference samples and room temperature must meet international specifications. Most equipment needs chilled environment for it to function appropriately. Some equipment needs re-calibration once power supply is disrupted, in a resource starve institute like NIPRD, recalibration of some equipment up to 10 times in a day is possible, this will not only affect output as it is time consuming, it is also expensive. The state of the environment affects the output of staff. If it is harsh, workers will not find it conducive to give their best. A harsh condition affects the general output of any study. A functional environment can only be achieved where power supply is relatively constant/steady. To achieve this, a scientific approach to power rationing was developed [13].

5.5 Training of employee

Empowerment of employees is a common concept in virtually all organizations. Such empowerment leads to effective, innovative and transformation needed in enhancing global market with burst changes in technology. One of the ways employees can be empowered is by training and re-training. Managers can empower employees through information sharing, provide structure to the organization, train people and canvass for team work instead of hierarchy; as this will raise the level of trust from the employee and create a sense of ownership. Training should be a continuous process, focused, planned and customized to suit a particular organization. In establishing total quality management at NIPRD, our training effort was aimed at an integrated approach to the instruction process. Training enables the employees to carry out his/

her current task with much smoothness and ease, increase capacity, knowledge and the competence to do work efficiently while saving extra time and resources. Our 24 months experience on this journey clearly shows that, to attain a state of total quality management, training of employees should not be taken likely; during the ISO 17025:2005 exercise in NIPRD, members of staff were trained and re-trained theoretically and practically on various scopes by the USP-PQM/USAID. This has not only empowered NIPRD employees but also developed them physically and mentally, enabling them to carry out any related task effectively and efficiently. Aside been ISO 17025 certified, this training has enabled NIPRD attain a state of total quality management. Training and re-training is a form of reward and recognition of the employee. It makes the employee feel meaningful and satisfied because he/she is being appreciated. Loss of brain and intelligence would be reduced. This will help the organization carry out proper succession planning to fill the important post within the company instead of hiring new employee and training them on each and every aspect of the organization [14, 15].

5.6 Control of the monitoring and measuring resources

Calibration is comparing the readings between a measuring instrument or system to an applicable unit of some defined system of measurement. It is an age long process. Calibration is done using a documented, validated and controlled method for making the comparison. Calibration and re-calibration are very essential for any equipment to function properly. It is a way of maintaining equipment. It is repeated at regular intervals to give progressive assurance that the functionality of the instrument is suitable for use. A calibrated procedure indicates a need for adjustment or repair, and always repeated to verify the proper measurement relationship. In a resource starved country like Nigeria, it is a very expensive process because only few organizations are internationally certified to conduct calibration of equipment. All calibrated equipment should be traceable to SI unit. A validated and reproducible result will only be achieved with equipment that its calibration is up to date. The totality of total quality management is customer satisfaction and faulty equipment cannot produce a result that will satisfy a customer. The NIPRD ISO 17025 organogram has an Internal Maintenance Unit that were trained by PQM with funding from USAID on equipment maintenance and calibration, this has helped NIPRD to be ISO certified and also attain a state of total quality management. Importantly, reference must always be made to tests and verification of any observed or recorded error(s) in Calibration certificates and test reports, this is because, a calibration or test without the verification of the error is absolutely useless.

6. Conclusions

Every organization is set up to fill a need, solve actual problems and satisfy the needs of their customers. Our walk to this path of quality *via* total quality management was a tedious task but the support of the USAID/USP/PQM through training and provision of infrastructure has helped us attain this feat. The experience gathered from this project shows that, unlike developed countries, developing country laboratories may do well to collaborate in all areas of total quality management with a view to upgrading their institutions to international standards. In this respect, many laboratories could form cocktails towards accreditation in such a way that, each laboratory could be accredited in specific scopes instead of one laboratory struggling to have accreditation in more than one or more scope.

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Conflict of interest

No conflict of interest declared.

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Section 2

Quality Control

Chapter 3

Sample Traceability in Toxicology

Laura Börgel Aguilera and Melissa Schulthess

Abstract

Sampling is an instrument that allows having a portion that represents a whole, and, quantitatively, it allows to measure a specific analyte or several analytes, for diagnostic, clinical, and forensic exposure or control over time, based in a pre-established and validated study plan. In clinical and forensic samples from one individual, the toxicokinetic and toxicodynamic factors should be considered in order to choose the most adequate matrix to study. In case of deceased individuals, additional matrices should be considered to the usual matrix. Sampling should be representative as for quality and quantity and should be associated to a chain of custody. Transport, storage, and analysis of samples are related to the type of matrix and the analyte to identify/measure. All samples should be traceable in any stage of the analysis and should receive an internal codification on entry. Also, the analytical method should be validated and associated to a traceable quality management system. Lastly, biosafety should consider the international recommendations for classification of mixtures and the residue management, in order to ensure the operativity of the technical working group.

Keywords: traceability, custody chain, experimental samples, clinical samples, forensic samples

1. Introduction

Sampling is an instrument that allows having a portion that represents a whole, and, quantitatively, it allows to measure a specific analyte or several analytes, for diagnostic, clinical, and forensic exposure or control over time, based in a pre-established and validated study plan.

According to the different standards, guidelines, or criteria, national and international or statistical criteria, the size of the samples will be defined. This applies specifically to studies of pharmaceutical drugs, pesticides, or productive procedures, and it also applies to clinical studies, experimental toxicology and ecotoxicology.

On the other hand, in clinical and forensic samples from one individual, toxicokinetic and toxicodynamic factors should be considered in order to choose the most adequate matrix to study.

2. Considerations

All sampling process must consider aspects related to the sampling, such as identity; name; ID or DNI, if applicable; court order; or customer's request. On the other hand, it's important to consider the type of container and specific requirements, such as moment or time of sampling. This is imperative for occupational

samples, where there is the need to assess the concentrations after a period of exposure. This also applies for the monitoring of drugs, where the time between sampling and ingestion will be important. This is relevant in cases of drugs at the workplace that may be sampled after a work accident or surprisingly as part of the company's alcohol and drug policy. The time lapse between the exposition and the sampling is also important in cases of post-environmental exposure when investigating a source of emission of a particular pollutant or part of it or in case of a drug or toxicokinetic study in which these parameters are being studied in order to achieve conclusions.

In addition to the above, it's also a necessity to specify the type of sample (nature), i.e., blood, urine, hair, gastric content, or other matrices. The latter type of sample is relevant in the forensic toxicology field, because it does not only include biological samples, but environmental, event site and clothes related to the case.

For this purpose, there must be an instrument that allows to submit the relevant information of the sampling (auditable record), with date, time, place, responsible of sampling and with its corresponding identification, circumstances or sampling objective (analyte), type of sample, quality of acceptability of this, both in quantity and added preservatives, and also rejection criteria. The person in charge of the packaging and transportation must be consigned. It's also important to register if the sample complies with the temperature conditions to proceed to quantify a certain parameter in it or, in the case of forensic samples, if the corresponding chain of custody is accompanied.

When entering the analytical area, a unique number or code of correlative sample income will be assigned. This code will be the new identity of the sample.

3. Sample selection

The choice of the sample depends on various factors to consider:

- Emergency patient in critical condition
- Monitoring of neurological, psychiatric, and chemotherapeutic treatment and dose readjustment
- Toxicokinetic and toxicodynamic factors of the agent
- Studies of environmental contaminants in work spaces and open spaces
- Quality control of productive processes of drugs, pesticides, and in general any industrial process
- Forensic studies of both the victim and the site of the event and its findings
- Laboratory equipment and validated analytical methods

There are several sources to determine quality and type of sample, where those based on validation processes stand out both in the United States and in Europe. In this context, the European Union created in 1993 the European Center for the Validation of Alternative Methods (ECVAM). This center labors it to coordinate the activities carried out in its territory and to cooperate with organizations in the United States such as the Johns Hopkins University Center for Alternatives to

Animal Testing (CAAT) (an academic institution) or the Interagency Coordination Committee for the Validation of Alternative Methods (ICCVAM). The latter is composed of representatives of the National Institutes of Health, the Environment Protection Agency (EPA), the Food and Drug Administration (FDA), and the Consumer Products Safety Commission [1].

Based on the National Institute for Safety and Hygiene and Work from Spain (INSHT) review, the following aspects should be considered for the selection of the most representative sample in the case of toxic substances [1].

3.1 Urine

The renal excretion of a toxin by urine depends on the partition coefficient of Nernst, the dissociation constant, the pH of the urine, the size and shape of the molecules, and the speed metabolic transformation in more hydrophilic metabolites and also depends on the functional capacity of the kidney.

The kinetics of the renal excretion of a toxic or its metabolite can be expressed in a curve of two, three, or four phases, depending on the distribution of the substance in the various body compartments, which present different rates of exchange with the blood.

Given the above, as an example, in the case of cocaine, it's possible to find during the first hours after single consumption only cocaine. Only after 12–24 h, its metabolite benzoylecgonine can be found, and it has a half-life in urine of approximately 72 h.

3.2 Saliva

Some drugs and metal ions can be excreted in the saliva through the mucosa of the mouth. Some examples are lead ("lead line"), mercury, arsenic, and copper, as well as bromides, iodides, ethyl alcohol, alkaloids, etc.

After its excretion through saliva, these toxins can be swallowed and reach the gastrointestinal tract, where they can be reabsorbed or eliminated in the stool.

3.3 Sweat

This applies for substances as ethyl alcohol, acetone, phenols, carbon disulfide, and chlorinated hydrocarbons.

3.4 Milk

Numerous metals, organic solvents, some organochlorine pesticides (i.e., DDT), and other persistent organic compounds (POPS) are secreted through the mammary gland in breast milk. This route is of great importance for the evaluation of risk by chronic exposure to these compounds, which can be dangerous for nursing infants.

3.5 Hair

Hair analysis can be used as an indicator of the homeostasis of some physiological substances. Exposure to some toxins, especially heavy metals and drugs of abuse, can also be assessed by this type of bioassay. In case of exposures to highly toxic concentrations of drugs, such as salicylic acids, these doses may be detected exceptionally in hair.

3.6 Other samples

The elimination of toxins from the body can be increased by using methods such as chelation tests with chelators of the type edetate monocalcium (Ca-EDTA), dimercaprol (BAL), aurintricarboxylic acid (ATA), dimercaptosuccinic acid (DMSA), or penicillamine. This method is indicated only in people under strict medical supervision. These compounds are usually administered, as a therapeutic measure, in order to remove heavy metals from the body of exposed workers. This method is also used to evaluate the total body burden and the level of a previous exposure mainly in the workplace due to chronic exposure.

The determination of toxins and metabolites present in the blood, exhaled air, urine, sweat, feces, and hair is a method increasingly used to evaluate human exposure (exposure tests) and/or the degree of intoxication. This is the reason that biological exposure limits (maximum permissible concentration (MAC) values and biological exposure indices (BEI)) have been recently established. Through these bioassays, it's possible to find the "internal exposure" of the organism, i.e., its exposure total in both the professional and general environment, and due to all entry routes. These are also referred to as "biomarkers" in "toxicology test methods."

3.7 Classic samples

In cases of patient care in emergency services, the samples of choice for toxicological studies will be blood, urine, or gastric content par excellence. One of the objectives of the care in the emergency services is to differentiate those serious processes that require immediate hospital treatment of other milder ones that can be studied or treated on an outpatient basis. The samples obtained in the emergency room are used for the diagnosis and determination of the treatment that is going to be undertaken there or to refer the patient to another service or to another institution. The decision of which analyte or analytes should be investigated depends on the physical examination and the complete clinical history, considering the patient's work history, environment, and habits. From this correlation, differential diagnoses may be proposed. All of them require confirmation or discarding, by means of specific tests. This decision is based on the toxicodynamics of the chemical substances in such a way that a series of symptoms and signs (effects) compatible with a limited number of agents can be counted. In this way, the exams must be ordered in a logical and rational manner according to the individual conditions of each patient. This achieves a reduction in the costs of medical care and increases the efficiency and effectiveness of the emergency service.

In patients who must initiate vital support measures, it is important to contemplate that the indicated therapeutic measures [2] can modify the results of the biomarkers. Therefore, it's important to proceed to the taking of samples before the beginning of these measures. As an example, if the diagnosis of carbon monoxide poisoning is being considered, the ideal is that this sample is taken before the administration of oxygen if it can be delayed for a short period. In case the treatment is initiated before sampling, due to the seriousness of the case, it should be considered that there will be interference in the results of carboxyhemoglobin. Similar situation will be in the case of the use of activated carbon in drugs with enterohepatic recirculation. In these cases, the concentrations in plasma or blood may be lower than expected by the action of activated charcoal (reduces the half-lives of drugs such as benzodiazepines, psychopharmaceuticals, oral hypoglycemic agents, and NSAI in general).

In addition, there are aspects of clinical urgency that must be pre-established in the sampling in critical patients, regarding the analyte and the characteristics that the sample collection itself must meet. These characteristics are sufficient quantity for analysis and confirmatory tests, preservative, type of syringe, venous or arterial sample, collection of urine or isolated sample, gastric content prior to the use of activated carbon and without preservatives, etc., in which the medical personnel must be acquainted.

3.8 Sampling material

It's important to have:

Order of use[a]	Type of tube/usual color[b]	Additive[c]	Mode of action	Application
1	Blood culture bottle (yellow-black striped tubes)	Broth mixture	Preserves viability of microorganisms	Microbiology—aerobes, anaerobes, fungi
2	Nonadditive tube			
3	Coagulation tube[d] (light blue top)	Sodium citrate	Forms calcium salts to remove calcium	Coagulation tests (protime and prothrombin time), requires full draw
4	Clot activator (red top)	Clot activator	Blood clots, and the serum is separated by centrifugation	Chemistry, immunology, and serology, blood bank (cross-match)
5	Serum separator tube (red-gray tiger top or gold)	None	Contains a gel at the bottom to separate blood from serum on centrifugation	Chemistry, immunology, and serology
6	Sodium heparin (dark green top)	Sodium heparin or lithium heparin	Inactivates thrombin and thromboplastin	For lithium level use sodium heparin, and for ammonia level use either
7	PST (light green top)	Lithium heparin anticoagulant and a gel separator	Anticoagulants with lithium, separates plasma with PST gel at the bottom of tube	Chemistries
8	EDTA (purple top)	EDTA	Forms calcium salts to remove calcium	Hematology, blood bank (cross-match) requires full draw
9	Blood tube (pale yellow top)	Acid citrate dextrose (ACD, ACDA, or ACDB)	Complement inactivation	HLA tissue typing, paternity testing, DNA studies
10	Oxalate/fluoride (light gray top)	Sodium fluoride and potassium oxalate	Antiglycolytic agent preserves glucose up to 5 days	Glucoses require full draw (may cause hemolysis if short draw)

ACD, acid citrate dextrose; DNA, deoxyribonucleic acid; EDTA, ethylenediaminetetraacetic acid; HLA, human leucocyte antigen; PST, plasma separating tube.
[a]"1" indicates draw first, and "10" draw last (if used).
[b]Verify with local laboratory in case local color codes differ.
[c]Gently invert tubes with additives to mix thoroughly; erroneous test results may be obtained when the blood is not thoroughly mixed with the additive.
[d]If a routine coagulation assay is the only test ordered, then a single light blue top tube may be drawn. If there is a concern about contamination by tissue fluids or thromboplastins, then a nonadditive tube can be drawn before the additive tube. The PST tube contains lithium and a gel separator; if used, draw in the order shown.

Table 1.
Recommended order of draw for plastic vacuum tubes [3].

- Blood sampling bottles/tubes of different types (anticoagulants) (**Table 1**)
- Sterile flasks with wide entry for urine collection samples and gastric content

With respect to the identification of the patient, this must be clearly stated on the label, as well as the time record, and responsible for taking the sample. This can be made by means of a simplified chain of custody (responsible for sampling, transfer, and reception in the laboratory). This is relevant in consideration of the potential legal medical aspects in cases of intoxication. It's also useful to have an additional form that consigns previous treatments to the sampling procedure and specific request of toxicological analysis.

Regarding the transport of these samples, they must be sent to the specialized laboratory with security seals that guarantee the inviolability of these and under the biosecurity norms. This means that samples must consider a primary container that corresponds to the tube or bottle, and a secondary container that corresponds to a sealed plastic bag, and polystyrene box with cooling unit.

The documentation must be complete and be presented folded outside the polystyrene box, in a sealed transparent bag, adhered to this box with tamper proof seals.

4. Laboratory

At the entrance of the samples to the toxicological laboratory, they must receive an internal coding, and caution must be maintained in the information of it. According to the type of analyte, the conditions of the sample must be verified, and the study plan established in accordance with the methodology to be used. These methodologies must be previously validated, and the procedures and instructions clearly established in the internal laboratory documents, all of them in accordance to GLP or ISO 17025. Also, it's important to have qualified and trained personnel. The results and their corresponding calculations must be registered for the review of the technical direction, approval, and issuance of the final report.

Likewise, there should be a storage system for samples and counter samples and a registry for the temperatures at which they will be maintained (5° for blood and 20° for urine and gas content). In case of other samples such as hair and nails, they do not require refrigeration [4]. These samples will be preserved for a minimum of 3 months. This is in order to support subsequent investigations of forensic type, or, in case that they are forensic samples, they must be kept, proceeding to a rigorous storage, until the specialized removal of these from the legal medical area, continuing the chain of custody initiated to the side of the patient.

The final report must contain the results, methodology used, reference values, and critical concentrations. The clinical area must be contacted, and the results communicated verbally and in writing media (email, cloud, or other previously established systems).

5. Standards for other samples

For other samples of experimental toxicological studies, the specific guidelines of the OECD should be followed according to the type of test to be developed, either studies in mammals or ecotoxicological experiments [5, 6].

For quality control samples of pharmacological or pesticide production, it's important to verify FDA, FAO, and DIN norms or the corresponding country's

standard body. The batch and date of manufacture should also be considered. In these samples, it's important to consider the number of the sample and which will be considered the control samples, that is to say, to define the universe according to these data of statistical probability. In an EPA document from 2002, there is an example of chlorpyrifos in apples (**Figure 1**) [5].

Similar situation should be considered in the sampling in the work environment, regarding the guides and sampling rules, where the sampling point, previous calibration of equipment, and analytical method to be used with the person responsible for the sampling itself should be consigned.

With regard to population sampling when possible environmental toxicology situations are investigated, a representative number of the sampling and control samples, based on epidemiological and biostatistical data, must be established (**Table 2**) [6].

For forensic samples, it must be specified if they correspond to samples from living individuals or corpses. In the case of living, blood, plasma, serum, urine, gastric content, hair, or nails will be useful **(Table 3)** [2].

For recent cadavers in which there are various organs for sampling as well as fluids, this will be available, blood, urine, and gastric content, in addition to samples of various viscera such as the brain, liver, kidney, lung, and spleen, among others, and also nails and hair and samples of bone marrow and bone [2].

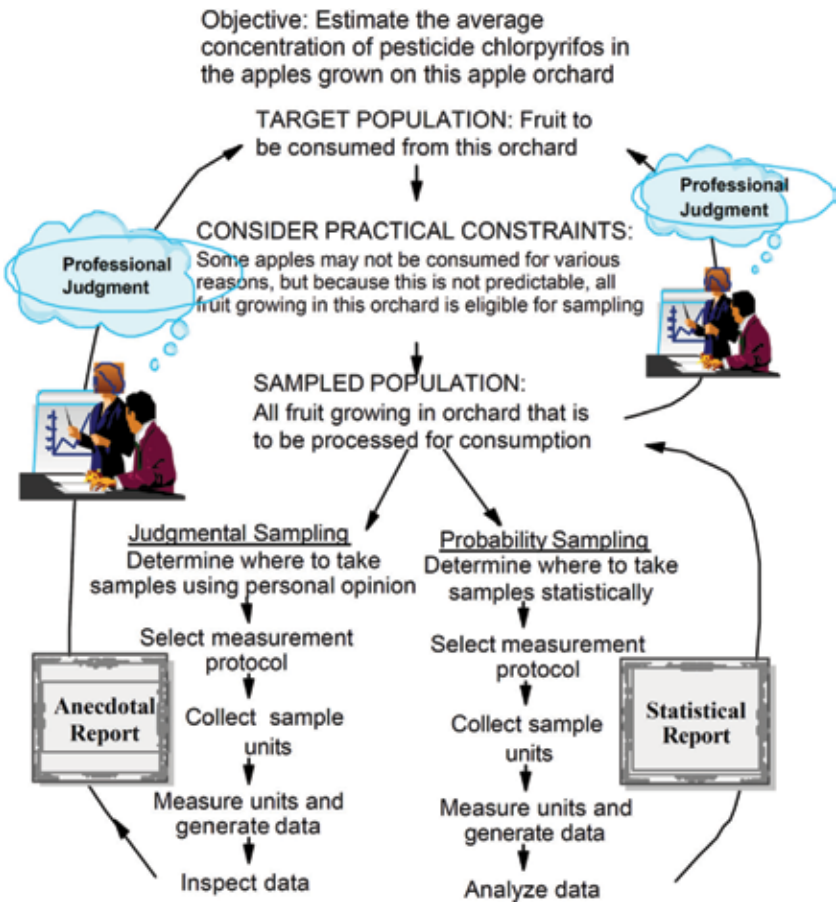


Figure 1.
Inferences drawn from judgmental versus probabilistic sampling designs [5].

Sampling design/protocol	Chapter	Use
Judgmental	4	Common
Simple random	5	Common
Stratified	6	Common
Systematic and grid	7	Common
Ranked set	8	Innovative
Adaptive cluster	9	Innovative
Composite	10, 11	Common

Table 2.
Sampling designs presented in this guidance [5].

For corpses that come from exhumation or skeletons, the soft tissues may no longer be available, but there can be cadaveric fauna or the remains of dusty material inside the urn or at the site immediately to the discovery, which are also the subject of the study. In these cases, bone samples, the area of growth cartilage in children by its vascularization, and bone marrow are very important, in addition to the hair and nails [2].

5.1 Chain of custody

The chain of custody is intended to safeguard the representativeness of a sample, as mentioned in the importance of this custody from the clinical area. This also applies to any analytical process in which the traceability of the samples and their corresponding backups must be maintained. All of them are subject to quality control, such as samples in which environmental contaminants are studied, where georeferencing data with their respective matrices and characteristics of the site must be added to the chain of custody [7]. A similar situation must be considered for forensic samples, in both open and closed spaces, in which the planimetrics and photographic records of the site of the event are added.

An example of a chain of custody is the following (**Figure 2**).

5.2 Traceability

It extends beyond the chain of custody and is related to the quality of the study and its representativeness regarding the validity of the results. This is an extremely important point in the toxicology laboratories. This is related to the existence of more than one analytical method for confirmation and that there are dedicated laboratories focused to these topics. They consider GLP in accordance to OECD Guidelines and ISO 17025 Standards as part of their work, all of this associated with continuous improvement.

5.3 Study plan

The study plan should consider the following aspects, in addition to the aspects of the guides and standards mentioned [6] (**Figure 3**):

- Selection of analytical suppliers
- Certified standards and technical standards

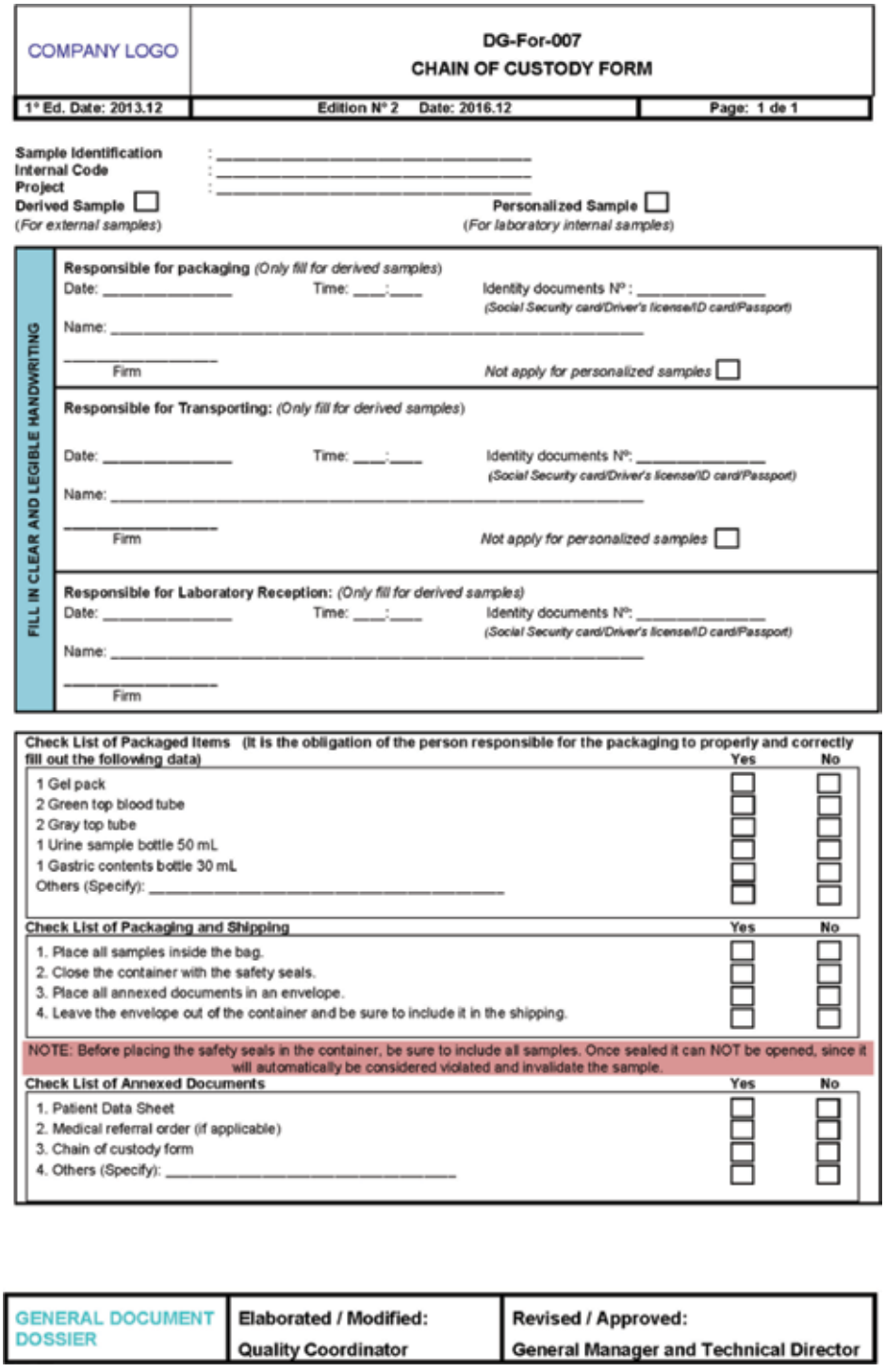
Sample type	Preservation	Justification to conduct study	Sampling method	Packaging and storage
Blood	Use at least 1.5% sodium fluoride and potassium oxalate or EDTA	Drug analysis and/or alcoholemia in incidents with no more than 3 days (72 h) since its occurrence	7.5 mL in a 10 mL vial or two tubes with 5 mL each It's preferably that vials are no more than ¾ full In case of volatile analysis (solvent abuse or solvent inhalation), these samples must be frozen within the first hour and must be kept frozen during transit	Tubes should be kept inside sealed plastic containers and, then, put inside tamper-evident bags It's better to keep samples under refrigeration conditions, but, if not possible, samples can be frozen (only blood sample tubes that are no more than ¾ full and no more than 20 mL of urine) The samples can be kept up to 4 weeks in refrigeration, and longer times are considered for frozen samples All samples should be sent for analysis as soon as possible, considering that some analytes could be undetectable due to instability of the matrix In case of toilet tissue, it must be labeled and kept in a tamper-evident bag. It should be considered as a biological forensic sample alongside condoms/sanitary towels and not as a toxicology sample. This kind of material should be storage frozen
Urine sample	1.5% sodium fluoride	Drug analysis and/or alcohol in incidents with no more than 5 days (120 h) since its occurrence This kind of sample is also necessary in cases of suspected drug-facilitated crime in the preceding 14 days It can be complemented with hair samples, which must be submitted to the laboratory as the first analysis matrix Urine samples can be stored for future analysis, if needed, as in the case of the detection of relevant drugs in hair	It's recommended that two urine samples are taken if the incident happened in no more than 24 h In case of incidents with more than 24 h, only one sample is enough The first sample should be obtained as soon as possible after the incident, and the second sample can be taken during the next urination after the first sample. It's preferably that this second sample is taken within an hour after the first urine sample, but it can also be taken whenever it's not within this hour Ideally, 20 mL of urine must be decanted in a tube of at least 25 mL (fill up to ¾ full) Both samples can be taken prior to full medical examination Only the defendant needs witness when the sample is taken When the sample is obtained, if the individual uses toilet tissue (sometimes provided in sample taking kits), to wipe afterward, this material should also be kept as part of the evaluation	

Sample type	Preservation	Justification to conduct study	Sampling method	Packaging and storage
Hair normally: it's hair from the head, but it can be obtained from other parts of the body if needed	No specific method applies	In cases of incidents up to 6 months prior to examination, in consideration that drugs may have been eliminated through urine in times no longer than 3 weeks If in doubt of the use of this kind of sample, it's important to contact the laboratory for advice	There exist some kits which include specific instructions, or it's possible to ask for advice to the specialist in the laboratory This sample should be taken after a minimum of 4–6 weeks after the date of interest The individual should be instructed not to cut or chemically treat (dye, bleach, or perm) their hair during the intervening period In drug abuse cases, it's a wide spread of information that these interventions from the individual can tamper the results; therefore, in these cases, it's possible to take hair samples from other places of the body	Hair samples should be packaged as described in the specific hair testing kit or in sterile urine tubes The sample should be placed in a tamper-evident bag This matrix for toxicological analysis must not be frozen or refrigerated, in order to preserve it These samples must be stored in a dry environment at normal room temperature
Nail clippings	No specific method applies	Fingernail or toenail clippings can be used for drug analysis, as an alternative in cases of the absence or lack of head/body hair or as a complementary sample for head/body hair	There exist some kits which include specific instructions, or it's possible to ask for advice to the specialist in the laboratory This sample should be taken after a minimum of 4 weeks after the date of interest	This matrix should be enclosed in a suitable packaging (i.e., a specific type of packaging specified in testing kit or a folded clean paper secured with tape), and, then, this sample must be placed in a tamper-evident bag This kind of sample, for toxicology, must be stored with the same conditions as hair, namely, not frozen nor refrigerated, only dry and at room temperature

Table 3.
Toxicology [4].

- Calibration and maintenance of equipment
- Type of sampling and risk of cross contamination (Figure 4)
- Instructions and procedures (POS)
- Validation of methods and SANCO recommendations for validation dossier
- Limits of detection and limits of quantification of the method
- Repetitiveness
- Error estimation
- Interlaboratory rounds

- Biosecurity and sample management, based on the type of samples and type of tests. That is why it is very important in the management of GHS knowledge for the classification of mixtures of chemical substances in the different instructions (POPs) that are part of a study plan.



COMPANY LOGO	DG-For-007 CHAIN OF CUSTODY FORM	
1° Ed. Date: 2013.12	Edition N° 2 Date: 2016.12	Page: 1 de 1

Sample Identification : _____
Internal Code : _____
Project : _____
Derived Sample ☐ *(For external samples)*
Personalized Sample ☐ *(For laboratory internal samples)*

FILL IN CLEAR AND LEGIBLE HANDWRITING

Responsible for packaging *(Only fill for derived samples)*
Date: _____ Time: ___:___ Identity documents N°: _____
(Social Security card/Driver's license/ID card/Passport)
Name: _____
_____ Firm
Not apply for personalized samples ☐

Responsible for Transporting: *(Only fill for derived samples)*
Date: _____ Time: ___:___ Identity documents N°: _____
(Social Security card/Driver's license/ID card/Passport)
Name: _____
_____ Firm
Not apply for personalized samples ☐

Responsible for Laboratory Reception: *(Only fill for derived samples)*
Date: _____ Time: ___:___ Identity documents N°: _____
(Social Security card/Driver's license/ID card/Passport)
Name: _____
_____ Firm

Check List of Packaged Items (It is the obligation of the person responsible for the packaging to properly and correctly fill out the following data)

	Yes	No
1 Gel pack	☐	☐
2 Green top blood tube	☐	☐
2 Gray top tube	☐	☐
1 Urine sample bottle 50 mL	☐	☐
1 Gastric contents bottle 30 mL	☐	☐
Others (Specify): _____	☐	☐

Check List of Packaging and Shipping

	Yes	No
1. Place all samples inside the bag.	☐	☐
2. Close the container with the safety seals.	☐	☐
3. Place all annexed documents in an envelope.	☐	☐
4. Leave the envelope out of the container and be sure to include it in the shipping.	☐	☐

NOTE: Before placing the safety seals in the container, be sure to include all samples. Once sealed it can NOT be opened, since it will automatically be considered violated and invalidate the sample.

Check List of Annexed Documents

	Yes	No
1. Patient Data Sheet	☐	☐
2. Medical referral order (if applicable)	☐	☐
3. Chain of custody form	☐	☐
4. Others (Specify): _____	☐	☐

GENERAL DOCUMENT DOSSIER	Elaborated / Modified: Quality Coordinator	Revised / Approved: General Manager and Technical Director

Figure 2.
Chain of custody (elaborated by L. Börgel, 2016).

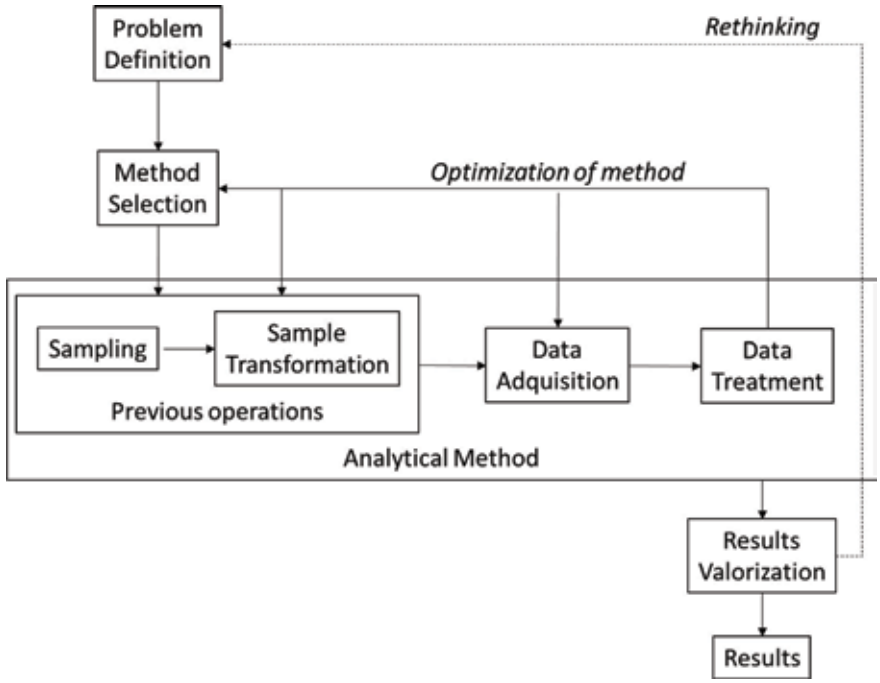


Figure 3.
Strategy for securing representativity of analytical results (elaborated by authors, 2018).

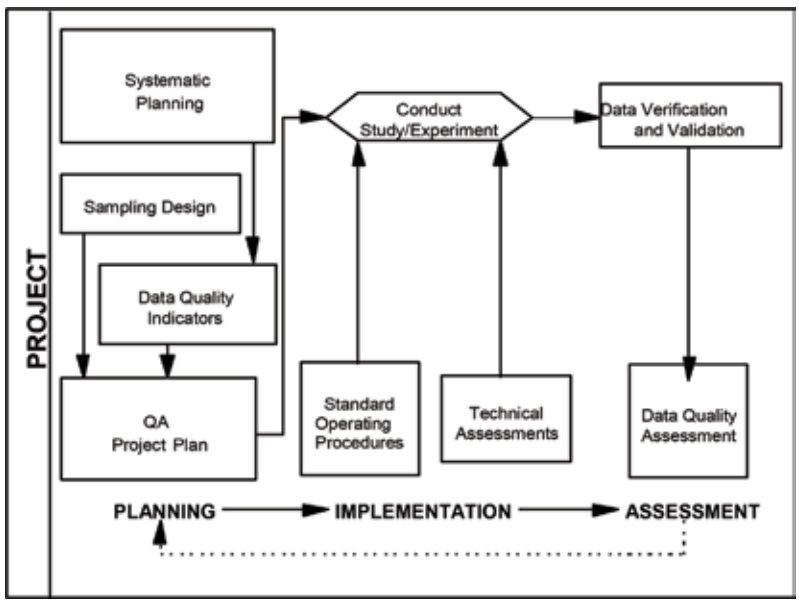


Figure 4.
Life cycle of data in the EPA quality system [6].

5.4 Classification in accordance to GHS for delusions in laboratory and decision to use personal protection systems

The application of the GHS criteria and the purple book are currently standardized instruments that allow classifying the mixtures or solutions to be used in the work instructions and also allow classifying the waste, pure reagents, and certified

or technical standards. This is in order to establish their dangerousness according to the different ways of entry to the body, to adjust the danger for each type of substance or mixture, and decide the correct use of safety systems [8].

5.5 Final disposition

Waste management in the laboratory is associated with quality work. The greater the control of the procedures and the better the compliance with instructions, the lower the load of residual materials to be generated in the laboratory. These must be classified as biological waste and others as chemical waste, and, in accordance with the regulations of each country, their final disposition must be fulfilled, with the respective labeling of the United Nations [5, 9].

6. Conclusions

Therefore, according to each sampling procedure, it's important to review the recommendations, guidelines, or standards that apply, and all of them should be established in the study plan.

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Conflict of interest

Both authors declare that there are no conflicts of interest.

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Chapter 4

Analytical Method Validation as the First Step in Drug Quality Control

Sigrid Mennickent and Marta de Diego

Abstract

The authors have developed and validated some chromatographic methods with the aim of quantifying drugs as drug substance and drug product, suitable for stability and quality control studies, as at original products as at its remainder doses. The stability of a pharmaceutical is defined by its resistance to different chemical, physical, and microbiological reactions that may change their original properties. The stability of a pharmaceutical product is closely related to its potency; therefore, whether the compounds are degraded, a decrease of the therapeutic effect or changes in their toxicological properties can be produced, affecting their efficacy and safety, which becomes important to maintain a stable pharmaceutical product and to have the analytical tools to demonstrate stability. Therefore, stability-indicating methods are required to the quality control of pharmaceuticals. Analytical methods presented here are useful stability-indicating methods to analyze drugs and have adequate linearity, precision, accuracy, selectivity, and LOD/LOQ values. The examples presented here are stability-indicating methods since they allow the determination of drugs in the presence of their degradation products, according to the International Conference on Harmonization (ICH) guidelines.

Keywords: drug stability, stress testing, method validation, stability-indicating methods, drugs

1. Introduction

1.1 Drug stability

Pharmaceutical stability is the capability of a dosage form included in a specific container to suffer minimum or no degradation during its transport, storage, and use. It can be influenced by intrinsic factors such as the chemical structure of the drug and environmental conditions, as temperature, humidity, oxygen, and light. Each ingredient, whether therapeutically active or pharmaceutically necessary (excipients), can affect the stability. The primary environmental factors that can reduce stability include exposure to adverse temperatures, light, humidity, oxygen, and carbon dioxide. Various types of reactions can cause chemical degradation of pharmaceuticals, which usually cause loss of active drug content and formation of degradation products. These reactions are hydrolysis, oxidation, photolysis, dehydration, isomerization, polymerization, decarboxylation, absorption of carbon

dioxide, and radiation-induced reactions. The most common reactions are hydrolysis and oxidation. Chemical degradation may result in a loss of potency or an increase in drug toxicity, so that the clinical use of a medicine must be unacceptable if the degradation is relatively great. When a drug dosage form is altered (by dissolution, pulverization, or addition to other materials) or the environment of the drug is modified by changes in storage conditions, the stability of a drug may be affected [1–4]. Stability is often expressed in quantitative terms as the shelf life, that is, the time from manufacture to the original potency or content of active constituent has been reduced by 10%. For most products, this 10% limit for chemical degradation is generally recognized as the minimum acceptable potency level [5].

Stability testing forms an important part of the process of drug development; its purpose is to provide evidence on how the quality of drug substance or drug product varies with time under the influence of a variety of environmental factors, such as humidity, temperature, and light, to establish a retest period for the drug substance or a shelf life for the drug product, and to recommended storage conditions. The studies are designed to include testing of attributes susceptible to change during storage and are likely to influence quality, safety, and efficacy.

Testing primarily covers physical, chemical, and microbiological attributes:

- Physical: appearance, melting point, water content, clarity and color of solution, pH, dissolution and disintegration characteristics, viscosity, crystal modification, or particle size

- Chemical: assay, degradation products, related substances, and residual solvents

- Microbial: growth in microorganisms and efficiency of preservative contents such as antioxidants and antimicrobial preservatives

Stability studies on active substances and manufactured dosage forms are conducted by means of accelerated, long-term studies and stress testing. Accelerated and long-term tests are developed at specific temperatures and relative humidity representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned. The aim of these studies is to determine the shelf life of the product. Stress studies are conducted to elucidate the intrinsic stability of the drug substance and are normally carried out under more severe conditions than those used for accelerated testing. Stress testing is the main tool that is used to predict stability problems, with the aim to anticipate the behavior of the drug substance when using it as a drug product [6, 7]. From the results of stress testing, useful information can be obtained for the manufacturing process, packaging development, and appropriate storage conditions of the products in order to avoid degradation [7]. The chemical stability is evaluated by testing the quantity of drug at different times during the storage [2, 3].

1.2 Pharmaceutical quality control/pharmaceutical assurance

The term drug quality control refers to the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical, as active ingredient and dosage forms. These procedures involve the identification of a pharmaceutical substance; potency, usually 90–110% of the labeled amount; uniformity of color; shape; size in dosage forms; bioavailability; and stability, in concordance with the requirements of pharmacopoeial monographs (International Pharmacopeia,

European Pharmacopeia, US Pharmacopeia, British Pharmacopeia, National Pharmacopeia), and it was carried out in quality control laboratories [8, 9].

Quality control (QC) is an essential operation of the pharmaceutical industry to guarantee a safe and effective product. QC measurements include stability testing of the drug formulation, dissolution testing, and analysis of raw material products majorly.

QC is the term usually employed; however, there are two terms about drug or pharmaceutical quality control:

1.2.1 Pharmaceutical quality assurance (QA)

Quality assurance involves the development and implementation of a system that ensures that the pharmaceutical is safe; effective, with standard quality; and acceptable to the patient. It is achieved with systematic activities implemented in a quality system to ensure that the requirements for product development are fulfilled and involve appropriate storage, distribution, monitoring and use by prescribers, dispensers and consumers.

1.2.2 Pharmaceutical quality control (QC)

All of activities are required to control the processes associated with the product manufacture and evaluation of product quality at various steps from raw materials to the final packaged product that reaches the consumer.

In this way, good manufacturing practices (GMPs) are part of the quality assurance activities that ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use and required by the drug regulatory authorities, for example, personnel, facilities, packaging, and quality control.

Assuring quality involves some aspects, as:

- Active ingredients are safe and efficient
- Providers have acceptable quality standards
- Active ingredients and pharmaceutical in dosage forms are monitored to meet quality standards
- Pharmaceutical packaging is optimal and protects from degradation
- Storage conditions of pharmaceutical are optimal
- Transportation conditions are adequate
- Product quality concerns are reported and monitored

Low quality medicines can produce a decrease of their therapeutic effect or changes in their toxicological properties, which can cause a prolongation of illness and even death, and an increase in health costs.

1.3 Stability testing for drug substances and drug products (pharmaceuticals)

Stability testing predicts behavior of a drug or pharmaceutical with any physical, chemical, or microbiological changes, with the aim to assess their security and efficacy and to establish their shelf life and optimal storage conditions [10–21].

1.4 Stress testing (forced degradation studies)

Stress testing is an important part of drug development process because it can help to establish the degradation pathways and the intrinsic stability of the molecule and help to develop stability-indicating methods. Stress testing helps to anticipate the behavior of drug substance and drug products and their mechanisms (hydrolysis, oxidation, thermolysis, or photolysis) and identify the degradation products, including their chemical structure. These studies are a regulatory requirement and scientific necessity during drug development, with the aim to generate more stable formulations. Stress testing includes the effect of temperatures and other appropriate conditions such as humidity, light exposition, and others. Because it is faster and less expensive than conducting longer-term storage tests, the technique is used for rapid selection and elimination tests. The samples generated from forced degradation can be used to develop the stability-indicating method that can be applied later for the analysis of samples generated from accelerated and long-term stability studies [1–4, 22].

The nature of the stress testing depends on the individual drug substance and the type of pharmaceutical product involved. Stress testing is likely to be carried out on a single batch of the active pharmaceutical ingredient. Generally, the goal of stress testing is to facilitate an approximate 5–20% degradation of the sample under any given condition, so as to avoid any secondary reactions. It should include the effect of temperature, above that for accelerated testing (in 10°C increments, e.g., 50°C, 60°C, etc.), humidity (75% RH or greater), oxidation, photolysis, and the susceptibility to hydrolysis on the active pharmaceutical ingredient (API) [7, 23].

Stress testing is likely to be carried out on a single batch of the active pharmaceutical ingredient. It should include the effect of temperature (in 10°C increments, e.g., 50°C, 60°C) above that for accelerated testing, humidity (25°C, 75% RH or greater) where appropriate, oxidation, and photolysis on the active pharmaceutical ingredient (API). The testing must also evaluate the susceptibility of API to hydrolysis and its photostability. Significant change for a drug substance is defined as failure to meet its specification [24].

2. Analytical method validation as the first step in drug quality control

To evaluate the stability of drug substances or drug product, qualitative and quantitative methods should be used, to allow evaluate the physical, chemical, biological and microbiological stability.

In relation to chemical stability, the assay methods chosen should be those indicative of stability. These methods will resolve all degradation products from the parent compounds and ideally from each other, so that the active compound content can be accurately measured without interference from degradation products [7]. The most used analytical method in drug quality control is still high-performance liquid chromatography (HPLC) coupled with UV or fluorescence detection. Other useful methods are LC coupled with mass spectrometry (MS) or with diode array (LC/DAD), refractive index (RI), electrochemical, light-scattering detection, size exclusion chromatography (SEC), UPLC, capillary electrophoresis (CE), and gas chromatography (GC). High-performance thin-layer chromatography (HPTLC) has the advantages of its fastness, solvent economy, and high throughput of samples. Chromatography of samples simultaneously with standards is another advantage, allowing to run up to 60 spots simultaneously. Sensitivity of HPTLC is normally in the range of nanograms in absorbance and picograms in fluorescence mode (www.europeanpharmaceuticalreview.com.Access: 30-10-2018; [25]).

2.1 Importance of analytical method validation used in drug quality control

Analytical method validation is an integral part of any good analytical practice. The results from a method validation procedure can be used to judge the quality, reliability, and consistency of analytical results. Analytical methods should be validated or verified, and the accuracy as well as the precision (standard deviations), limit of detection (LOD) and limit of quantification (LOQ), sensitivity, linearity, and applicability should be recorded. The tests for related compounds or products of decomposition should be validated to demonstrate that they are specific to the product being examined and are of adequate sensitivity. Validated analytical methods play a major role in achieving the quality and safety of the final product especially in the pharmaceutical industry [26]. Among the FDA, some other useful protocols can be addressed by the International Council on Harmonization (ICH), current good manufacturing practice (CGMP), US Pharmacopeia (USP), Turkish Pharmacopeia, European Medicines Agency (EMA), International Organization for Standardization (ISO), Association of Analytical Chemists (AOAC), and the American Public Health Association [3, 6, 24, 26, 27–31].

2.2 Some stability-indicating methods developed and validated by authors

The authors have developed and validated some chromatographic methods suitable for quality control studies of bulk drugs and drugs in dosage forms.

2.3 Chemical stability of haloperidol injection by high-performance thin-layer chromatography

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor. Enalapril (**Figure 1**) is a prodrug and has little pharmacological activity until hydrolyzed in the liver to enalaprilat (**Figure 2**). Enalapril is the ethyl ester of enalaprilat [1, 4, 32–35].

Enalapril is used alone or in combination with other classes of antihypertensive agents for the management of hypertension. It is reported that enalapril drug substance or pharmaceutical preparation degrades to two major degradation products, enalaprilat and diketopiperazine (DKP) derivative, under different storage conditions, resulting in drug loss and potency reduction [1, 4, 32–35].

A stability-indicating high-performance thin-layer chromatographic (HPTLC) method was developed and validated by the authors, with the aim of determination of enalapril maleate in tablets.

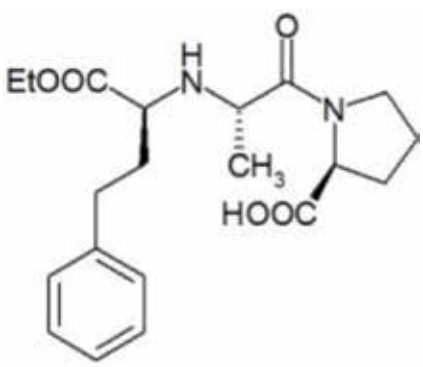

Figure 1.
Chemical structure of enalapril.

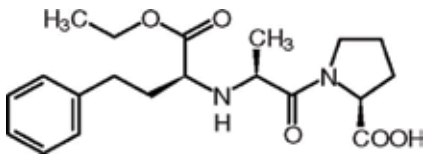

Figure 2.
Chemical structure of enalaprilat.

Chromatographic separation was achieved on precoated silica gel F 254 HPTLC plates using a mixture of 1-butanol, glacial acetic acid, and water (12:3:5, v/v) as a mobile phase. Quantitative analysis was carried out at a wavelength of 207 nm. The method exhibited an adequate linearity with a correlation coefficient of 0.998, over the concentrations range of 200 to 1200 ng/μL (200 to 1200 ng/ band). Limit of detection (LOD) was 23.78 ng/ band, and limit of quantification (LOQ) was 72.01 ng/band. The method exhibited a good precision, with an intra-assay variation between 1.14 and 1.43% and an inter-assay variation between 1.27 and 3.67%; an adequate accuracy, good selectivity (Rf was 0.52 for enalaprilat, 0.62 for enalapril, and 0.82 for diketopiperazine (DKP) , a degradation product. Also, the selectivity between enalapril and hydrochlorothiazide, the more common compounds in the commercial mixtures of enalapril, was studied. The Rf was 0.52 for enalaprilat, 0.62 for enalapril, and 0.83 for hydrochlorothiazide (**Figures 3** and **4**) [36].

Stability-indicating capability of the HPTLC assay was studied by forced decomposition of 5 mL of a solution of enalapril 1 mg/mL, with 10 mL of 0.1 N hydrochloric acid, 10 mL of 0.1 N sodium hydroxide, and 10 mL of 3% H_2O_2. The mixtures

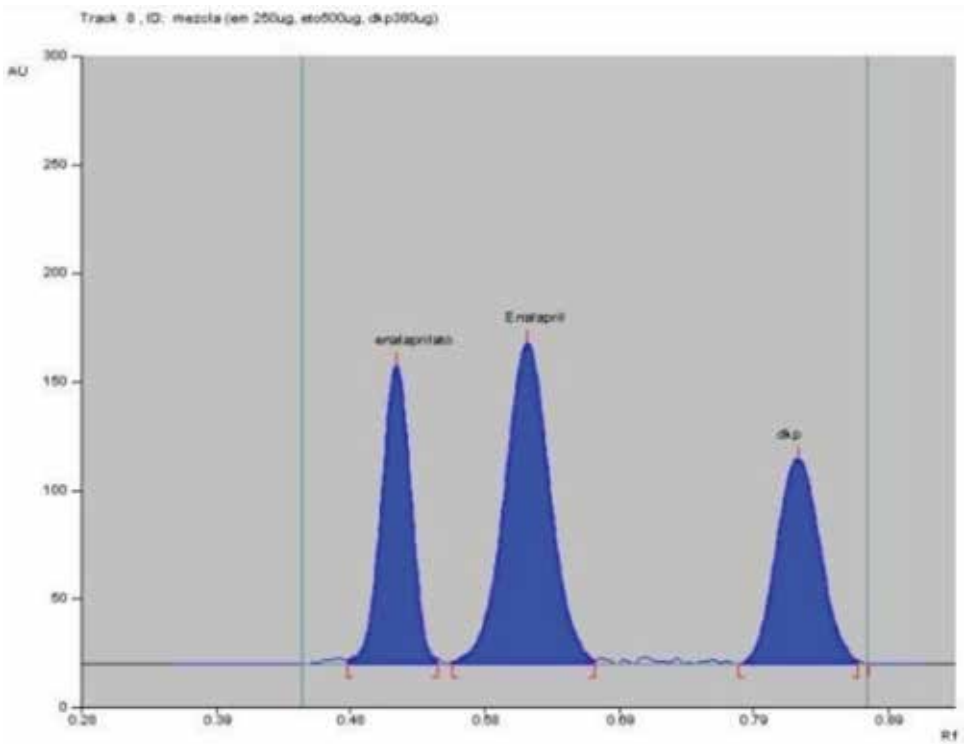

Figure 3.
Selectivity of the method. A study with enalapril, enalaprilat, and DKP. Peak observed: enalaprilat, enalapril, and DKP. Rf, retarding factor; AU, absorbance unit.

with NaOH and with HCl were heated on hot plates at 60°C for 60 min. The mixture with H_2O_2 was stored at room temperature (25°C) for 60 min. Then, each mixture was diluted with ethanol to 100 ng/μL and analyzed. Also, stability-indicating capability of the assay was proven by conducting forced degradation conditions of UV and VIS radiation on enalapril standard, as solution of 100 ng/μL. Degradation was found significantly in basic stress condition only, during the time of the study. The degradation products for enalapril mentioned in the literature are enalaprilat and DKP [34, 36]. The degradation product was well resolved from the main peak, proving the stability-indicating power of the method (**Figure 5**) [37].

2.4 Validated instrumental planar chromatographic method for quantification of fluphenazine hydrochloride in injections

Fluphenazine (**Figure 6**) is a phenothiazine antipsychotic agent. The drug is a propylpiperazine derivative of phenothiazine and is structurally similar to perphenazine but differs from perphenazine in the substitution of a trifluoromethyl group for chlorine at the two positions of the phenothiazine nucleus.

Drug therapy with fluphenazine is integral for the management of acute psychotic episodes with violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes.

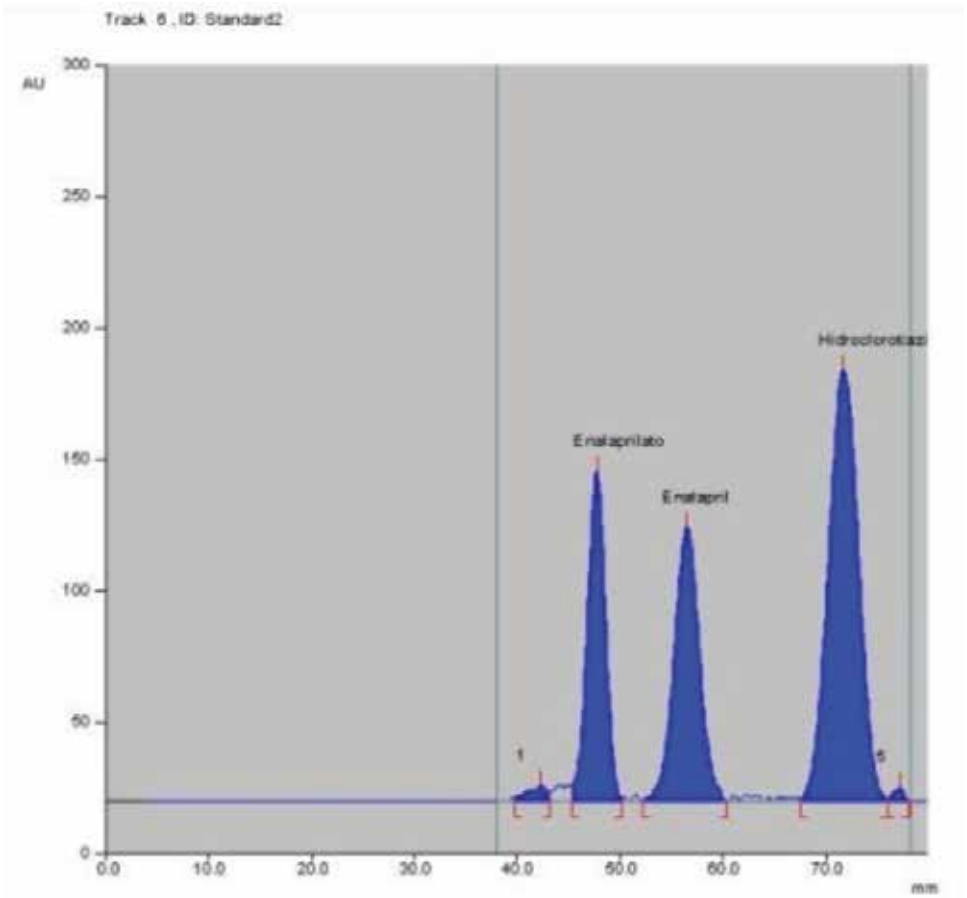

Figure 4.
Selectivity of the method. A study with enalapril, enalaprilat, and hydrochlorothiazide. Peak observed: enalaprilat, enalapril, and hydrochlorothiazide. Rf, retarding factor; AU, absorbance unit.

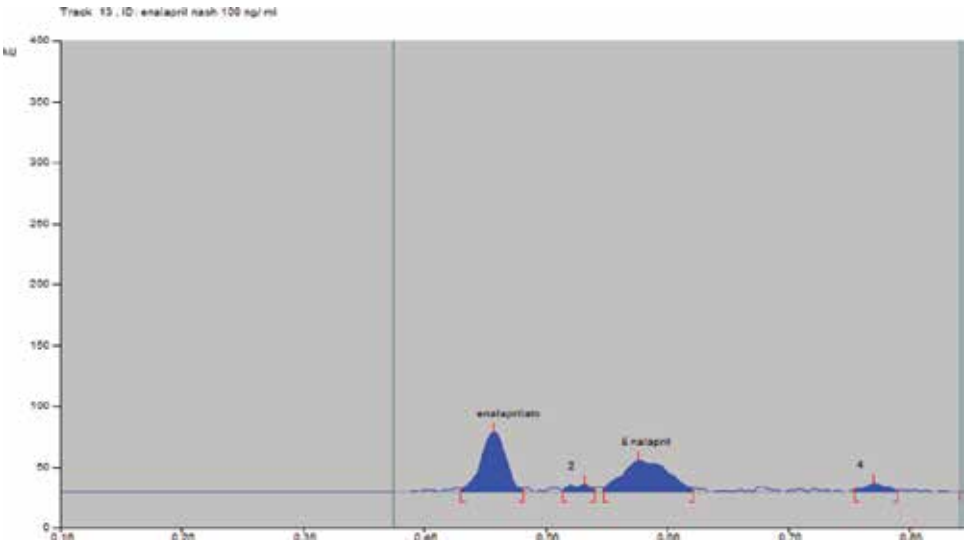

Figure 5.
A study at forced degradation of enalapril with 0.1 N NaOH. Peak no. 1, enalaprilat; peak no. 2, enalapril; and peak no. 3, DKP. Axis X: retarding factor (Rf). Axis Y: absorbance unit (AU).

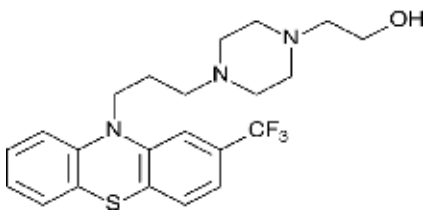

Figure 6.
Chemical structure of fluphenazine.

Other uses for fluphenazine are for the treatment of mania, bipolar disorder, severe anxiety, and behavioral disturbances. Fluphenazine is administered as the hydrochloride by mouth or intramuscular injection; longer-acting decanoate or enantate esters of fluphenazine are given by intramuscular or sometimes subcutaneous depot injection [32, 35, 43].

Fluphenazine hydrochloride, decanoate, and enantate are all sensitive to light. Therefore, it is very important to determine the quantity of fluphenazine in its dosage forms because in the presence of light, photolysis occurs rapidly, resulting in drug loss and potency reduction [2, 4, 32–35].

Chromatographic separation was done on precoated silica gel F 254 HPTLC plates. The mobile phase consisted of methanol/purified water (9:1, v/v). Densitometric analysis was carried out at 306 nm. The calibration curves were linear in the range of 100 ng/μL to 500 ng/band with a correlation coefficient of 0.998. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 1.45 ng and 4.40 ng, respectively. The intra-assay and inter-assay precisions, expressed as the relative standard deviation (RSD), were in the range of 0.73–1.77% and 1.18–1.86%, respectively. The recovery of fluphenazine hydrochloride was between 98.29 and 101.53%, with a RSD not higher than 1.87%. The method was selective for fluphenazine hydrochloride from the preservatives of the injections (Rf for fluphenazine hydrochloride was 0.33, whereas parabens run to the solvent front) (**Figures 7** and **8**) [38].

Drug content was found to be within the limits (95–110% of the labeled content of the formulations) of the prescribed value, when the method was applied to quantify fluphenazine hydrochloride in real pharmaceutical samples.

Stability-indicating capability of the HPTLC assay was studied by forced decomposition of 5 mL of a solution of fluphenazine 1 mg/mL, with 10 mL of 0.1 N hydrochloric acid, 10 mL of 0.1 N sodium hydroxide, and 10 mL of 3% H_2O_2. The mixtures with NaOH and with HCl were heated on hot plates at 60°C for 60 min. The mixture with H_2O_2 was stored at room temperature (25°C) for 60 min. Then, each mixture was diluted with ethanol to 100 ng/μL and analyzed.

Also, stability-indicating capability of the assay was proven by conducting forced degradation conditions of UV and VIS radiation on fluphenazine standard, as solution of 100 ng/μL.

One degradation product was found after treatment of fluphenazine with HCl, and two degradation products were found after treatment with NaOH. Rf for fluphenazine was 0.30, whereas Rf for degradation product with HCl was 0.01, and Rf for degradation products with NaOH were 0.03 and, 0.23 respectively (**Figure 9**). None degradation product was found with H_2O_2.

When the drug was exposed to force degradation with VIS radiation, another peak different from the peak of fluphenazine was found; therefore, it could be a degradation

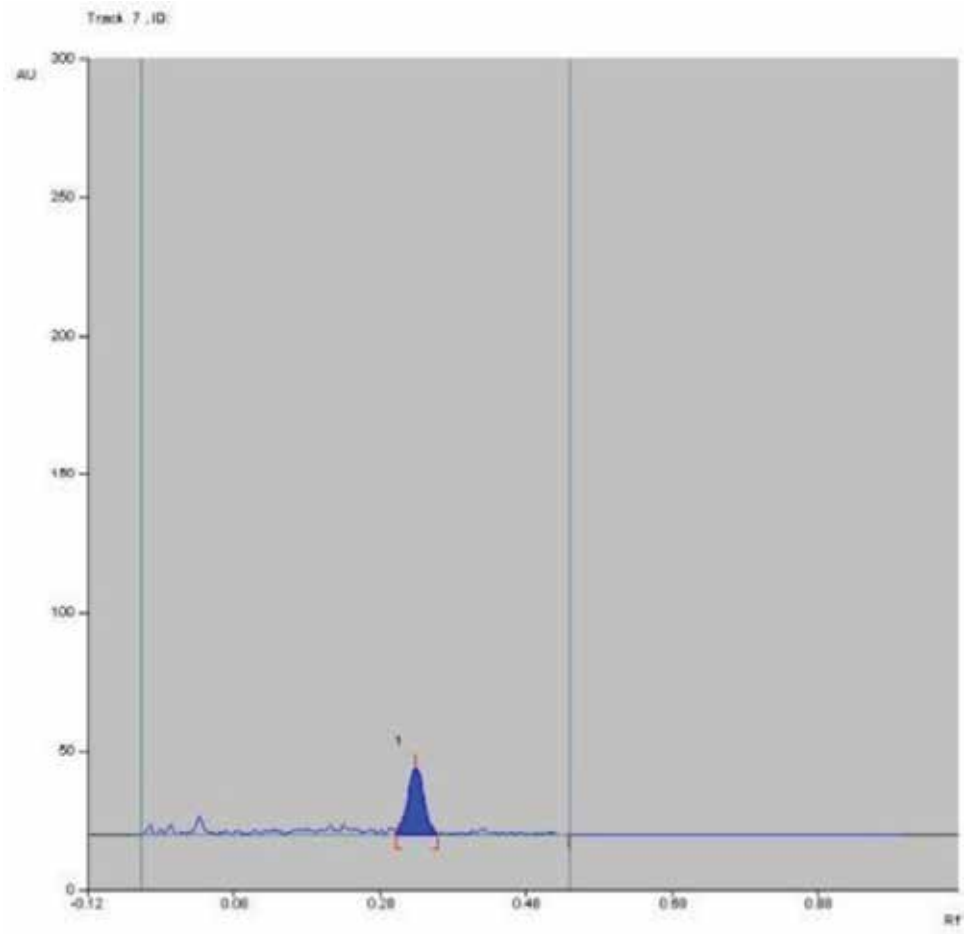

Figure 7.
Selectivity of the method. A study with parabens. Peak observed: fluphenazine. Rf, retarding factor; AU, absorbance unit.

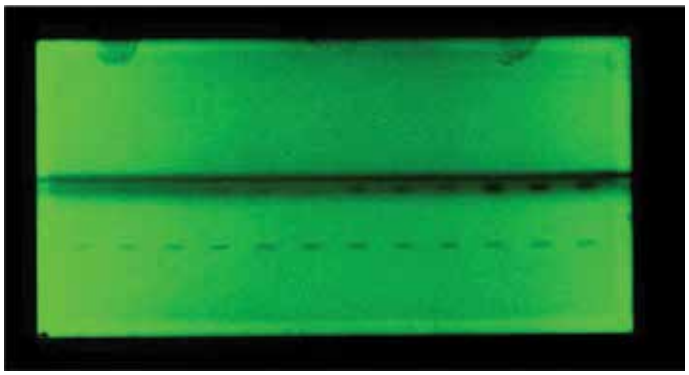

Figure 8.
Picture (video store, CAMAG) of plate at selectivity with parabens. Tracks 1–3, fluphenazine hydrochloride; tracks 4–6, fluphenazine hydrochloride + methylparaben; tracks 7–9, fluphenazine hydrochloride + propylparaben; and tracks 10–12, fluphenazine hydrochloride + methylparaben + propylparaben. Bands of parabens can be observed at the solvent front.

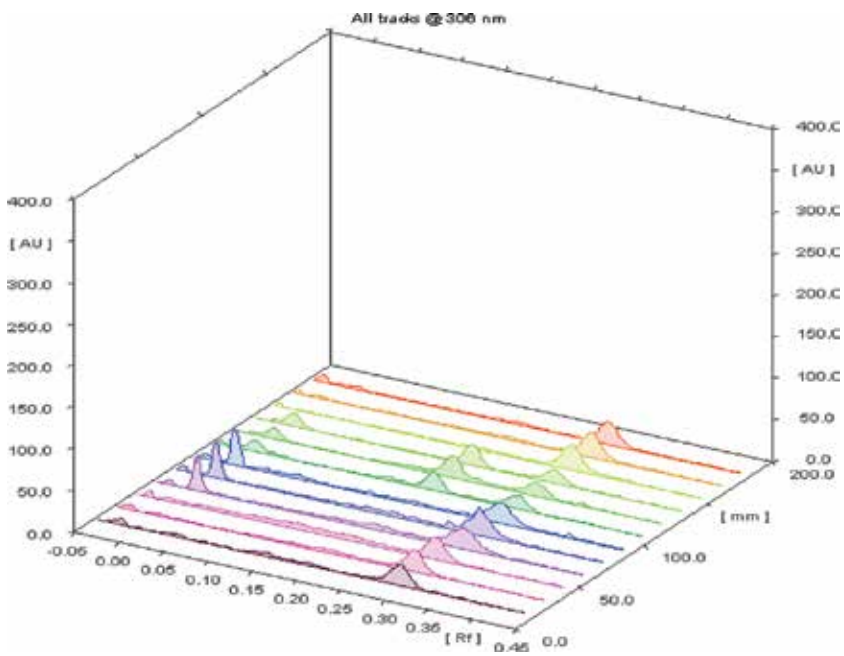

Figure 9.
Degradation study of fluphenazine with HCl, with NaOH, and with H_2O_2. Tracks 1–3 (from bottom side to the upper side), fluphenazine; tracks 4–6, fluphenazine + HCl; tracks 7–9, fluphenazine + NaOH; and tracks 10–12, fluphenazine + H_2O_2. Rf peak fluphenazine = 0.30. Other peaks at tracks 4–9: degradation products. Rf, retarding factor; AU, absorbance unit.

product. Rf for fluphenazine = 0.30 and Rf for degradation product = 0.56 (**Figure 10**) [38]. One of the products of photolysis mentioned in literature is a sulfoxide [2].

2.5 Stability-indicating HPLC method for quantification of risperidone in tablets

Risperidone is a benzisoxazole derivative (**Figure 11**), a second-generation antipsychotic agent, that is chemically unrelated to other antipsychotic drugs. It is used for the treatment of schizophrenia, bipolar disorder, and irritability in children with autism. The major impurity products in the dosage forms, including degradation

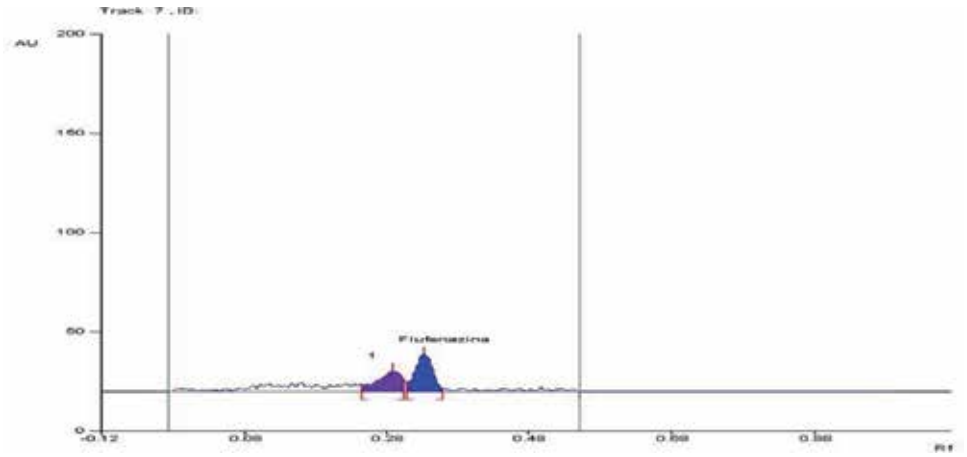

Figure 10.
Degradation study of fluphenazine with VIS radiation. Peak no. 1 (from left to right), fluphenazine, and peak no. 2, degradation product. Rf, retarding factor; AU, absorbance unit.

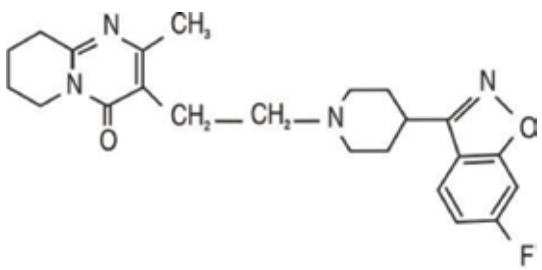

Figure 11.
Chemical structure of risperidone.

products, described in USP are Z-oxime, bicyclo risperidone, and cis-risperidone N-oxide [3]. Some degradation products found in work investigations had been 9-hydroxyrisperidone and N-oxide of risperidone [32–35].

A stability-indicating LC method was developed and validated for the determination of risperidone in tablets. Quantitation was achieved by LC/DAD at 294 nm over the concentration range of 25.00–250.00 μg/mL. Mobile phase was a mixture of water, glacial acetic acid 0.5%, triethylamine 0.8%, and acetonitrile (65.00, 0.32, 0.52, 34.16, v/v), using a Purospher STAR RP-18e 250 × 4.5 mm (5 μ) column (Merck KGaA, Darmstadt, Germany) and paroxetine as internal standard. The method exhibited an adequate linearity, with a correlation coefficient of 0.999, selectivity, precision (RSD ≤ 0.847%), and accuracy (recoveries from 99.55 to 101.35%).

Risperidone was subjected to the stress conditions of oxidative, acid, base, thermal, and photolytic degradation. Risperidone was found no degrade in basic or acid stress conditions, neither in thermal stress exposition (50, 70, and 100°C) nor at visible or UV stress conditions, during the time of the study. Only two degradation products were observed with peroxide oxidation, well resolved from analyte peak, proving the stability-indicating power of the method. The drug was highly labile to hydrogen peroxide (3%) at room temperature. After 6 hours, steep fall in the drug peak area was observed. Major degradation products appeared at tR = 2.0 and tR = 5.3. These peaks were resolved from risperidone (tR = 3.5) (**Figure 12**). Risperidone was degraded to 35.00% when it was exposed to room light for 8 days, and it was degraded

to 17.00% when it was exposed to 80°C for 6 hours (**Figure 13**) [39]. One degradation product found in work investigations had been N-oxide of risperidone [3, 32].

2.6 Stability HPLC methods for stress testing studies of quinapril/ hydrochlorothiazide and candesartan/hydrochlorothiazide

Quinapril hydrochloride (QUIN), hydrochlorothiazide (HCTZ), and candesartan cilexetil (CAN) are drugs that are widely used in the management of a highly prevalent disease such as hypertension. They are used alone or as combination therapy; the association of QUIN/HCTZ and CAN/HCTZ is used as combination therapy in the treatment of patients whose blood pressure is not adequately controlled with any of the substances alone. QUIN (**Figure 14**) is an angiotensin-converting enzyme (ACE) inhibitor used alone or in combination with other classes of antihypertensive agents; it is a prodrug and has little pharmacological activity until hydrolyzed in the liver to quinaprilat [32, 34]. HCTZ (**Figure 15**) is a thiazide diuretic and antihypertensive agent [32], and CAN (**Figure 16**) is an angiotensin II receptor antagonist (AT_1) used alone or in combination with other classes of antihypertensive agents; CAN is a prodrug and has little pharmacological activity until hydrolyzed during absorption in the gastrointestinal tract to candesartan [32, 34]. All three drugs have chemical structures susceptible to degradation; therefore, it is important to determine their stability.

In order to assess the chemical stability of a compound, it is very important to have the appropriate analytical method, i.e., they must be stability-indicating [3]. The main target while developing these methods was to have a single method for separation between QUIN/HCTZ or CAN/HCTZ and their degradation products. A stability- indicating LC methods with DAD and ELSD detection were developed by the authors for the simultaneous determination of CAN/HCTZ [40] and QUIN/HCTZ [41].

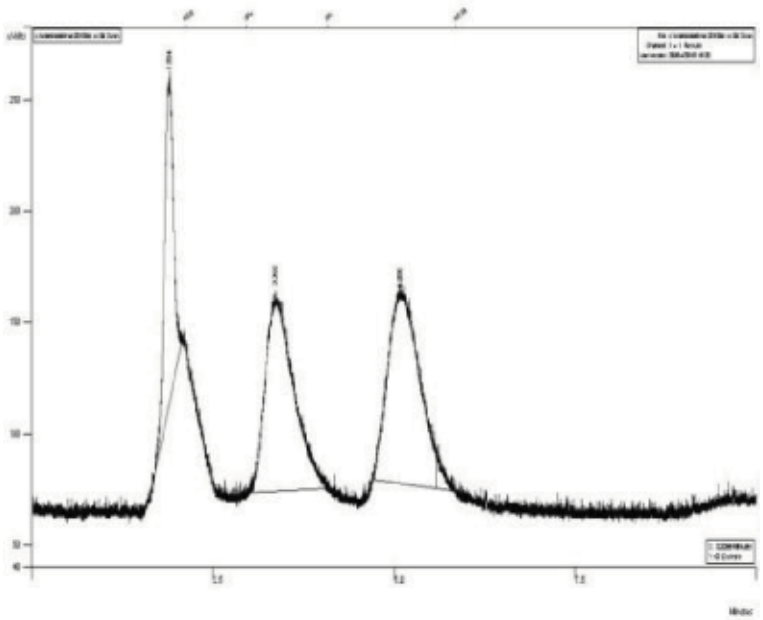

Figure 12.
Study at forced degradation of risperidone with 3% H_2O_2 at room light for 8 days and with 3% H_2O_2 at 80°C for 6 h. Peak 1 (tR = 2.0): degradation product. Peak 2 (tR = 3.5): risperidone. Peak 3 (tR = 5.3): degradation product.

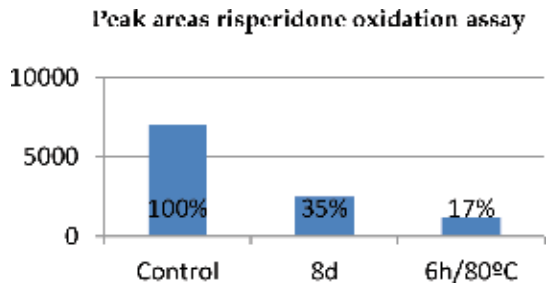

Figure 13.
Risperidone degradation at 3% H_2O_2 exposition.

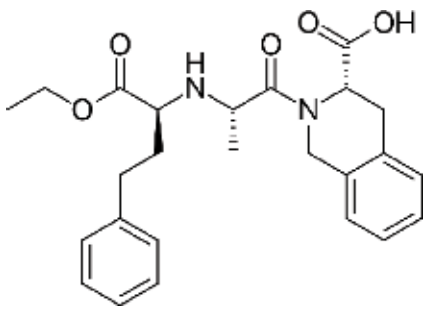

Figure 14.
Chemical structure of quinapril.

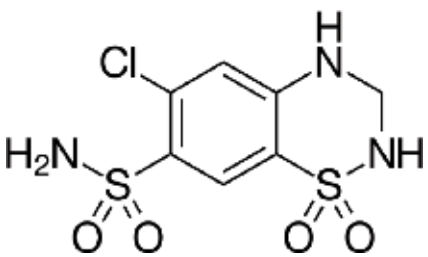

Figure 15.
Chemical structure of hydrochlorothiazide.

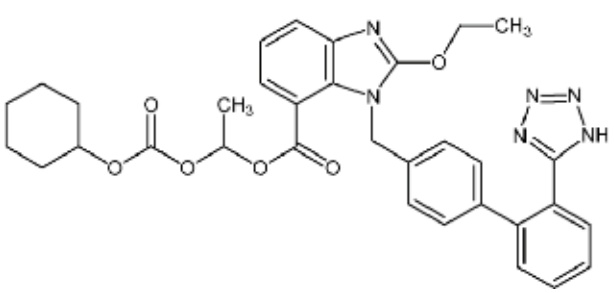

Figure 16.
Chemical structure of candesartan.

2.6.1 CAN/HCTZ

HPLC analyses were carried out on a Purospher® RP-18 column (125 mm × 4 mm, 5 μm; Merck KGaA, Darmstadt, Germany). Valsartan was used as internal standard (IS) at 70.0 μg min^{-1}. For LC/DAD method, the mobile phase consisted of acetonitrile (A) and phosphate buffer (pH 6.0; 0.05 M) (B) in a gradient mode. The flow rate was set to 1 mL min^{-1}, with UV detector wavelength fixed at 225 nm, and the column temperature was set at 30°C. For LC/ELSD method, the mobile phase consisted of acetonitrile (A) and water with acetic acid (0.175 M) and triethylamine (0.06 M) (pH 4.1) (B) in a gradient mode. The flow rate was set to 0.8 mL min^{-1} and the column temperature was set at 35°C. ELSD evaporation temperature was set at 40°C, the gain was 7, and the nebulizer gas pressure was kept at 3 bar. The response with ELSD was fitted to a power function and the DAD response by a linear model over a range of 32–160 μg/mL for CAN and 25–125 μg/mL for HCTZ. The precision and accuracy of the methods were similar, with RSD below 3.0% and recovery between 98.1 and 103.9%. The drugs were subjected to stress conditions of hydrolysis, oxidation, photolysis, humidity, and temperature. Both drugs were mainly degraded by hydrolysis, showing the formation of one degradation product for HCTZ identified by MS/MS as 4-amino-6-chloro-1,3-benzendisulfonamide (DSA) and two for CAN cilexetil identified as candesartan and desethyl candesartan cilexetil. The degradation products were satisfactory separated from the main peaks and from each other as shown in **Figure 17**.

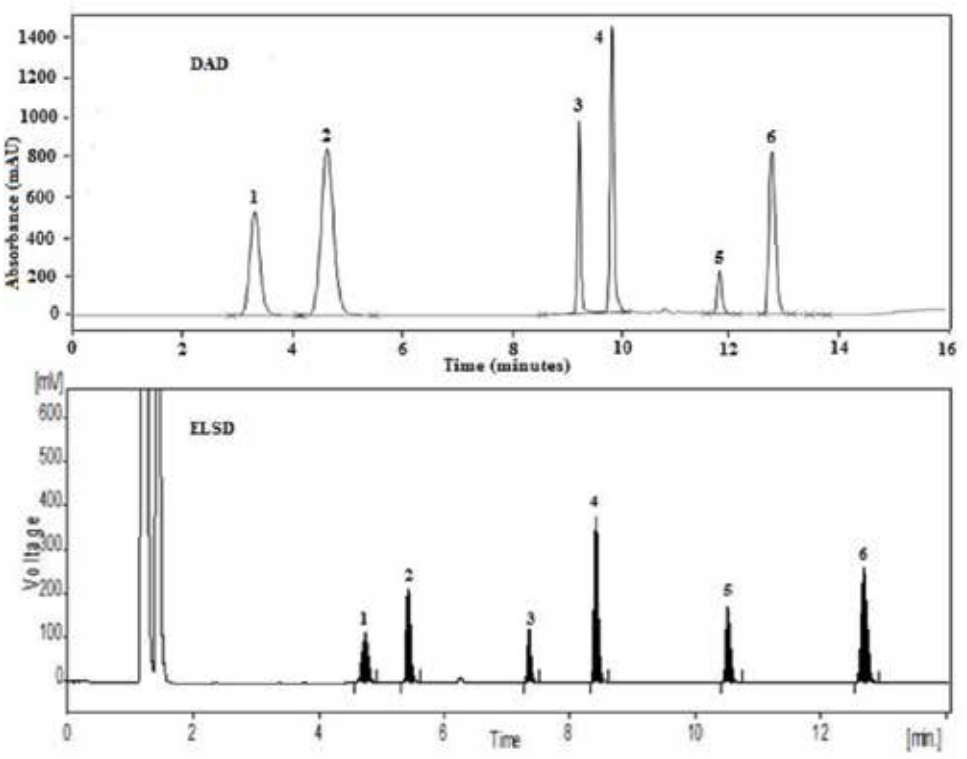

Figure 17.
(1) degradation product of HCTZ (DSA), (2) HCTZ, (3) alkaline degradation product of CAN (candesartan), (4) IS (valsartan), (5) acidic and neutral degradation product of CAN (desethyl candesartan cilexetil), and (6) CAN.

2.6.2 QUIN/HCTZ

HPLC analyses were carried out on a Chromolith® High Resolution RP-18 column (100 mm × 4.6 mm). For LC/DAD method, the mobile phase consisted of acetonitrile (A) and phosphate buffer (pH 3.0; 0.01 M) (B) in a gradient mode. The flow rate was set to 1.5 mL min^{-1} with UV detector wavelength fixed at 215 nm, and the column temperature was set at 30°C. For LC/ELSD method, the mobile phase consisted of acetonitrile (A) and water with acetic acid (0.086 M) and triethylamine (0.007 M) (pH 3.3) (B) in a gradient mode. The flow rate was set to 1.0 mL min^{-1}, and the column temperature was set a 35°C. ELSD evaporation temperature was set at 40°C, the gain was 7, and the nebulizer gas pressure was kept at 3 bar. The analytes were eluted within 7 minutes in both methods. The response

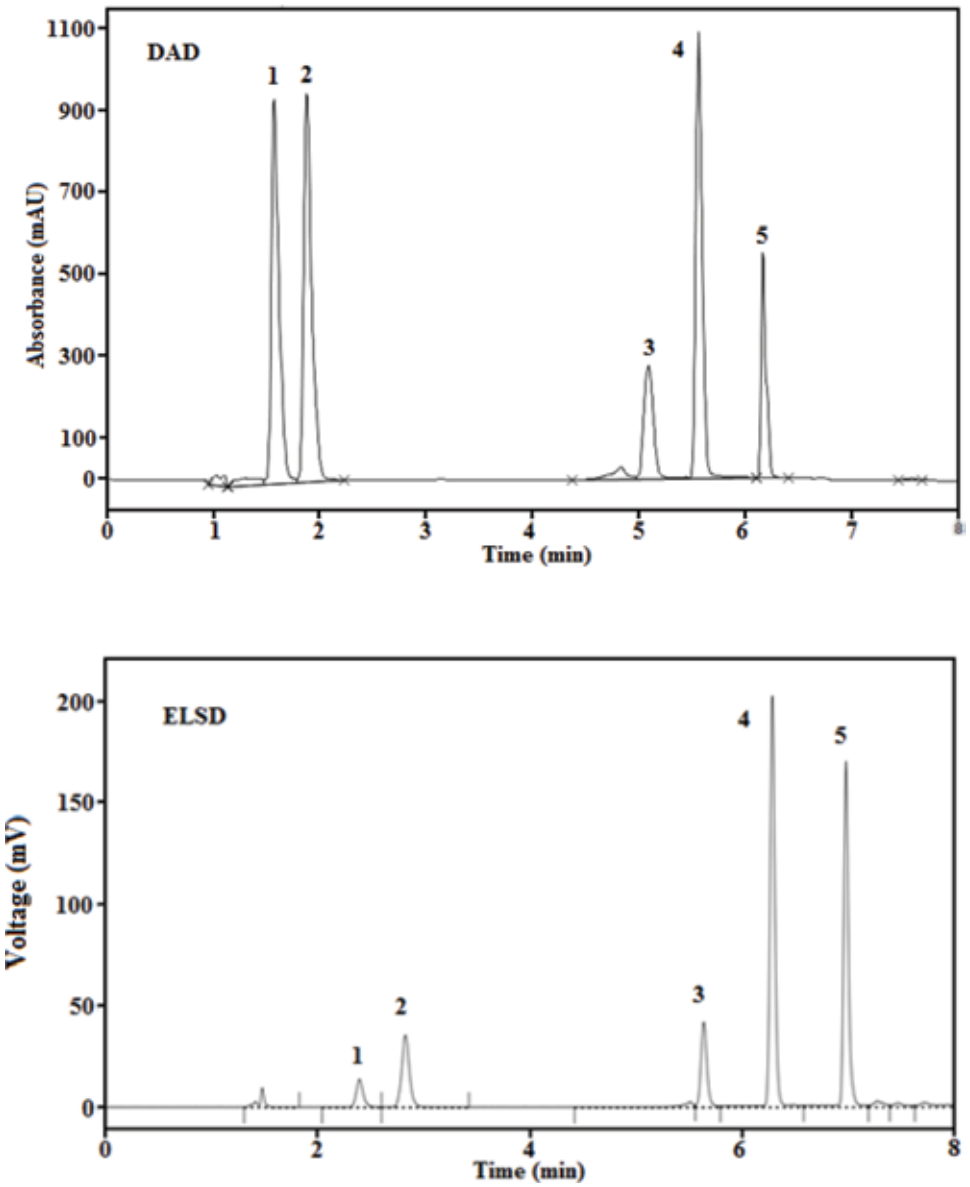

Figure 18.
Chromatogram with DAD and ELSD: (1) DSA, (2) HCTZ, (3) quinaprilat, (4) QUIN, and (5) DKP.

with DAD was linear, and the response with ELSD was fitted to a power function, for quinapril and hydrochlorothiazide concentrations of 20–160 μg mL^{-1} and 12.5–100 μg mL^{-1}, respectively. DAD method achieved better precision than ELSD method, the LOQ of DAD was lower, and the accuracy of the methods was similar. Quinapril was subjected to hydrolytic, oxidative, thermal, humidity, and photolytic stress conditions. Quinapril was degraded by hydrolysis and thermal stress, showing the formation of quinaprilat and quinapril diketopiperazine as degradants, which were identified by MS/MS. Degradation products were well resolved from the main peaks and from each other, proving the stability-indicating power of the methods as shown in **Figure 18**.

2.7 Stability-indicating HPLC method for quantification of vortioxetine in bulk and tablets

Vortioxetine hydrobromide (**Figure 19**) is a serotoninergic novel antidepressant with multiple pharmacologic activities [32, 41], approved by the US Food and Drug Administration in 2013 [42] for the treatment of major depressive disorder in adults. It is a phenylpiperazine derivative. Although the precise mechanism of action is not fully understood, it is thought to be related to enhancement of serotoninergic activity in the central nervous system through inhibition of serotonin reuptake [32, 42]. It has a chemical structure susceptible to degradation; therefore, it is important to determine its stability by suitable analytical methods.

A simple HPLC method with photodiode array detection (DAD) was developed and validated by the authors [43], for determination of VOR in bulk and tablets, in the presence of its major degradation products. A C-18 column was used, with mobile phase consisting of acetonitrile and water with acetic acid and triethylamine in isocratic elution mode, with detection at 228 nm and 1.0 mL/min flow rate. Under these conditions, all the analytes were eluted within 15 min. Bromazepam was used as internal standard at 25 μg/mL. The assay was linear in the 25–125 μg/mL concentration range. For precision, the RSD was lower than 1.8%, the recovery was between 100.0 and 101.6%, and the method demonstrated adequate selectivity (**Figure 20**). The drug was subjected to oxidative, hydrolytic, and photolytic stress conditions, showing significant degradation under oxidation with complete degradation after 1 day of stress, and was stable under acid, alkaline, neutral, and photolytic conditions. One main oxidative degradation product was formed, which was identified by ESI-MS/MS as the benzylic alcohol of VOR (**Figure 21**).

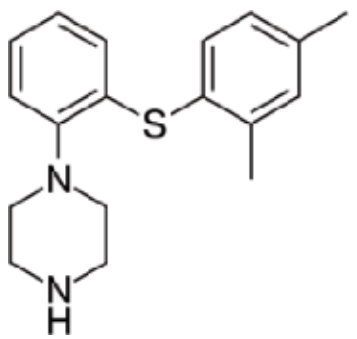

Figure 19.
Chemical structure of vortioxetine.

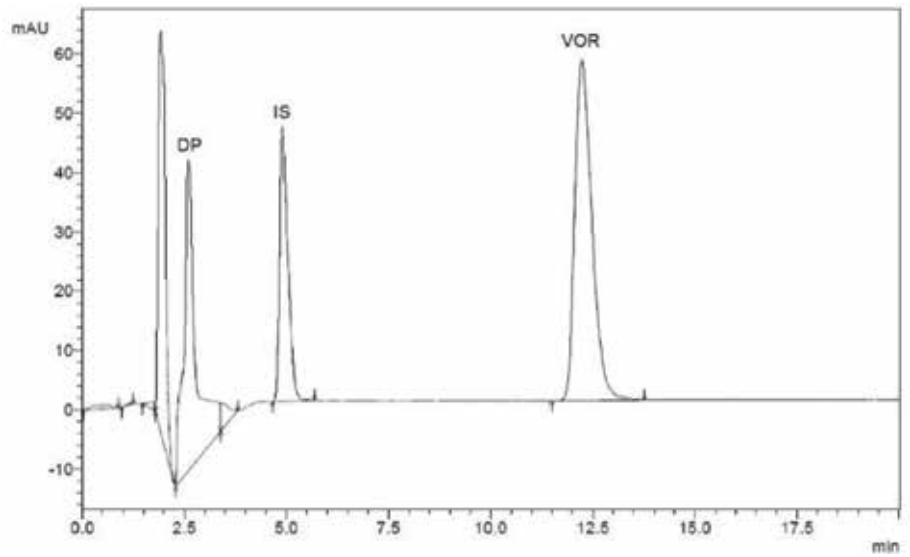

Figure 20.
Chromatogram of VOR, internal standard (IS), and oxidative degradation product (DP).

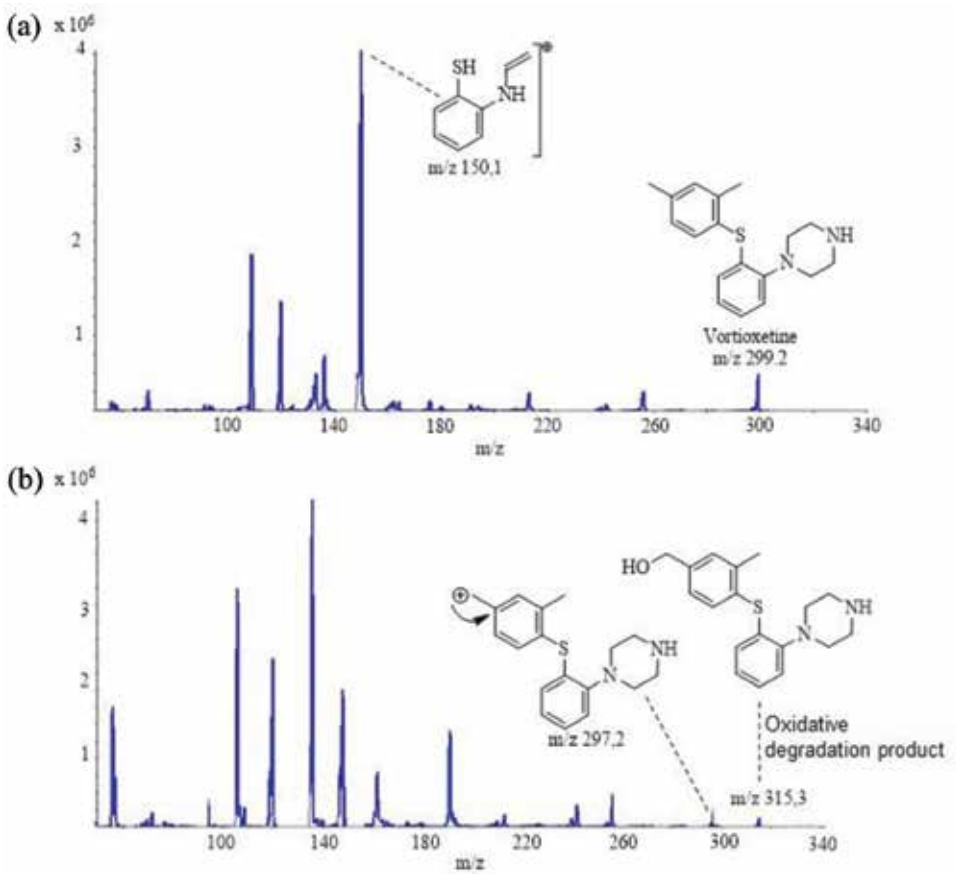

Figure 21.
The mass spectrum of vortioxetine standard (a) and oxidative degradation product (b).

3. Conclusions

The stability of a pharmaceutical is defined by its resistance to different chemical, physical, and microbiological reactions that may change their original properties. The stability of a pharmaceutical product is closely related to its potency; therefore, whether the compounds are degraded, a decrease of the therapeutic effect or changes in their toxicological properties can be produced, affecting their efficacy and safety, which becomes important to maintain a stable pharmaceutical product and to have the analytical tools to demonstrate stability. Therefore, stability-indicating methods are required to the quality control of pharmaceuticals.

The examples presented here are stability-indicating methods since they allow the determination of drugs in the presence of their degradation products, according to the International Conference on Harmonization (ICH) guidelines.

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Conflict of interest statement

Authors have no conflict of interest.

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Chapter 5

Quality in Testing Laboratories: A Real Case in a Spanish Fuel Laboratory

Mª Mercedes del Coro Fernández-Feal, Luis R. Sánchez-Fernández and Blanca Sánchez-Fernández

Abstract

Quality management is the chosen option by those organizations that maintain a strong commitment to excellence in their products, services, and processes. The technical competence of a testing laboratory is essential to provide confidence in the results issued to its clients: administrations, companies, or individuals who request their services. The implementation of a quality system, with international recognition, facilitates and enables laboratory projection in national and international forums. The study shows the steps followed by a fuel laboratory (R + D + i), integrated in a Spanish university, to implement the quality standards established in ISO/IEC 17025 and ISO 9001. Despite its small size, the laboratory maintains high-quality standards. Obtaining ISO/IEC 17025 accreditation has allowed the laboratory to recognize its technical competence at a national and international level, greater visibility, and better positioning among laboratories that offer the same services, which has increased the number of customers and has achieved their loyalty.

Keywords: testing laboratory, ISO/IEC 17025, ISO 9001, technical competence, integrated quality

1. Introduction

Practically all fields of science are moving forward at an increasingly rapid rate thanks to the results obtained from laboratories.

A laboratory [1] is a place equipped with all of the resources needed to carry out scientific, technological, or technical research, experiments, practices, and works, with the appropriate level of rigor:

- It ensures that foreign influences, other than those specifically set out, do not occur and alter the result of experiment or measurement.

- It guarantees the repeatability of the experiment or measurement, i.e., any other laboratory could repeat the process and obtain the same result.

How can we ensure the confidence of the results of the tests carried out by the laboratory?

Accreditation is the internationally established tool to build trust on the performance of a very specific type of organizations, named, in such a way, Conformity Assessment Organizations (CAO) (**Figure 1**), including testing laboratories, calibration laboratories, inspection agencies, certification bodies, and environmental verifiers [2].

The main objective of the Conformity Assessment Organizations (CAO) is to demonstrate the society (administration, companies, and consumers at large) that the products and services made available comply with certain requirements related to quality and security. These requirements can be set by law, and therefore have a regulatory nature, or can be specified by standards, specifications, or other voluntary documents.

Accreditation arouses both controversy and interest; multiple studies try to deepen in the subject from different perspectives [3–7].

1.1 The benefits of accreditation

1.1.1 For accredited organizations

- Builds organization recognition.
- Competitive advantage: accreditation provides independent assurance that your staff is competent.
- Market access: accreditation is recognized and accepted in over 90 countries worldwide.
- Fosters a continuous improvement dynamic within the organization.
- Facilitates access to government contracting: accreditation has increasingly become an important criterion in the public procurement procedures.

1.1.2 For government

Accredited bodies, both public and private, are already being used by governments as an effective market-led tool for delivering policy more efficiently, resulting in a substantial reduction in costs as well as best practice.

Figure 1.
Conformity assessment organizations.

Figure 2.
Accreditation organizations of different countries.

1.1.3 For business

By selecting an accredited body, businesses:

- Reduce downtime and control costs.
- Minimize risks.
- Increase its customer confidence.
- Increase its product acceptance in other markets.
- Open up opportunities for competent supplier selection.
- Reduce the risk of failures.

Accreditation organizations of different countries (**Figure 2**) perform their task pursuant to the same international criteria, using equivalent and transparent assessment methods, providing the necessary confidence to allow the mutual acceptance of results.

The ISO/IEC 17025 Standard was designed to be used by testing and calibration laboratories in the development of their quality, administrative, and technical management systems.

Working under the standards of ISO/IEC 17025, the technical competence of the laboratory and the validity of its results are recognized, responding to the requirements of the organizations or entities that contract it and offering credibility to its clients [8].

2. State of the art

Product or service quality is the consumer's perception of it and should be defined within the context under review.

From a value-added perspective, quality means bring value to the customer, i.e., offer product or service conditions of use superior to those that the customer expects to receive and at an accessible price.

For good product or service quality [9], there are three very important points which we need to bear in mind:

- **Technical dimension:** it encompasses scientific and technological aspects that affect the product or service.

- **Human dimension:** it attends to relations between customers and organizations.

- **Economic dimension:** it attempts to minimize costs both for the customer and the organization.

In 1957 and 1988, respectively, the European Organization for Quality (EOQ) and the European Foundation for Quality Management (EFQM) are founded in Europe to promote total quality management; among the most important European quality infrastructure organizations are testing laboratories.

When you commission a laboratory to test products, to determine its characteristics, as part of the quality control or to determine compliance with particular requirements of standards or specifications, it is necessary to be sure that they supply you with accurate and reliable results. In other words, this is a laboratory technically competent.

In order to ensure the reliability of its products or services, minimize risks, and increase customer confidence and product acceptance in other markets, it is essential for the organizations to call on a laboratory with the highest degree of technical competence.

2.1 The normative evolution

The first version of Standard ISO/IEC 17025 dates from 1999. The ISO/IEC 17025:2017 Standard on General Requirements for the Competence of Testing and Calibration Laboratories is currently in force, but it has had a long way before it arrived here from that first version in 1999.

The ISI/IEC 17025:1999 Standard replaced the ISO/IEC 25:1990 former guide (General Requirements for the Competence of Calibration and Testing Laboratories) and the European EN 45001:1989 Standard (General Criteria for the Operation of Testing Laboratories), introducing new requirements in relation to responsibilities and commitment of upper management and giving greater emphasis to continuous improvement according to Deming method or PDCA (plan-do-check-act) (**Figure 3**) and to dialog with the customer.

The ISO/IEC 17025 Standard emerged in 1999 as a reference generic guideline for Testing or Calibration Laboratories; the existence and evolution of the quality

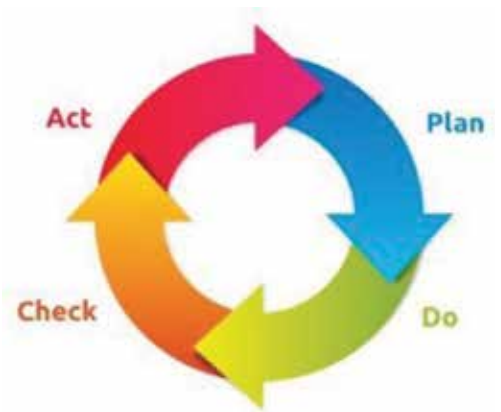

Figure 3.
Deming cycle.

management regulation stipulated in ISO 9001 Standard led to a revision to determine their alignment with the ISO 9001:2000 Standard in 2005 (**Figure 4**).

In 2017, to adjust its form to the structure of the rest of 17,000 Series Standards and with the objective of adapting to the latest changes in the laboratories sphere and to the new information technologies applied to work practices, the ISO/IEC 17025 Standard was once again reviewed. The revised standard is in line with ISO terminology, with a set of terms and definitions common to all the standards related to conformity assessment (**Figure 5**).

The ISO/IEC 17025 [10] goes to show that laboratories that implement this standard:

- Operate an effective quality management system based on ongoing improvement

The laboratory implements a quality management system to administer and use its documentation, both in management and in technical areas.

- Are technically competent

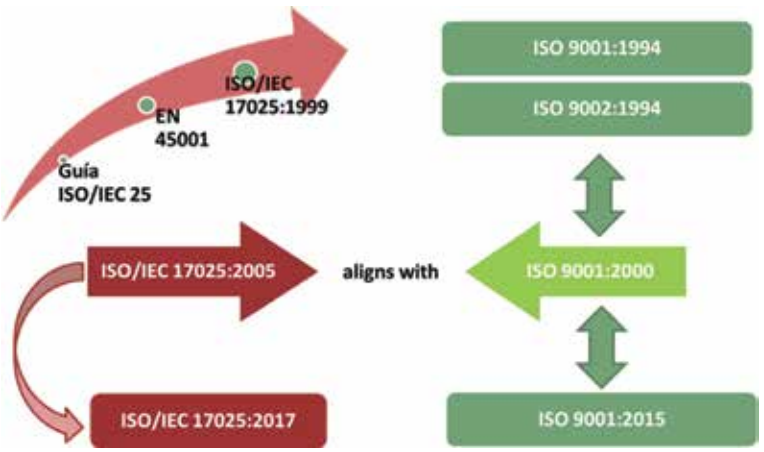

Figure 4.
Chronological evolution ISO/IEC 17025.

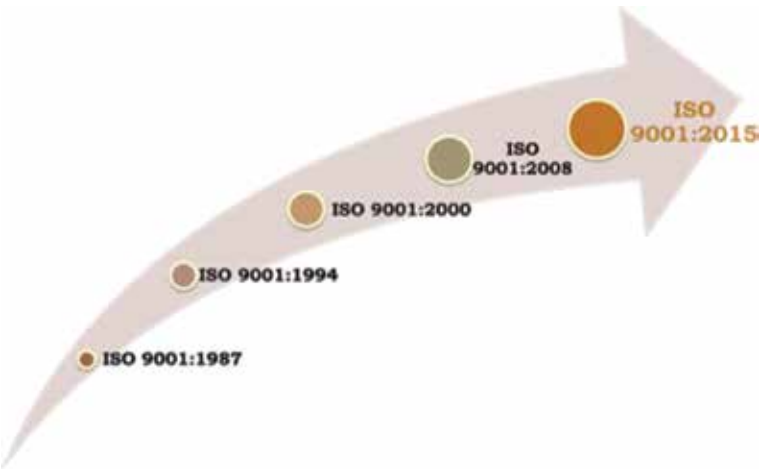

Figure 5.
Chronological evolution ISO 9001.

The laboratory demonstrates technical competence of staff, appropriate facilities and environmental conditions, validity of test methods, reliable test equipment, and reference standard materials with traceability to the international system of units.

- Are capable of producing testing or calibration reliable results

The laboratory implements quality assurance programs, which generate technically valid results.

The ISO 17025 Standard introduces two types of requirements:

- Management requirements

These requirements are related to the laboratory quality management. Requirements analogous to those set out in the ISO 9001 Standard.

- Technical requirements

These requirements are related to aspects with direct influence over the testing result.

We should bear in mind that conformity with the scope defined in the ISO/IEC 17025 Standard does not mean that the laboratory quality management system meets all the requirements of the ISO 9001 Standard. Likewise, conformity of the laboratory quality management system with standard ISO 9001 requirements alone is no guarantee of the laboratory competence to generate theoretically valid data and results (**Figure 6**).

The laboratory certification guarantees compliance with requirements of the ISO 9001 Standard; the laboratory accreditation guarantees the technical competence for testing activities (**Figures 7** and **8**).

According to data from the ENAC, in Spain in 2010, there were 1040 accredited testing laboratories, and their number has soared to over 1138 in 2013. In 2014,

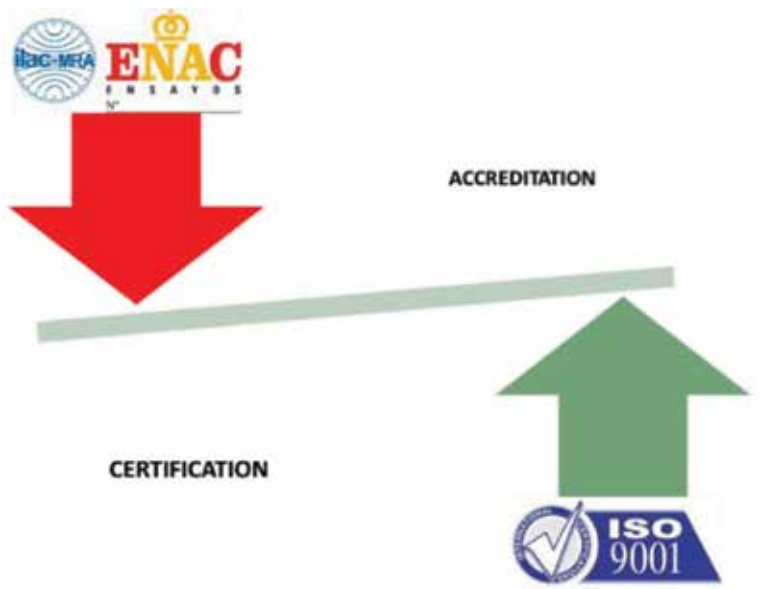

Figure 6.
ISO/IEC 17025 versus ISO 9001.

due to the financial crisis, the number of accredited laboratories decreased significantly to 1043: some temporarily suspended accreditation while others even go out of business. Since 2015, is noted a constant and moderate growth; at the end 2017, there were already 1081 laboratories accredited (**Figure 9**).

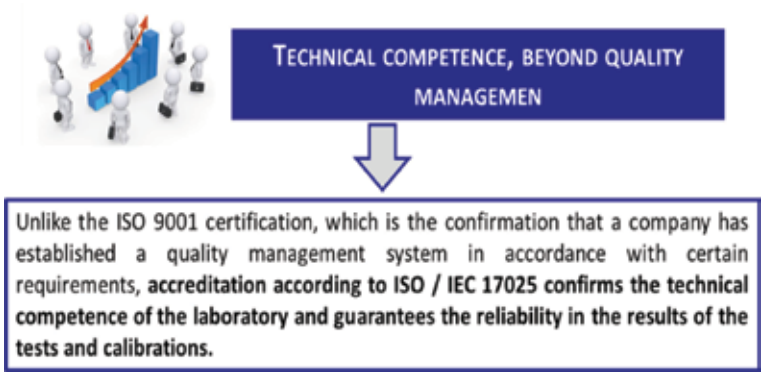

Figure 7.
Technical competence beyond quality management.

STANDARDS	ISO/IEC 17025	ISO 9001
Scope	Testing and Calibration Laboratory	Company
Maim facets	Management and technical competence	Management
Auditig entity	ENAC, UKAS, EMA...	Certification entities (AENOR, SGS...)
Status of the audited entity	Accredited Laboratory	Certified company
Guarantee	✓ It has a system quality management ✓ Produce theoretically valid data and results	✓It has a system quality management

Figure 8.
Relationship between the standards ISO/IEC 17025 and ISO 9001.

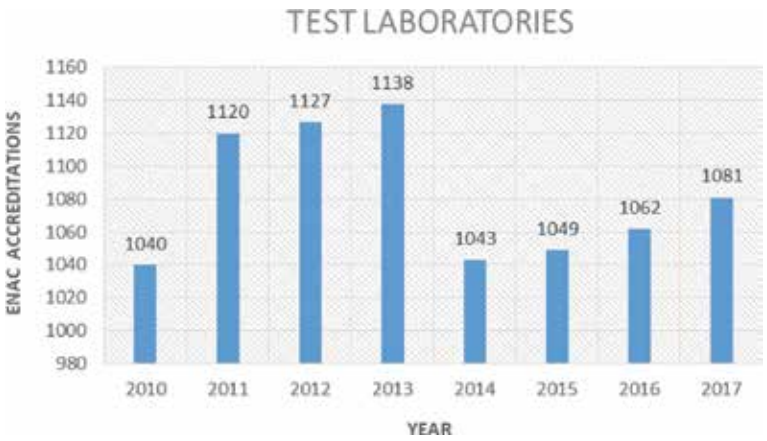

Figure 9.
ENAC accreditations of testing laboratories (2010–2017).

3. Case study: LABCOMB accreditation

The small size of a laboratory is not an impediment to the implementation of the ISO/IEC 17025 Standard; but the size and the laboratory characteristics have to take it into account to design the proper quality management system, trying to simplify.

3.1 Objective

A Fuel's laboratory (R + D + i) accreditation. The laboratory is a member of a research center at a Spanish university.

To establish the procedure to be followed, the path to the system established by the ENAC (National Accreditation Entity—Spain) to accredit a testing laboratory, LABCOMB, under internationally established criteria.

3.2 Preparation of documentation

The accreditation is a declaration of the technical competence of the laboratory to perform the activities included in the scope of the accreditation. This competence is established through the evaluation of laboratory compliance with the requirements established to that effect in international standards.

The accreditation system for testing laboratories establishes the accreditation requirements to be met by the laboratories, as well as the accreditation framework and procedure. The accreditation granted is valid and is fully accepted in Spain and internationally.

The accreditation does not imply in any case the acceptance or validation by the ENAC of the results of each test, nor does it exempt the laboratory from its responsibility in case of erroneous results.

3.2.1 Documentation prepared by LABCOMB according to the general criteria for accreditation

The ISO/IEC 17025 Standard establishes the general requirements related to the technical competence of the testing laboratories that ENAC uses as criteria for accreditation.

The laboratory identifies in its Quality Manual: MC/LABCOMB, the legal personality that assumes its legal responsibilities, defines its quality policy, and records all the documentation prepared in order to meet the criteria established in the ISO/IEC 17025 Standard:

- Management requirements
- Technical requirements

The documentary structure of LABCOMB's quality management system consists of:

- The Quality Manual:

MC/LABCOMB, Quality Manual ISO 17025

- General procedures:

P/LABCOMB/01	Staff skills
P/LABCOMB/02	Internal staff training program
P/LABCOMB/03	Document and record control
P/LABCOMB/04	Procurement management and subcontracting
P/LABCOMB/05	Supplier evaluation
P/LABCOMB/06	Complaint handling
P/LABCOMB/07	Development of testing procedures
P/LABCOMB/08	Validation procedures
P/LABCOMB/09	Uncertainty calculation
P/LABCOMB/10	Test process
P/LABCOMB/11	Equipment and reagent management
P/LABCOMB/12	Regulation and legislation review
P/LABCOMB/13	Internal audits
P/LABCOMB/14	Nonconformity treatment
P/LABCOMB/15	Corrective and preventive action management
P/LABCOMB/16	Revision of the system by the general direction

- Technical procedures: test procedures (PE) and calibration procedures (PC)

PE/LABCOMB/01	Determination of flash point, Pensky-Martens method
PE/LABCOMB/02	Determination of cold filter plugging point (CFPP)
PE/LABCOMB/03	Determination of cloud point
PE/LABCOMB/04	Determination of distillation characteristics at atmospheric pressure
PE/LABCOMB/05	Determination of sulfur content for UVF method
PE/LABCOMB/06	Calculation of cetane index by the four-variable equation
PE/LABCOMB/07	Determination of density by the hydrometer method
PE/LABCOMB/08	Determination of sulfur content for UVF method (<3 ppm)
PE/LABCOMB/09	Determination of water, Karl-Fischer method
PE/LABCOMB/10	Determination of water, Karl-Fischer method (>1%)
PE/LABCOMB/11	Determination of kinematic viscosity
PE/LABCOMB/12	Determination of flash and fire points, Cleveland method
PE/LABCOMB/13	Determination of combustion heat
PE/LABCOMB/14	Determination of water by distillation

PE/LABCOMB/15	Determination of sulfur content, XRF method
PE/LABCOMB/16	Determination of nickel and vanadium content, RXF method
PE/LABCOMB/17	Determination of ash
PE/LABCOMB/18	Determination of sulfated ash
PE/LABCOMB/19	Determination of free water and particulate contamination
PE/LABCOMB/20	Determination of water and sediments by the centrifuge method
PE/LABCOMB/21	Corrosiveness to copper. Copper strip test
PE/LABCOMB/22	Commercial butane and propane. Analysis by GC
PE/LABCOMB/23	Determination of ASTM color of petroleum products
PE/LABCOMB/24	Estimation of net and gross heat of combustion
PE/LABCOMB/25	Determination of total sulfur content. Method of elemental analysis
PE/LABCOMB/26	Determination of pour point
PE/LABCOMB/27	Natural Gas. Analysis by GC

PC/LABCOMB/01	Calibration of thermal equipment
PC/LABCOMB/02	Calibration of volumetric material
PC/LABCOMB/03	Calibration of thermometers
PC/LABCOMB/04	Calibration of stopwatches
PC/LABCOMB/05	Calibration of hydrometers
PC/LABCOMB/06	Calibration of viscometers
PC/LABCOMB/07	Calibration of thermostatic baths

3.2.2 Scope

The laboratory is not accredited to perform all the tests included in its offer. Accredited tests are included in the Scope.

The accreditation scope describes the technical competence declared by LABCOMB (**Figure 10**) in order to be assessed by the ENAC. It finally constitutes the Technical Annex to the "Accreditation Certification," and it should, therefore,

ENAC
Entidad Nacional de Acreditación

Acreditación nº 814/LE1688
Anexo Técnico Rev. 6
Fecha: 28/07/2017
Hoja 1 de 3

ANEXO TÉCNICO
ACREDITACIÓN Nº 814/LE1688

Entidad: LABORATORIO DE COMBUSTIBLES. CENTRO DE INVESTIGACIONES TECNOLÓGICAS DE LA UNIVERSIDADE DA CORUÑA

Dirección: Centro de Investigaciones Tecnológicas. Campus de Esteiro; 15403 Ferrol (A Coruña)

Norma de referencia: UNE-EN ISO/IEC 17025:2005

Ensayos en la siguiente área:

Combustibles y productos petrolíferos 1

Combustibles y productos petrolíferos

Categoría 0 (Ensayos en el laboratorio permanente)

PRODUCTO/MATERIAL A ENSAYAR	ENSAYO	NORMA/PROCEDIMIENTO DE ENSAYO
Productos Petrolíferos	Densidad mediante aerómetro *(0,70 - 1,00 g/ml)*	UNE-EN ISO 3675:1999 UNE-EN ISO 3675:1999 ERRATUM:2011
	Viscosidad cinemática a 40 y 50 ºC *(7 - 500 mm^2/s)*	UNE-EN ISO 3104:1996 UNE-EN ISO 3104:1996 ERRATUM UNE-EN ISO 3104/AC:1999
	Agua por destilación *(0,05 - 25 %v/v)*	UNE 51027:1978 ASTM D95-13e1
	Corrosión a la tira de cobre a 50 ºC	UNE-EN ISO 2160:1999
	Color ASTM	ASTM D1500-12
	Agua y sedimentos por centrifugación	UNE 51028:1965
Gasóleos y gasolinas	Destilación a presión atmosférica *(20 ºC a 370 ºC)*	UNE-EN ISO 3405: 2011
	Azufre total por fluorescencia ultravioleta *(3 a 50 mg/Kg)*	UNE-EN ISO 20[illegible]

ENTIDAD NACIONAL DE ACREDITACIÓN
ENAC

Figure 10.
LABCOMB present scope (sheet 1).

LABCOMB is responsible for establishing the accreditation scope, although ENAC establishes the type of information that should be included to ensure its proper definition.

LABCOMB accredited tests include:

PE/LABCOMB/01	Determination of flash point, Pensky-Martens method
PE/LABCOMB/02	Determination of cold filter plugging point (CFPP)
PE/LABCOMB/03	Determination of cloud point
PE/LABCOMB/04	Determination of distillation characteristics at atmospheric pressure
PE/LABCOMB/05	Determination of sulfur content for UVF method
PE/LABCOMB/06	Calculation of cetane index by the four-variable equation

PE/LABCOMB/07	Determination of density by the hydrometer method
PE/LABCOMB/11	Determination of kinematic viscosity
PE/LABCOMB/14	Determination of water by distillation
PE/LABCOMB/19	Determination of free water and particulate contamination
PE/LABCOMB/20	Determination of water and sediments by the centrifuge method
PE/LABCOMB/21	Corrosiveness to copper. Copper strip test
PE/LABCOMB/23	Determination of ASTM color of petroleum products

3.3 Accreditation request

3.3.1 File opening

The accreditation process begins with the opening of the file in March 2010. ENAC understands that when applying for accreditation, LABCOMB complies with all the legally established requirements to carry out the activity for which accreditation is requested.

If at any time during the accreditation process it becomes clear that this is not the case, ENAC proceeds to stop the process until the laboratory provides evidence that the detected problem has been adequately resolved.

ENAC can request evidence of compliance with these legal requirements before initiating the accreditation process.

The information received by ENAC, both in the application and throughout the entire accreditation process, will be considered as CONFIDENTIAL for all purposes with the following limitations:

- Those established, as the case may be, by law.
- In activities that take place in the regulated field or in those in which the laboratory operates with an administrative authorization, ENAC may, at the request of the competent administration, inform the latter of the results of the evaluations.
- If the laboratory is accredited by other accreditors, ENAC can exchange information with them, in accordance with what is established by the cross-border accreditation procedures established by international accrediting organizations.

3.3.2 Acceptance of the request

ENAC acknowledges receipt of the application and reviews the documentation provided in order to verify that the activity is susceptible to be accredited. Inform LABCOMB of the ENAC technician responsible for the follow-up of your file. If there is any legal, statutory, or other reason that prevents accreditation, it is communicated to the laboratory.

ENAC evaluates whether the activity corresponds to the accreditation scheme under which it is requested, if the scope is clearly defined and the documentation is complete and adequate. ENAC can request, at this time or in subsequent phases of the process, additional information to ensure the correct execution of the accreditation process.

Within any of the phases of the accreditation process, if more than 1 year passes without a response from the laboratory to a request for information, ENAC will consider the annulment of the file.

ENAC may consider the convenience of making a preliminary visit to the laboratory, in order to prepare the following stages of the accreditation process so that it can be carried out as efficiently as possible.

3.3.3 Appointment of the audit team

ENAC appoints, from its auditors and qualified experts, the members of the audit team that will carry out the evaluation process.

The number of members of the audit team is a function of the scope of accreditation requested but in any case, with a chief auditor, and as many technicians as necessary in the tests for which the laboratory requests accreditation.

The laboratory is informed in advance of the names of the members of the audit team and, if appropriate, of the organization to which they belong. The laboratory could recuse them in writing, providing that the reasons that they understand could compromise their independence and impartiality. In this case ENAC will analyze the reasons given and will communicate its decision to the applicant.

3.4 The audit process

3.4.1 Study of the technical documentation

The accreditation process begins with the study of the documentation by the auditors appointed to evaluate the adequacy of the procedures within the scope of accreditation requested. If the result of that documentary study is satisfactory, the audit will proceed.

3.4.2 Audit

On the date agreed with the laboratory, the designated audit team conducts an audit visit, the purpose of which is to verify compliance with the accreditation criteria. Prior to the visit, the chief auditor sends the audit plan to the laboratory.

The audit takes place in three phases:

1. Initial meeting: it takes place between the representatives of LABCOMB and the audit team. During this initial meeting, the appropriate presentations are made, the audit plan and the scope of the audit are confirmed, and the system to be followed is indicated.

2. Development of the audit: the audit team proceeds to observe the operation of the laboratory and to assess compliance with the accreditation requirements.

The realization of some tests, of those included in the scope to be evaluated, to verify the correct performance of them is requested.

3. Final meeting: its main purpose is to present to the laboratory managers a summary of the results of the investigation.

3.4.3 Audit team report

The audit team, within a period of no more than 15 business days from the date of the audit, prepares a report with the results and information gathered during the audit, which is sent to the laboratory for its information.

The report of this audit has a validity period of 6 months from its date of issue. After this period it may be necessary to carry out a new audit to decide on the accreditation of the laboratory.

3.4.4 Laboratory response

Once the audit report is received, LABCOMB acts as indicated in Operational Note NO-11 "Deviations, classification, and treatment," responding to the possible "nonconformities" and "observations" raised in the report. The laboratory can claim those extremes of the report with which it is dissatisfied.

The decision of accreditation must be made within the validity period of the audit report; to ensure that the decision can be made within that period, the laboratory sends the response before the prescribed period is met.

3.5 Accreditation decision

To grant accreditation, the Accreditation Commission must rely on the technical competence of LABCOMB to carry out the activities for which it requests accreditation and must trust that the accreditation requirements are met and the deviations detected in its case have been adequately addressed.

The Accreditation Commission analyzes the information generated during the evaluation process and based on this adopts the decision of "grant accreditation" in July 2010.

3.5.1 Certificate of accreditation

After a favorable decision and once LABCOMB pays the corresponding costs, ENAC issues a Certificate of Accreditation, which attests to the granting of accreditation in favor of the laboratory.

3.6 Use of the ENAC trademark

Once accredited, the laboratory has the right to make use of the ENAC trademark or reference to its accredited status under the conditions established in document CEA-ENAC-01 "Criteria for the use of the ENAC trademark or reference to the status of accredited."

3.7 Validity of the accreditation

Laboratory accreditation is considered valid as long as LABCOMB continues to meet the criteria established by ENAC and the obligations resulting from its accreditation.

The laboratory may, at any time, request a voluntary temporary suspension of all or part of the scope of accreditation. The voluntary temporary suspension implies the temporary prohibition of the use of the ENAC trademark or reference to the status of accredited as established in document CEA-ENAC-01.

3.8 Maintenance of accreditation

The maintenance of the accreditation is structured in a first cycle of 4 years and subsequent cycles not exceeding 5 years in which LABCOMB was submitted by ENAC to the following activities:

- Follow-up audits between reevaluation periods
- Reassessment audits: 2014 and 2018

In order to maintain accreditation, the Accreditation Commission must trust that the laboratory maintains its technical competence for the activities included in its accreditation scope, the accreditation requirements continue to be met and the detected deviations, if any, have been adequately addressed.

In 2010, LABCOMB included five tests in the requested scope. Currently, the number of accredited tests is 13: between 2010 and 2018. LABCOMB has not only maintained accreditation but has also increased the number of tests within its scope.

4. Conclusions

Obtaining the ISO/IEC 17025 accreditation by LABCOMB has allowed the laboratory to recognize its technical competence both nationally and internationally, which allows it to:

- Work regularly for various strata of Spanish public administration
- Greater visibility and better positioning among laboratories that offer the same services, which has increased the number of customers and has achieved their loyalty
- Work for the European Commission, Directorate General, Joint Research Centre, Directorate-D, Institute for Reference Materials and Measurements from the certification of the cold filter plugging point (CFPP) and the cloud point (CP) in gasoil and biodiesel

The implementation of the ISO 9001 and ISO/IEC 17025 Standards has improved the overall management of the laboratory in all its activities and has made it possible to demonstrate its technical competence; but also, since it is a university laboratory, the staff that works and is trained in it gets a curricular bonus that makes it valuable for different companies that look for personnel trained in high-quality standards.

In the near future, LABCOMB plans to extend its commitment to quality and consider Integrated Quality Management. There are many similarities between the concepts of quality management, environmental management, and management of occupational risk prevention, since the principles of good management are the same, as well as their implementations and regulatory points.

Integrated Quality Management is an increasingly recurrent option that is chosen by those organizations that maintain a strong commitment to excellence in their products, services, and processes.

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Chapter 6

Determination of Essential Parameters for Quality Control in Fabrication of Piezoelectric Micropumps

Matej Možek, Borut Pečar, Drago Resnik and Danilo Vrtačnik

Abstract

Quality control of piezoelectric micropumps is presented through design, fabrication process, operation, and characterization. The presented study resulted in the extraction of a minimal set of monitored parameters, which is a prerequisite for reliable and stable micropump operation. Micropump fabrication process steps, especially bonding process quality, in correlation with quality control of micropump constituent components (housing, elastomer, and piezoelectric actuator) provided an explanation for deterioration of common micropump characteristics, such as flow vs. backpressure, suction pressure, and excitation signal. These characteristics also manifested in deterioration of other important micropump properties, such as self-priming ability, bubble tolerance, long-term stability, heat dissipation, and temperature operating range. Besides air and DI water pumping, chemical compatibility of constituent materials was confirmed during successful long-term testing of micropumps by pumping media with different viscosity and aggressive media with low pH value. The extracted set of parameters defines input control for micropump fabrication process while at the same time establishes safe operating area of fabricated micropumps. The presented set of parameters provides quality control guidelines and enables a direct comparison from pump-to-pump or run-to-run variations and extraction of influencing design or fabrication parameters.

Keywords: microcylinder pump, self-priming, bubble tolerance, PZT actuator

1. Introduction

Micropumps are essential components of microfluidic systems. Due to their small size, energy efficiency, low fabrication cost, high performance, and reliability, they are extensively versatile in vital areas of human activities. Application fields for micropumps span from microprocess engineering, medical applications, and diagnostics, to cooling the electronic devices, microtool lubrication, and beyond. Among those activities, an important segment of use includes controlled flow management of the reagents in microfluidic chips for biomedical applications [1], chemical process engineering [2], biochemistry [3], and pharmacy [4], where they can be employed in the system separately or in an integrated form. In order to fully

understand the micropump behavior in various applications, micropump as a whole and its constituent parts (piezoelectric disk, elastomer, interlayer adhesive, and plastic housing) have to be thoroughly characterized by taking into account a wide range of parameters. Deterioration of inherent micropump characteristics, such as flow vs. backpressure, suction pressure, and excitation signal are manifested in deterioration of other important properties of micropumps, such as self-priming ability, bubble tolerance, long-term stability, and temperature operating range. Additionally, the quality of micropump system performance is affected by other factors such as viscosity and pH of pumping media, as well as waveform, amplitude, and frequency of excitation signal. All these factors can be explained by the analysis of physical parameter measurements related to evaluation of individual micropump components. Correlations between abovementioned deterioration origins result in a minimal set of dominant monitored parameters, prerequisite for reliable and stable micropump operation. Extracted parameters define input control for micropump fabrication process, while at the same time establishing safe operating area of fabricated micropumps.

The chapter will briefly present micropump design and operation, followed by the description of above-listed micropump characterization methods, which enable quality control. Beside the typical flow rate and backpressure characteristics of the micropump, influence of properties, such as self-priming, bubble tolerance, pumping media compatibility, long-term stability, and temperature dependencies, has been under investigation, and their impact on overall micropump performances has been evaluated. Characterization methods and protocols were established for each of the abovementioned micropump parameters under investigation. Among them, the most relevant characterized parameters for reliable micropump operation will be defined, and correlations which are leading back to constituting components and correlations among them will be presented. Microsystem interactions through pumping media and excitation signal will be thoroughly analyzed, and a resulting set of input parameters in the fabrication of piezoelectric micropumps will be determined. This set of parameters provides quality control guidelines and enables a direct comparison from pump-to-pump or run-to-run variations and extraction of influencing design or fabrication parameters.

2. Case study: microcylinder pump

An innovative microcylinder pump, developed in our laboratory, was selected for a case study of micropump quality control. Microcylinder pump design does not employ any check valves. Instead, it operates on a principle of active sequential expansion (opening) and compression (closing) of the centrally placed inlet cylindrical rectifying element and outlet throttle rectifying element. The expansion/compression is performed by an actuated glass membrane that is loosely attached via a resilient elastomer to the top of the supporting glass. Exploded view of a typical thermoplastic (TP) microcylinder pump structure with constituent materials and corresponding bonding processes is shown in **Figure 1**.

The TP microcylinder pump comprises polydimethylsiloxane (PDMS) elastomer layer with molded micropump chamber, fluidic microchannel, and rectifying elements (**Figure 1c**). Additionally, two through-holes are punched into an elastomer, one into the center of the micropump chamber and the other one at the end of the channel. PDMS elastomer layer (**Figure 1c**) and PDMS fluidic connections (**Figure 1e**) are covalently bonded to the supporting TP substrate (**Figure 1d**) by employing developed amine-PDMS linker bonding process. One inlet and one outlet fluid port is drilled through a supporting TP substrate that supply and drain the

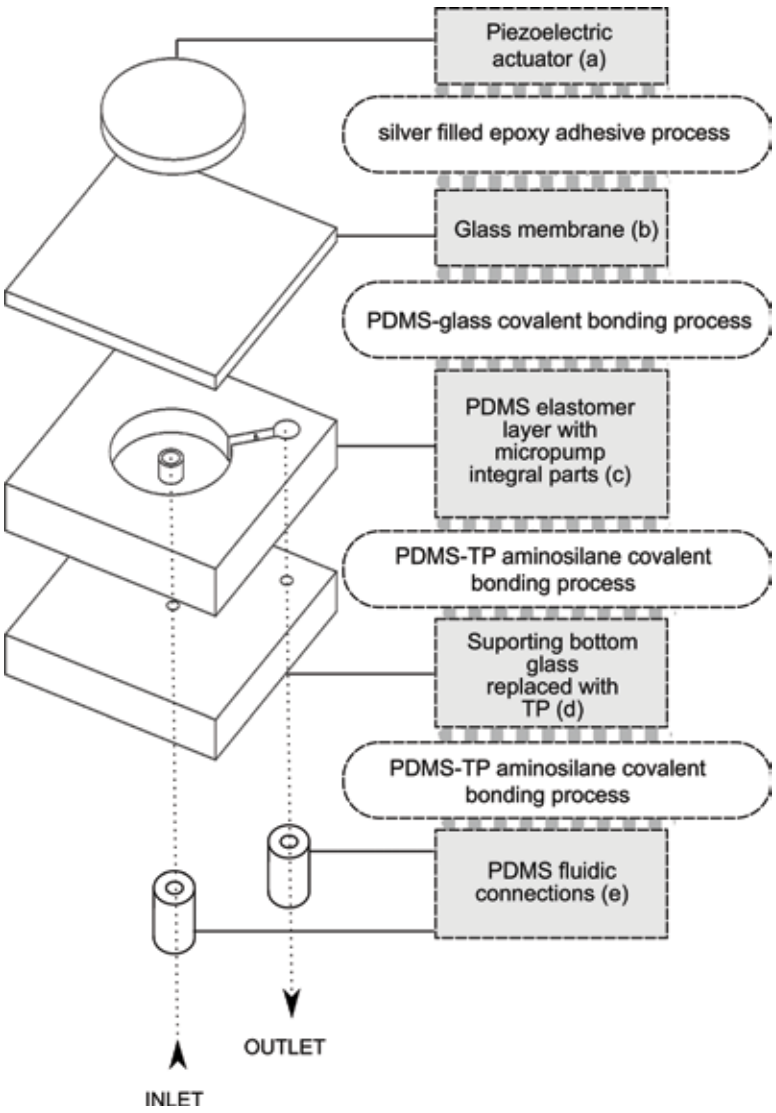

Figure 1.
Exploded view of a typical TP microcylinder pump structure with constituent materials (a - Piezoelectric actuator, b - thin glass membrane, c - PDMS elastomer layer with micropump chamber, fluidic microchannel, and rectifying elements, d - supporting TP substrate, e - PDMS fluidic connections) and corresponding bonding processes (dimensions are not to scale).

fluid into and out of the pump. The micropump chamber and the microchannel are sealed with a thin glass membrane (**Figure 1b**) by employing oxygen plasma PDMS-glass covalent bonding process. Piezoelectric actuator (**Figure 1a**) is positioned in the axis of a micropump chamber, coupled rigidly to the micropump membrane through silver-filled epoxy adhesive (EPO-TEK EE129-4, Billerica, MA, USA).

Microcylinder pump operation is depicted in **Figure 2**, which is showing (a) the micropump with no excitation signal applied and two distinctive operation cycle phases, (b) pumping phase and (c) suction phase. During excitation, loosely attached glass membrane and PDMS elastomer layer deform in a controlled manner, which enables compression and expansion of the centrally placed inlet cylindrical port, micropump chamber, and outlet throttle shaped port with a specific phase lag, contributing to efficient micropump operation.

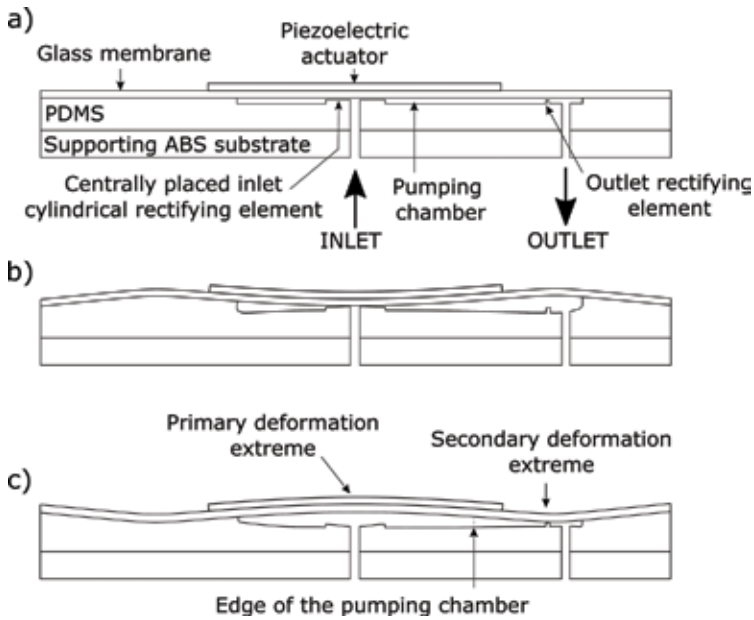

Figure 2.
Microcylinder pump operation cycle: (a) No excitation signal applied, (b) suction phase (membrane expansion), and (c) pumping phase (membrane compression).

Detailed microcylinder operation and fabrication process is reported elsewhere [5].

3. Fabrication quality control

3.1 Quality control of micropump housing

Micropumps were first developed on flat ABS substrates. In this case, surface flatness of ABS is usually in the range 5–7 μm and does not introduce any notable stress in glass membrane after covalent bonding, which would result in micropump performance deterioration. In a more mature phase of development, efforts were focused toward industrial product. Therefore, ABS housing was developed with corresponding changes to adapt all the previous assembly steps. The influence of specific housing construction and adapted process steps should be therefore carefully evaluated in terms of micropump performances. The flatness of the injection molded ABS housing, which serves as a micropump substrate, was found to be critical, since the PDMS and glass membrane are attached by covalent bonding directly on flat part of ABS housing. Irregular flatness of ABS substrate directly transfers on the membrane via strong chemical bonds and results in a local mechanical stress.

Quality of the surface relief should be closely monitored in the stage of injection molding by adjusting the process parameters. Prior to optimization, the surface topography scans (**Figure 3a**) showed flatness tolerance around 40 μm with high gradients that resulted in poor yield and low flowrate and backpressure performances. The stress in glass membrane can further affect the pump behavior via severely decreasing the throttle valve gap, consequently causing spontaneous sticking of PDMS and glass and ultimately a malfunction.

After adjusting the injection molding process parameters, we were able to achieve flatness comparable with flat substrates and were below 10 μm across 2×2 cm^2 area of the housing size, which is shown in **Figure 3b**.

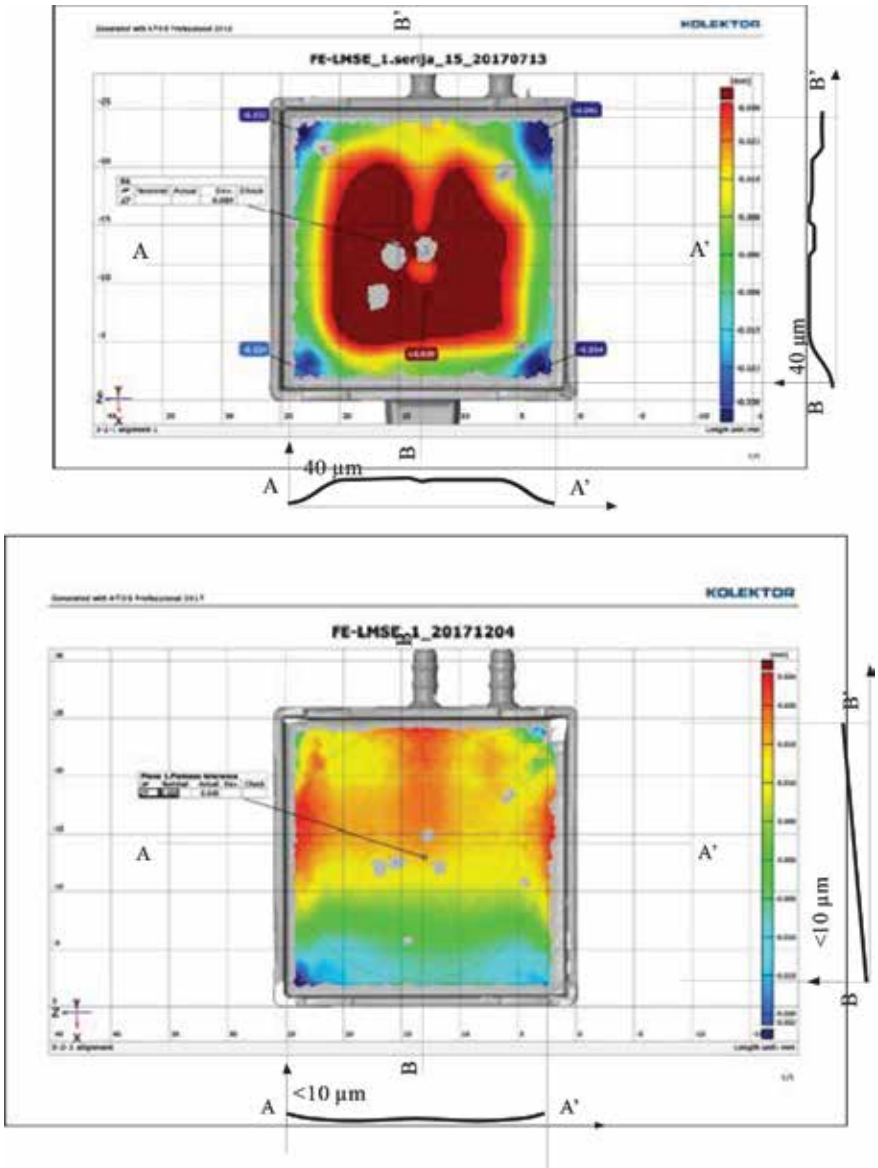

Figure 3.
Flatness profiles of (a) irregular surface in the early stage of development causing frequent micropump malfunction and (b) surface that fulfills the tolerance range of micropump performances and reliable operation (Kolektor Group, Idrija, Slovenia).

Flatness tolerance below 10 µm was found to accommodate bonded layers, keeping them in low-stress regime, thus, without affecting the pump performance. This measurement with established tolerance was found to be one of the prerequisites in a sequence of quality control steps.

3.2 Quality control of micropump bonding process

Covalent bonding of constituent micropump components during fabrication process has many advantages over use of adhesives. Covalent bonding does not introduce any additional materials, which would get in contact with aggressive pumping media. Due to absence of glue, micropump fluidic structures cannot be contaminated or even clogged during fabrication process.

Many strategies for plastic-PDMS bonding have been reported, such as sol-gel coating approach, chemical gluing approach, and organofunctional silanes approach [6, 7], where thermoplastics in the presence of amine undergo aminolysis followed by chain scission of the carbonyl backbone, forming a strong urethane bond. One of organofunctional silanes is amine-PDMS linker (poly [dimethyl siloxane-co-(3-aminopropyl) methyl siloxane]). Amine-PDMS linker incorporates an amine functionality at one terminal and a segment of low-molecular-weight PDMS at the other, which provide better hydrolytic bond stability over commonly employed organofunctional silane APTES [8].

In our micropump fabrication process, thermoplastic (TP) substrates are cleaned in ultrasonic bath, followed by silylation of the surfaces through the use of amine-PDMS linker. After plasma activation, the activated surfaces of the two substrates are brought into contact, using methanol as an aligning medium. Detailed bonding process procedure was reported elsewhere [9].

It is reasonable to evaluate bond strength by employing effective destructive methods on simple burst pressure test devices rather than on fabricated micropumps. Pressure regulated air supply is connected to the inlet of the test device and the pressure at which the device fails is determined. Burst pressure test devices enable optical observation of bond failure at fluidic channel sharp corners, where the structural stress caused by applied fluidic pressure is the largest. Burst pressure tests should be performed with water and compressed air.

Our burst pressure tests confirmed hydrolytic stability of TP-PDMS bonds established through amine-PDMS linker [9]. It is speculated that the water-repelling nature of the PDMS component in amine-PDMS linker prevents penetration of the aqueous solutions at the interface improving bond hydrolytic resistance [10, 11].

3.3 Elastomer mechanical properties control

Mechanical properties of viscoelastic PDMS material, which is one of the crucial parts of here discussed micropump, are mainly influenced by mixing ratio, curing temperature process, and additional aging at moderate temperatures to stabilize the polymer. It is therefore mandatory to determine the appropriate parameters in the preparation phase that can later affect the micropump operation.

According to our measurements and evaluations performed, micropump flow rate and backpressure performance depend strongly on curing temperature of PDMS polymer as shown in **Figure 4**.

In this particular experiment, four microcylinder pumps were fabricated differing only in PDMS elastomer curing temperature setting during fabrication process. First sample underwent our standard curing temperature of 80°C, and three others underwent curing temperatures of 110, 150, and 200°C. Curing time at all selected curing temperatures was set to 2 hours. After the micropumps were assembled, they were additionally exposed to a setting temperature of 80°C for 14 hours. This process step is a standard step in our well-established micropump fabrication process and was initially introduced in order to stabilize covalent bonds between constituent materials.

It was shown that DI flow rate can be reduced by more than 50%, if curing temperature is increased from 80 to 200°C. Correspondingly, Young modulus of elasticity (E) from the literature [12] increases by 61% in this temperature range. Increased PDMS curing temperature reflects in greater stiffness of elastomer layer, which impairs the magnitude of membrane deformation, pumping stroke volume, and rectifying elements efficiency. By taking into account the same base to

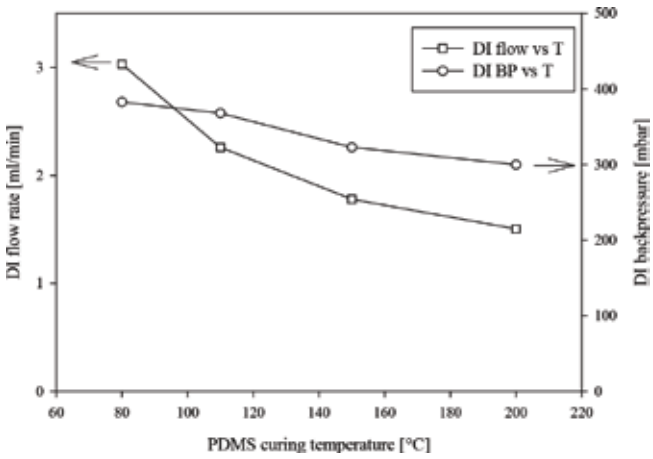

Figure 4.
Micropump flow rate and backpressure performance vs. curing temperature of PDMS polymer.

polymerization component ratio, increased Young modulus of elasticity is in agreement with reduced DI flow rate.

4. Essential micropump measurements for quality control

An automated system for micropump characterization was designed. Such system comprises a high voltage waveform generator, which is connected to a PC and a dedicated computer software that automatically drives the micropumps and simultaneously saves measured flowrate or back pressure data. Instantaneous water flowrate can be measured with flow meter or as in our case computed by gravimetric method ($Q = dm/dt\ \rho$), employing a precision scale connected to a PC. If gravimetric method is used, the water level of collecting tank on the scale should be matched with water level of storage tank by placing the tank on laboratory elevator. To minimize evaporation of water from a surface of an open collecting tank, the tank can be shaped as a cylinder with a small diameter. Falling droplets can be avoided by pre-filling the collection tank with tare amount of water.

In our case, excitation signal frequency at constant amplitude or vice versa is swept automatically (0–300 Hz with step of 5 Hz every 10 s and 0–250 V with step of 5 V every 10 s, respectively). Instantaneous air flowrate is measured with Microbridge Mass Airflow Sensor (AWM3150V, Honeywell, NJ, USA), while instantaneous backpressure/suction pressure of both water and air is measured with calibrated differential pressure sensor (HCX005D6V, First Sensor AG, Berlin, Germany). Both are connected to PC via digital multimeter Keithley 2700 (Keithley instruments, OH, USA).

First, frequency sweeps are performed up to 300 Hz at maximum admissible amplitude in order to determine optimal performance frequency for a given pumping medium. After the optimal frequency is evaluated, the amplitude sweeps are performed up to maximum admissible value at optimal excitation frequency. In both measuring procedures, flowrate or backpressure/suction pressure data are simultaneously acquired. An example of measured performance characteristics is shown in **Figure 5** [5].

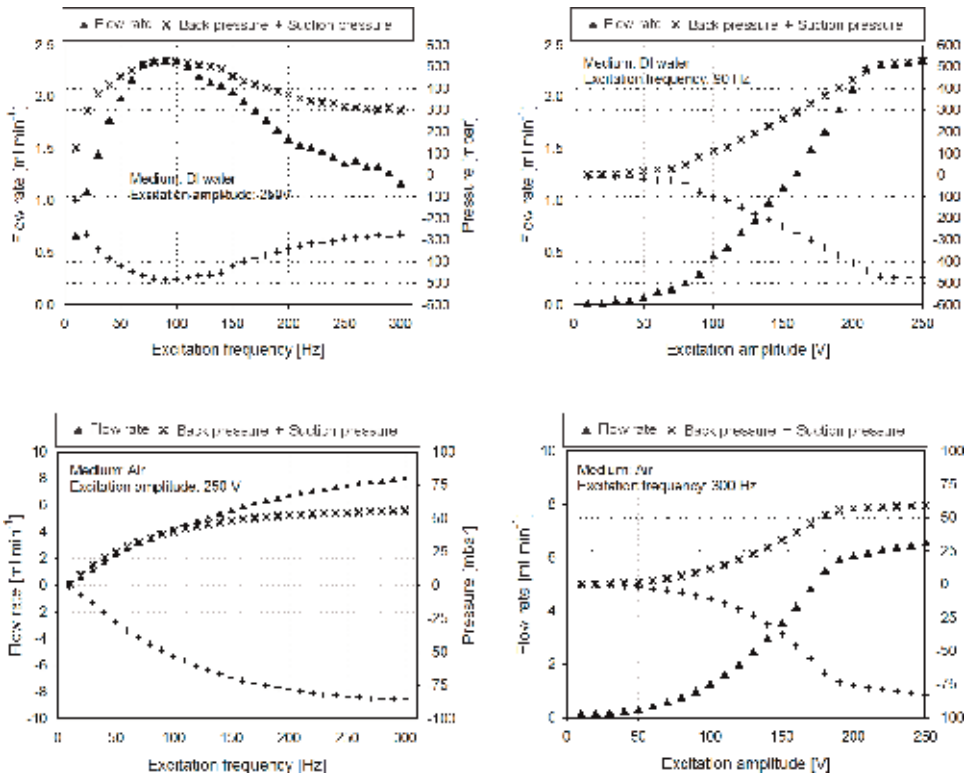

Figure 5.
Flow rate, backpressure, and suction pressure vs. excitation signal frequency and excitation signal amplitude characteristics for DI water and air.

5. Additional parameters for assessing pump quality

5.1 Quality control of PZT actuator

PZT actuator converts one part of electrical energy into mechanical energy needed for micropump operation. Ferroelectric ceramics are subjected to degradation either during electrical loading (fatigue) or with time in the absence of an external mechanical or electrical load (aging) [13].

To assess the stability of piezoelectric actuator, piezoelectric d_{33} modulus measurements were performed first on unattached piezoelectric actuators using d_{33} piezometer PM10 (@100 Hz). Measuring of d_{33} modulus is fast and easy to perform in opposition with d_{31} modulus that requires advanced and time-consuming measuring methods. It was assumed that measured d_{33} modulus and essential d_{31} modulus that affect micropump operation are proportional to each other. Degradation of d_{31} modulus is our core concern as it directly affects micropump flowrate and backpressure performance stability.

Piezometer d_{33} system implements Berlincourt method. After clamping the sample and subjecting it to a low frequency force, the system processes the electrical signals from the sample, compares it with a built-in reference, and calculates d_{33} modulus. Modulus d_{33} implies an induced strain in direction of PZT disc rotation axis per unit electric field applied in the same direction.

First, d_{33} modulus stability over time was evaluated by applying stable square excitation waveform and custom generator waveform on unattached PZT samples

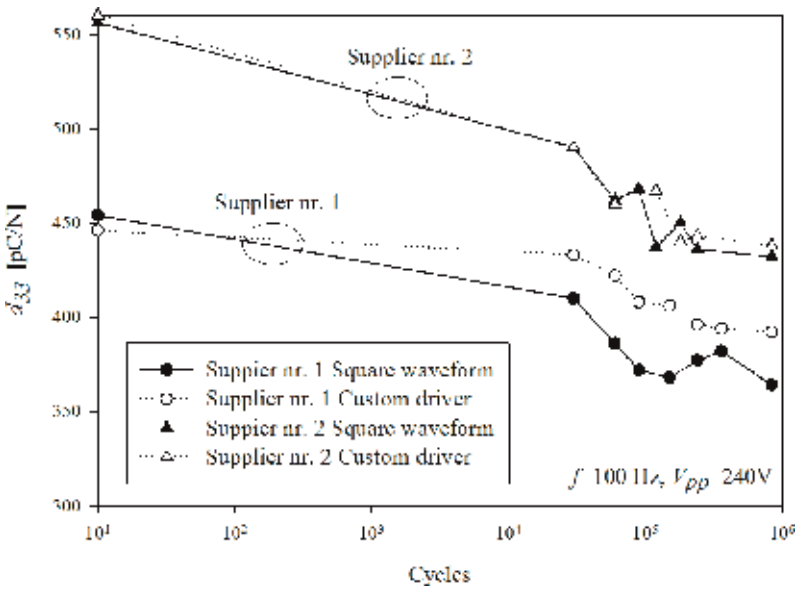

Figure 6.
PZT d_{33} modulus stability vs. switching cycles.

for 140 minutes in total. In between, the samples were repeatedly disconnected, clamped into d_{33} piezometer, measured, and then connected again to the driver. To minimize measurement error, samples were always clamped on the same central spot. **Figure 6** shows measured d_{33} modulus vs. number of switching cycles for two commercially available PZT samples for two applied waveforms with a frequency of 100 Hz and with an excitation amplitude of 120 V. For both PZT samples, d_{33} modulus decreased mainly in the first 10^5 switching cycles (−21% for manufacturer nr. 1 and −19% for manufacturer nr. 2), after that the downward trend was significantly reduced.

As expected, d_{33} modulus stability was affected also by excitation signal shape. In our case, square excitation waveform yielded greater decline (+9.3% for manufacturer nr.1 sample and + 6.3% for manufacturer nr. 2 sample) in d_{33} modulus in first 10^5 switching cycles compared to custom driver waveform.

Next, d_{33} modulus stability was investigated regarding the amplitude of applied excitation signal. Before each d_{33} measurement, samples were driven with square excitation waveform for 10 seconds at preselected excitation signal amplitude values. Measurements on samples after initial operation by applying electric field yielded higher d_{33} values compared to measured off-the-shelf d_{33} values. It is also known from the literature that after poling step, the material microstructure tends to relax the in logarithmical manner, thus decreasing the initial d_{33}.

After gradual incensement of excitation signal amplitude, d_{33} modulus decreased at a rate of −0.445 pC/NV and − 1.2 pC/NV for manufacturer nr. 1 and nr. 2, respectively. Although manufacturer nr. 2 sample yielded higher initial d_{33} values compared to manufacturer nr. 1 sample, both performed equally at excitation signal amplitude of 160 V. However, manufacturer nr. 2 sample failed permanently at 180 V. Next, d33 modulus stability was investigated regarding the amplitude of applied excitation signal (**Figure 7**).

Regarding micropump operation, PZT fatigue effect is the most evident when measuring the dependency of flow rate vs. applied voltage on PZT. This is the property that deserves close attention when setting the safety margins (safe

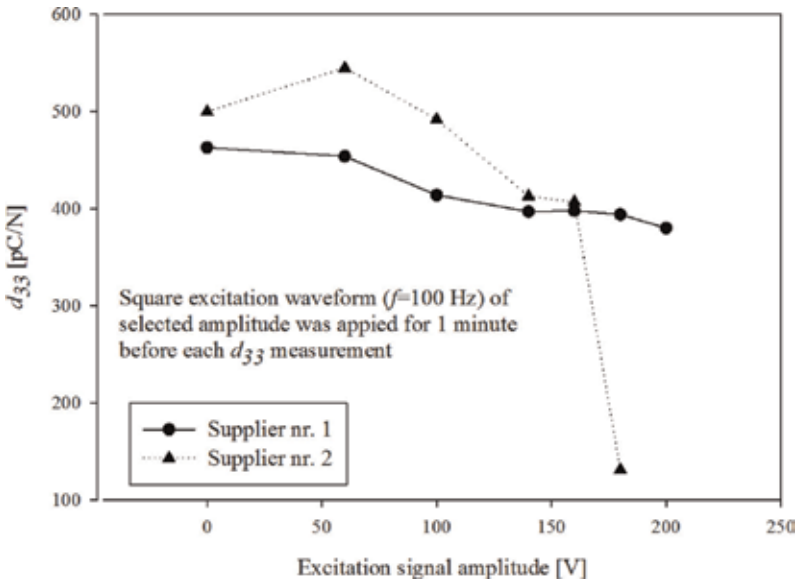

Figure 7.
PZT d_{33} modulus stability vs. excitation signal amplitude.

operation area) and is one of quality criteria finally reflected through the pump performance deterioration.

Figure 8 shows how flow rate increases linearly with excitation amplitude and is stable with time. This is true at each point shown until the amplitude level of 110 V for the presented case. However, when abovementioned amplitude was exceeded (which might be below the value specified by manufacturers), the flow does not respond in a linear manner and also the time stability of flow rate (as being checked at each point shown) is not maintained. After reverting to lower voltages again, the flow is irreversibly reduced, showing that PZT actuator is severely affected when

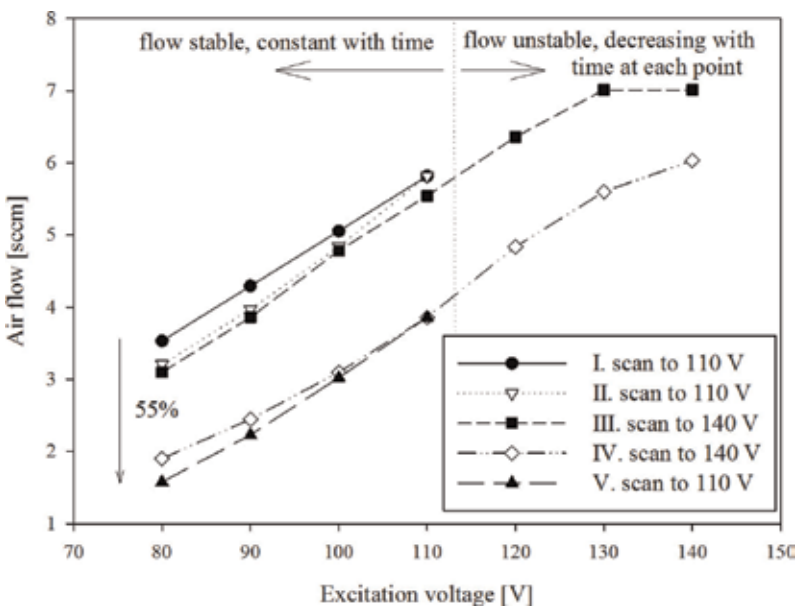

Figure 8.
Excitation amplitude safe operation range and reduced flow when exceeding the limiting amplitude.

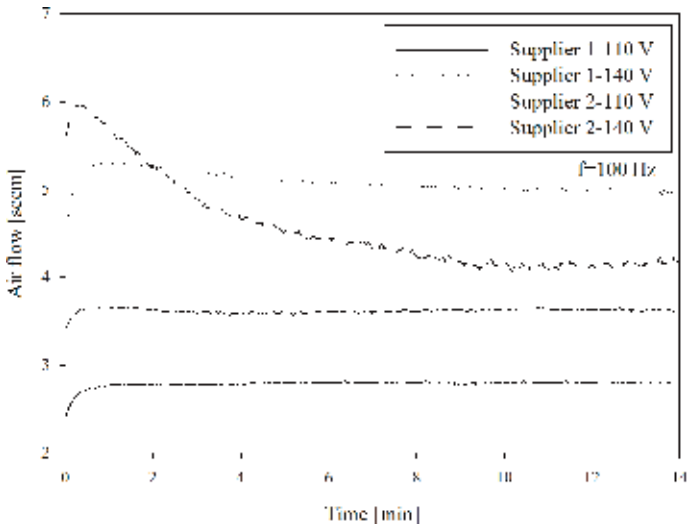

Figure 9.
Time stability for two types of PZT, driven at limiting amplitudes.

overdriven. Instead, it behaves as shown in **Figure 9**, and at 140 V, (shown for two distinct manufacturers) one preserved the air flow stability, the other deteriorated rapidly.

5.2 Micropump chemical compatibility

Constituent materials of the micropump being in direct contact with medium, each having its specific chemical and mechanical properties, should withstand long-term micropump operation without failure. It is therefore mandatory to determine their chemical resistance and fatigue issues. In this respect, a variety of media with distinct pH and different viscosities should also be included in micropump quality control test set. To provide reliable data in the specification list, the micropump tests were performed under continuous operation in the time period between 10 and 300 hours. A set of presented tests, summarized in **Table 1**, comprised common

Medium (/)	Dynamic viscosity (mPas)	pH (/)	Density (g/cm^3)	Test time (hours)	Flow rate (ml/min)
DI water	1	6.5	1	24	1.73
City water	1	7.1	1	24	1.68
Glycol DG372	32	10	1.09	6	0.033
Saline 0.9% NaCl	1	7	1	6	1.62
PBS	1.07	7.4	1.06	6	1.61
Sn bath	NA	1	1.62	48	0.49
Ni bath	NA	4	1.64	90	0.37
1 M H_2SO_4	1.12	1	1.07	136	0.45
DI water after tests	1	6.5	1	1	1.71

Table 1.
Typical micropump performance evaluation for different media.

liquids that might be potentially encountered for pumping in a laboratory or industrial R&D environment.

Micropump materials exposed directly to the chemicals in the presented case are Tygon ND 100-65 tubes, ABS polymer substrate, glass membrane, and PDMS channel. Tests were performed by continuous pumping from a 5 ml reservoir of fluid in a closed loop system.

One criterion to reassure quality and compatibility was to monitor the flow rate variations over period of time. It can vary due to deterioration of materials themselves or due to particles that can cause obstructions in pumping chamber or in throttle region, since the tests were performed without any additional filtering. After the tests were completed, the flow rate of DI water should be maintained as compared to values obtained prior to tests. This will confirm that the constituent materials are chemically resistant to the media tested. Careful optical inspection of potential obstructions was found at throttle only due to unfiltered tap water and none of potential products (aggregates) due to unexpected chemical reaction between the aggressive media and pump materials. It should be kept in mind that for high viscosity medium, such as glycol, the excitation frequency should be lowered to obtain optimal flow rate. Phosphate-buffered solution (PBS) and physiological solution (0.9% NaCl) were also successfully pumped for 6 hours with constant flow rate, showing the pump is useful for biological experiments.

Furthermore, micropump was subdued to even more rigorous tests with a set of aggressive media to evaluate chemical resistance. One of the potential proposed applications of micropump was to periodically replenish small amounts of solutions in electroplating tin and nickel baths. Exact compositions of solutions given by industrial partner were not revealed, but are commonly used in metal electroplating industry. First, we determined pH and specific gravity of each to convert it into flow rate. It should be mentioned that during these tests, the same pump was used for all three liquids. DI water purging between each medium test was performed and exactly measuring a reference DI flow rate prior to, between the tests and after tests. Short term stability was first monitored for 2 hours for each media (**Figure 10**), followed by separate long-term tests (**Figure 11**). The properties of aggressive media, flow rate, and test duration are given in **Table 1**. The raw data can be further used to set the flow control loop.

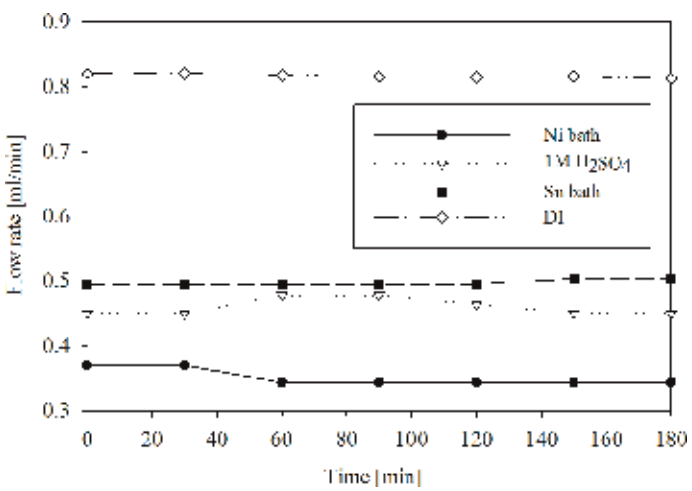

Figure 10.
Continuous short-term pump operation for three aggressive media and DI water.

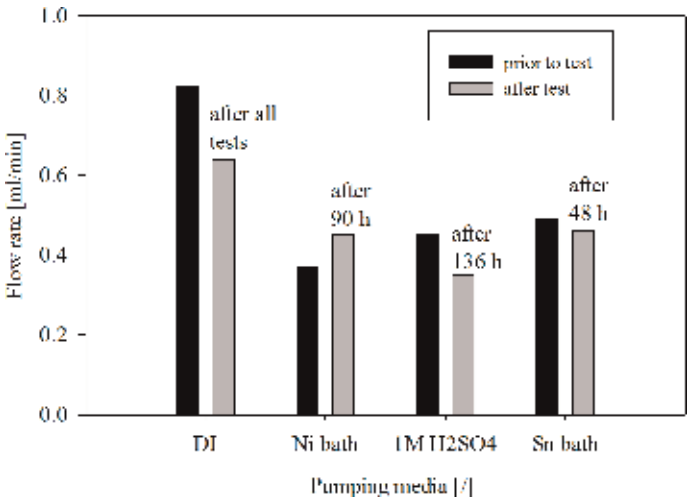

Figure 11.
Continuous long-term pump operation for three aggressive media and DI water.

Alcohols and solvents are particular group of media that require careful consideration. PDMS, which is used in presented micropumps, is not compatible with latter as it is subdued to swelling when exposed to solvents. It was determined that swelling reduces the geometry of gaps and obstructs the flow irreversibly.

5.3 Self-priming

In principle, presented micropumps are intended to pump liquids, however, one of the figures of merit is the pump self-priming parameter, that is, the ability of the dry micropump to pump air until the liquid is dragged into the micropump chamber from the reservoir, which might be in certain cases located below the micropump level.

After several experimentally performed priming tests, it was determined that one should strictly distinguish between three approaches to define micropump priming property as the values may differ significantly: First approach is to measure air suction pressure (SP) at pump inlet by means of pressure sensor, with the outlet open to atmosphere. The second approach is to suck the liquid from the reservoir located well below the pump level and measure the height of water column in the tube up to which the pump drags the medium and holds it there (named "quasi priming"). It was determined that the latter two values do not necessarily exhibit the same values. Third, the most rigorous approach and the only relevant priming value is accomplished when the pump drags the water column from the reservoir below into the pumping chamber and fluid appears at the pump outlet. The height difference between a water level in a reservoir and the pump in this "real priming" gives always lower values (35–50%) than the previous two priming criteria. The differences and a noteworthy proportionality of the obtained values for a representative run of eight micropump samples are presented in **Figure 12**(left). Quality control should as well consider users scenarios such as semi dry pump priming (e.g., usage after extended periods in idle state with partially remained water inside). Micropumps have to be repeatedly tested to reveal the safety margins and to set the user specs, so the pump survives a potential misuse. In addition, self-priming is a function of actuator driving parameters, such as voltage, signal waveform, and frequency as shown in **Figure 12**(right). Here, the priming response is linear with increasing frequency for voltages below or equal 110 V, while above this

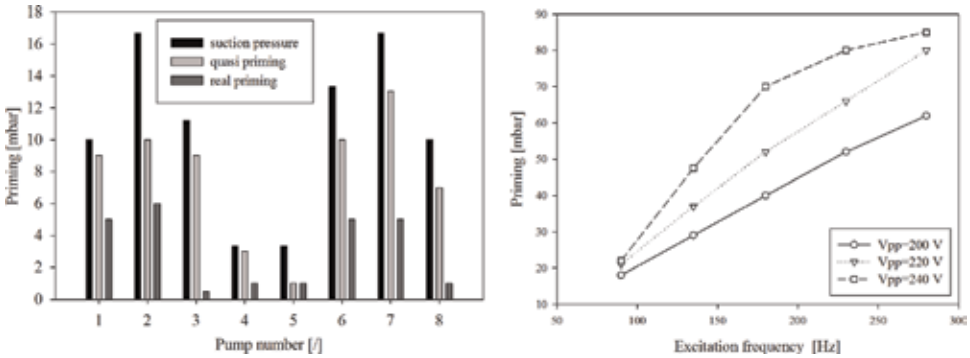

Figure 12.
Micropump priming comparison, based on self-priming methods (left). Self-priming vs. actuator driving voltage, signal waveform and frequency (right).

value tends to be influenced by PZT degradation and/or self-heating as shown previously in **Figures 8** and **9**.

5.4 Bubble tolerance

In particular cases, when the media flow in the pump supply line is disrupted by sporadic gas bubbles, formed from various reasons [14], the pump has to be able to continuously operate with both media; not only at open outlet (without load) but as well at defined load (backpressure-BP), which should be considered a common situation in real application. This is so called bubble tolerance (BT) parameter and is an additional micropump figure of merit. It is mainly a function of cylinder, throttle, and chamber design and geometry. By narrowing the gaps between membrane and cylinder/throttle and by decreasing micropump chamber depth, rectifying elements efficiency and compression ratio, respectively, are improved [15]. A combination of high rectifying elements efficiency yielding good backpressure for pumping liquid (load dependent) and high compression ratio yielding ability to pump air (expelling air from the cylinder) lead to bubble tolerant micropump. There are approaches to avoid such air bubble disruptions but require additional devices or degassing methods, which is inconvenient [14]. In our methodology, bubble tolerance test is performed by interrupting a continuous DI water flow with the introduction of air slugs, 2–4 mm long into the pump suction inlet tube (ID = 1.5 mm) every 10 seconds. This was performed as long as the water column at the outlet tube built up. Final height of output water column is proportional to the maximal backpressure at which the pump still digests air bubbles and continuous DI water pumping is ceased. The operating safe area should be set below this point, according to its known flow rate vs. backpressure characteristics. As determined empirically, qualitative criterion can be obtained as well from other measured parameters. By comparing seven measured micropump parameters for each of five pumps from the same run (**Figure 13**), it was determined that there is the strongest correlation of bubble tolerance with air flow and water backpressure performances as discussed above. In quality control process, this enables us to evaluate the property without performing explicit, time-consuming BT testing for each micropump.

5.5 Temperature dependency of flow rate

It is well-known that micropump flow rate is inversely proportional to medium viscosity as given by Poiseuille expression for flow inside the microchannel. In this

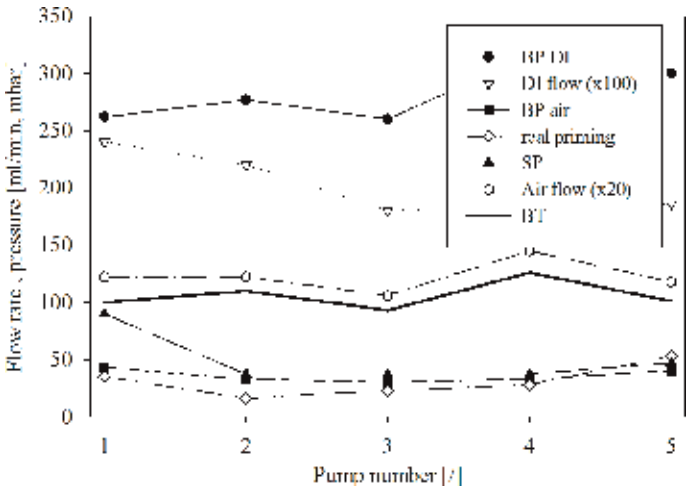

Figure 13.
Bubble tolerance correlation with other micropump performance parameters for run of five micropumps.

respect, it is further very important to take into account as well the strong temperature dependency of the medium viscosity, which is additionally affecting the flow-pressure performance. For example, water dynamic viscosity is known from the literature to decrease by ca. 30% in the temperature range between 20 and 35°C, while the water density decreases only by 0.4% in the same temperature range and is therefore negligible if we want to introduce correction method. It was experimentally determined that for deionized water, the increase of flow rate with temperature closely follows the well-known decrease of viscosity but only up to 42°C (**Figure 14**). As shown, flow rate above this temperature tends to decrease rapidly. It is assumed that above this point, the temperature dependency of material properties, such as PDMS and PZT actuator tend to deteriorate the pump performances. Besides, at higher temperature, additional microfluidic phenomena such as degassing and cavitation might contribute to flow rate decrease. Based on these experimental data, we included the above temperature-dependent viscosity

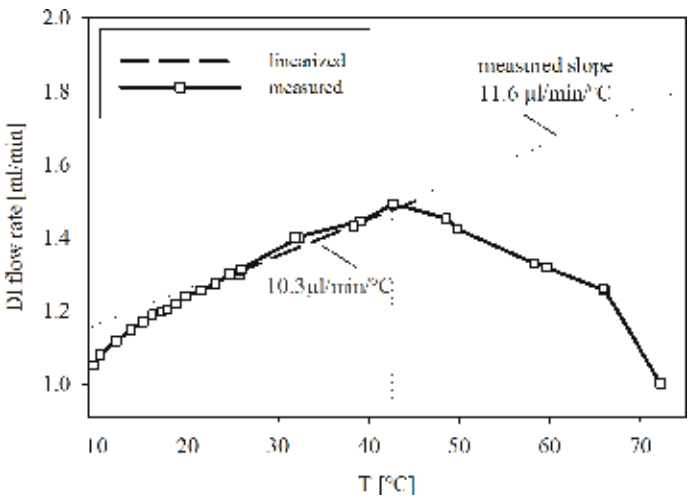

Figure 14.
Pump flow rate vs. DI water temperature.

correction factor in the results of our long-term flow rate stability tests as shown in **Figure 15**. Two micropumps were continuously pumping DI water in closed loop for a period of 27 weeks without particular ambient temperature control. The temperature and flow rate variations were measured periodically. It is very evident that flow rate variations (lines without symbols) are closely related to temperature variations (**Figure 14**, full circles). By implementing the correction for a temperature dependency of viscosity obtained from **Figure 15**, the apparent flow rate variations were mitigated, meaning that pump performed more stable that shown by raw data. In general, taking into account the correction around reference temperature, 20°C, which accounted for 0.9%/°C the flow rate variations for pump A is realistically improved from a 26% decrease over 27 weeks to 12% and similarly for pump B (**Figure 15**, hollow symbols).

5.6 Heat dissipation

In most applications, PZT actuators are driven at high electric field magnitudes and/or high frequencies. Beside the useful conversion into mechanical work, a significant amount of heat is generated within nonideal PZT. Heat generation can considerably affect the reliability and piezoelectric properties of micropump actuators, and may also limit their application since it heats the adjacent materials, and at last but not least also the pumping medium. Self-heating, that is, heat generation within the piezoelectric actuator due to electrical and mechanical losses, is a major concern for high-frequency applications, where increased stress and even degradation of the actuator is expected. In sinusoidal excitation, the average power dissipation P in a piezoelectric actuator can be estimated using the expression below,

$$P = \frac{\pi}{4} fC \tan\delta U_{pp}^2 \tag{1}$$

where $\tan\delta$ is the dielectric dissipation factor, C is apparent PZT actuator capacitance, U_{pp} is peak-to-peak operating voltage, and f is the operating frequency.

To be able to evaluate the thermal response of the micropump as a thermal system, it is necessary to know the geometry and thermal properties of individual materials such as thermal conduction, free surfaces, fluid type, and flow for the

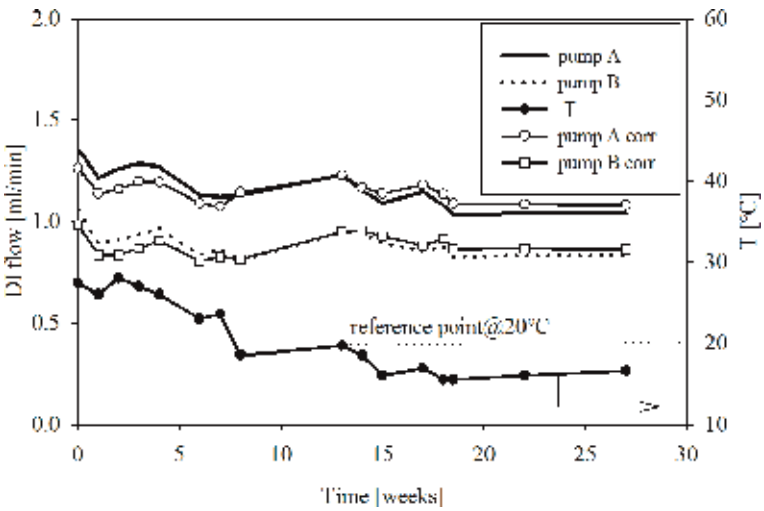

Figure 15.
Long-term testing and flow rate correction due to temperature dependent viscosity of water.

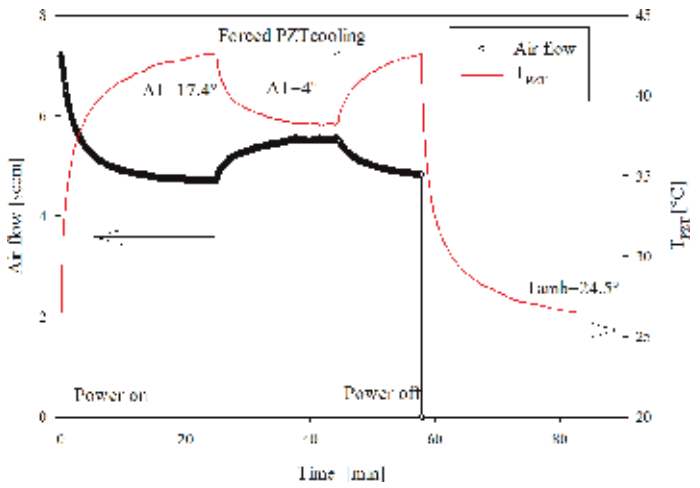

Figure 16.
Interrelation of temperature due to PZT heat dissipation and micropump air flow rate.

evaluation of natural or forced convection. It has to be noted as well that piezo ceramics has low heat conductivity but rather high heat capacity, which affects the thermal time constants. It can be found in the literature that for a standard PZT actuator under small-signal conditions, up to 2% of the electrical energy flowing through the actuator is converted into heat. In large-signal conditions, however, 8–12% of the electrical energy pumped into the actuator is converted to heat. Therefore, increased operating temperature can strongly affect the piezo actuator dynamics.

Our recommended approach to determine and characterize how a particular micropump system behaves thermally is to monitor temperature of PZT and/or pumping medium directly by using a temperature sensor mounted on/near the PZT and perform measurements during the micropump operation. This should be correlated with measurements of flow rate or other performance variations. A miniature Pt-100 temperature sensor in our case was mounted atop the PZT disc with special emphasis not to disturb the operation and minimize damping. Once knowing the temperature conditions of PZT, temperature sensor can be placed next to PZT on glass membrane for continuous monitoring purposes.

A very illustrative example of interrelation between PZT temperature and air flow rate is given in **Figure 16** for micropump driven at normal actuating regime. The proposed type of measurements is very useful particularly in pumping systems, where high-flow rate accuracy is required. The measured temperature dependency of flow rate can be further included in compensation algorithm of control loop.

6. Conclusion

For a case study of piezoelectric micropumps quality control, an innovative microcylinder pump developed in our laboratory was selected. Quality control is given by extensive evaluation methodology for assessing mechanical properties of constituent micropump components (Young's modulus of PDMS elastomer and d_{31} modulus of PZT actuator), reliability, and stability of micropump operation (self-priming, bubble tolerance, pumping media chemical compatibility, and heat dissipation) and quality of fabrication process (covalent bond strength, bond hydrolytic stability, and plastic housing surface flatness). Namely, irregular flatness of ABS

substrate directly transfers on the membrane via PDMS elastomer layer. This results in sticking of rectifying elements thus causing micropump malfunction. It is shown herein that micropump operating stability is closely related to PZT excitation signal amplitude, which might cause deterioration of piezoelectric actuator. Degradation of d_{31} modulus due to PZT depolarization or fatigue directly effects micropump flowrate and backpressure performance. In this respect, safe operating area needs to be determined. The methodology to determine self-priming ability criteria is given. It is further shown that in quality control of micropump operation, the bubble tolerance can be estimated indirectly through the micropump airflow and water backpressure performance. Finally, it is shown that temperature dependency of flow rate has to be taken into account. It was determined that it reflects mainly through variations in viscosity at lower temperatures and temperature dependency of material properties of PZT and PDMS at elevated temperature.

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Chapter 7

Determination of Impurities in Pharmaceuticals: Why and How?

Kung-Tien Liu and Chien-Hsin Chen

Abstract

The presence of impurities, particularly the API-related impurities, i.e., degradation-related impurities (DRIs) and interaction-related impurities (IRIs), may affect the quality, safety, and efficacy of drug products. Since the regulatory requirements and management strategies are required to be established and complied, sources of impurities shall be carefully classified prior to take subsequent steps such as development of analytical methods and acceptance criteria. Current international regulatory requirements for the management of impurities in pharmaceuticals were reviewed. Procedures for the identification of DPIs in pharmaceuticals, i.e., ethyl cysteinate dimer, (R)-N-methyl-3-(2-bromophenoxy) -3-phenylpropanamine, sestamibi, etc., using high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS) were studied. Scheme for the establishment of analytical methods and acceptance criteria of process-related impurities (PRIs) and DRIs in accordance with the requirements of International Council for Harmonization (ICH) and algorithm to perform the identification of DPIs by using LC-MS/MS has been proposed. Practice of kinetic study to distinguish PRIs and DRIs, determination of the potential core fragments coupled with a predicted list of relevant transformations for conducting MS/MS scans, applications of stable isotope distribution patterns or natural abundances, practice of mass balance, etc., have been well demonstrated to justify the reliabilities of identification results.

Keywords: pharmaceutical products, impurities, regulatory requirements, analytical strategy, structural identification, validation, verification, LC-MS/MS, kinetic study, stable isotope distribution patterns

1. Introduction

As defined by the United States Pharmacopeial (USP), impurity is "any component of a drug substance that is not the chemical entity defined as the drug substance and in addition, for a drug product, any component that is not a formulation ingredient" [1].

Impurities in drug substance (i.e., active pharmaceutical ingredient, API) or drug product can arise due to synthetic/manufacturing processes, degradation, storage conditions, container, excipients, or contamination. They can be identified or unidentified, volatile or nonvolatile, organic or inorganic species [1–3].

Since different regulatory requirements and management strategies are required to be established and complied, sources of impurities shall be carefully classified

prior to take subsequent steps; for instance, to distinguish an impurity which is simply derived from API alone or actually derived from interaction products of API-excipient, excipient-excipient, or API-residual impurities existing in excipients [4–6].

Despite an increase in the research of impurities, a number of problems are still arisen in the development of identification technologies for degradation products and pathways. The first aim of this research is to address a brief review of the current major international regulatory requirements regarding the management of impurities in pharmaceutical products. Then secondly, a general scheme to establish an analytical method and acceptance criteria of degradation-related impurities (DRIs) and process-related impurities (PRIs) can be proposed, accordingly. Finally, our research will focus on developing a practicable algorithm to perform the identification of DPIs by using high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS). Meanwhile, verification method for the justification of reliabilities regarding identification results will be assessed.

1.1 Classification of impurities

According to the definitions of International Council for Harmonization (ICH), Food and Drug Administration (FDA), and USP, impurities are classified into DRIs, PRIs, residual solvents, and heavy metals as shown in **Figure 1** [1, 2, 7].

Two types of impurities might be API-related. The first type of API-related impurities is generated by degradation of API itself under specific storage conditions, e.g., oxidation, dehydration, carbon dioxide removal, etc. The other type is occurred due to the interaction between API and excipients, container, or residual impurities in excipients, reagents, or solvents [8, 9]. API-related impurities are potentially genotoxic, mutagenic, and carcinogenic risk due to their structure-activity relationship (SRA) [10, 11].

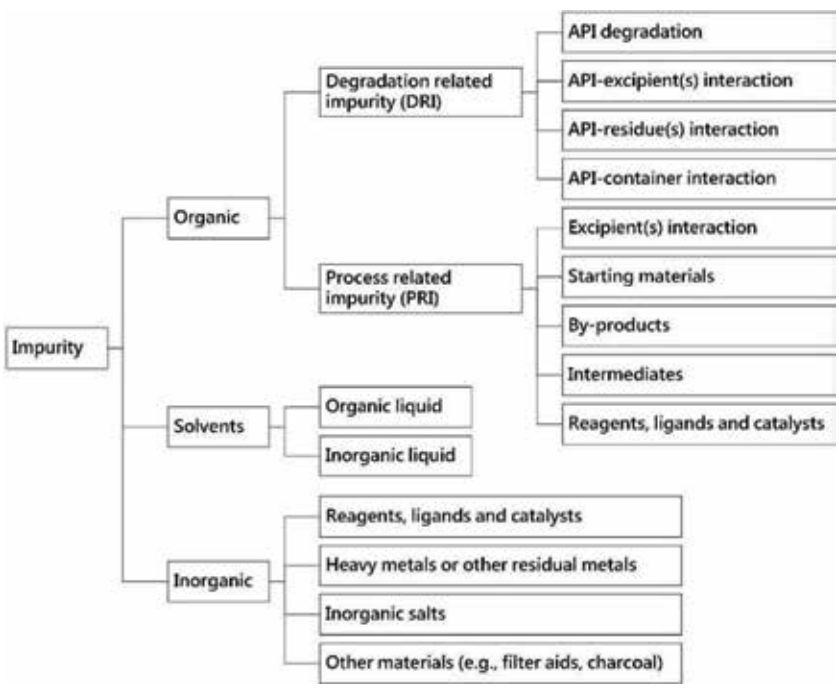

Figure 1.
Classification of impurities [1, 2, 7].

It is well known that excipients or the residual impurities in excipients can be very likely to cause instability of the API and drug product. A lot of impurities in excipients, such as presence of reactive peroxides or high water content in povidone or polyethylene glycols (PEGs), antioxidants in magnesium stearate, aldehydes in lactose, benzaldehyde in benzyl alcohol, formaldehyde in starch, lignin and hemicelluloses in microcrystalline cellulose were illustrated to demonstrate how reactive chemical entities are commonplace in excipients and incompatible to API. Some specific functional groups in API may be susceptible to degradation mechanisms, i.e., hydrolysis, oxidation, polymerization, etc. [4–6, 12–14].

Additionally, extractables and leachables such as initiators/catalysts, storage stabilizers, antioxidants, processing aids, light stabilizers, antistatic agents, colorants, lubricants associated with pharmaceutically relevant materials may also produce uncertain risks to the stability or quality of products [15].

Regardless of the classes of impurities, presence of impurities may have the potential to affect the quality, safety, and efficacy of drug products. Therefore, studies of impurities are one of the most important works in the development of APIs and drug products [1, 16, 17].

1.2 Aims to conduct impurity study

Study of impurities in pharmaceuticals is one of the most highly regarded topics; it is essential, but time consuming and challenging. In terms of regulations and technology, we must keep pace with the times [18, 19]. Comprehensively speaking, aims to develop an impurity study have two major directions as follows: regulatory requirements and scientific/technical demands (**Table 1**).

From the perspective of regulatory requirements, impurities may affect the quality of APIs and DPs and ultimately affect the safety of the patient. Views for the dealing of impurities may differ between biologists, toxicologists, and analytical chemists, and therefore need to be integrated [20]. Potential genotoxic impurities can be determined according to the published literature, results of gene mutation in bacteria, in vitro and in vivo tests of chromosomal damage in mammalian cells or rodent hematopoietic cells, or/and comparative structural analysis to identify chemical functional moieties correlated with mutagenicity [16]. Moreover, daily exposure, duration of exposure on the effects of degradation products and genotoxic impurities, and theoretical clinical dose, whereas potential

Regulatory requirements	Scientific and technical requirements
• Quality and safety of products • Method validation, i.e., specificity • Acceptance criteria determination • Expiry date, retest date, and shelf-life evaluation • Stability and storage conditions study • Threshold limits evaluation, i.e., threshold of toxicological concern (TTC), permitted daily exposure (PDE), etc.	• Synthetic and production processes optimization • Formulation development and optimization • Efficacy improvement • ADME and toxicology study • Manufacturing of reference materials • Stability improvement • DPIs and pathways prediction • Cost consideration

Table 1.
Examples of the aims to conduct impurity studies [20, 23, 25–27].

mutagenic impurities must be controlled to levels less than the threshold of toxicological concern based on lifetime exposure shall be evaluated as a risk consideration [16–18].

Adequate qualification must include genotoxicity and repeat-dose toxicology studies of appropriate duration to support the proposed indication. Moreover, other specific toxicity studies, e.g., embryofetal developmental toxicity study may be appropriate. Genotoxic impurities and degradation products pose an additional risk and should be controlled in accordance with the requirements of ICH M7(R1), unless they are qualified for safety [18, 21].

In addition to the regulatory requirements, internal and external scientific and technical needs are the second perspective to conduct an impurity study. Impurity determination and forced degradation studies are two of the basic requirements as a tool to predict potential DPIs, to develop analytical method, synthetic processes, and formulation, to receive a better understanding of storage conditions, stability of drug product, and to obtain information of degradation products/pathways, as well as to evaluate the specificity (selectivity) of assay method [22–25].

2. Regulatory requirements for the management of impurity

A number of international/local guidelines and guidances for the evaluation and control of impurities in drug substances and drug products have been published [1–3, 7–9, 21, 28–38]. Comparison of the application scopes in line with the impurity categories was drawn as indicated in **Figure 2**.

As said by the requirements of ICH Q3A(R2), all types of impurities present in API at a level greater than (>) the identification threshold must conduct studies to characterize their structures, no matter they are shown in any batch manufactured by the proposed commercial process or any degradation product observed in stability studies under recommended storage conditions. Specified identified impurities shall be included in the list of impurities along with specified unidentified impurities that are estimated to be present at a level greater than the identification threshold [2, 7, 33].

Briefly, five major steps for the management of degradation products, no matter they are degradation products of API or reaction products of API with excipient(s) or container closure system, have been requested by the ICH Q3B (R2) and summarized as follows [3]:

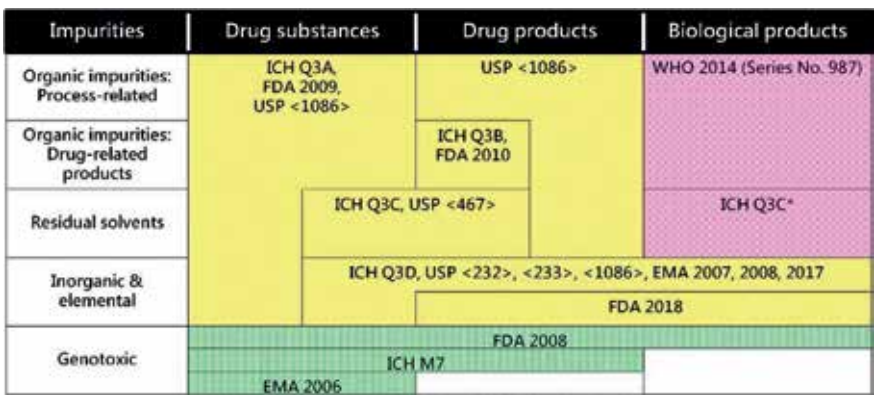

Figure 2.
*Comparison of the application scopes of regulatory guidelines/guidance for the management of impurities in pharmaceutical products [7, 28–34]. *Not clearly stated in the regulation.*

1. Confirm which impurities are degradation products?

2. Monitor and/or specify the amount of all degradation products.

3. Summarize all degradation products during manufacture and stability studies.

4. Elucidate and justify a rational evaluation of possible degradation pathway in the drug product or interaction with excipients or container closure system.

5. Establish specifications of all degradation products, including specified identified, specified unidentified, unspecified degradation product with an acceptance criterion of not more than (≤) identification threshold described in Q3B (R2), and their total amount.

Specificity (selectivity) of the method applied to determine specified and unspecified degradation product shall be validated. This includes subjecting of API or drug products to stress studies of light, heat, humidity, acid and base hydrolysis, and oxidation to evaluate the HPLC separation resolution, mass balance, etc. [3, 22, 24, 25].

Although Q3B (R2) was developed by ICH to provide guidance on impurities in drug products for new drug applications (NDAs), it is also considered to be applicable to the drug products of abbreviated new drug application (ANDAs) [33].

Regulation requirements regarding genotoxic, mutagenic, and carcinogenic impurities have been published and revised by European Medicine Agency (EMA), FDA, and ICH in 2006, 2008, and 2017, respectively, to describe how to perform assessments and controls, including prevention and reduction of impurities [21, 28, 32].

Concept of threshold of toxicological concern (TTC) has been developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects [21]. In general, exposure level of 1.5 μg per person per day (i.e., TTC) for each impurity can be considered as a common acceptable qualification threshold for supporting marketing application. Any impurity found at a level below this threshold generally does not need further safety qualification for genotoxicity and carcinogenicity concerns. The threshold is an estimate of daily exposure expected to result in an upper-bound lifetime risk of cancer of less than 10^{-6} (one in a million), a risk level that is thought to pose negligible safety concerns [21, 32].

Currently, ICH Q3C is the major guideline related to the management of residual solvents in API, excipients, and drug products (**Figure 2**). In general, solvents that are used in the manufacturing procedures are the required parts to determine [8]. Types of solvents are sorted according to their carcinogenic and genotoxic risks as follows [8, 37]:

1. Class 1: solvents obviously confirmed or strongly suspected to cause cancer in humans.

2. Class 2: nongenotoxic and possible carcinogenic risks in animals.

3. Class 3: low-toxic solvents.

Elemental impurities may arise from residual catalysts that were added intentionally in synthesis, or may be present as impurities, e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product. Because elemental impurities pose toxicological concerns and do not provide any therapeutic benefit to the patient, their levels in drug

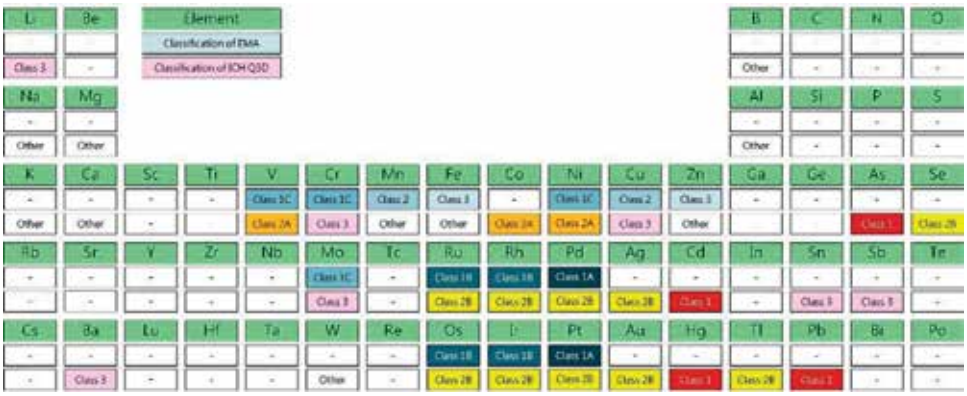

Figure 3.
Comparison for the classification of residues of metal and elemental impurities in pharmaceutical products by requirements of EMA and ICH Q3D [9, 29, 30].

products should be controlled within acceptable limits. Appropriate documentation demonstrating compliance for detailed risk assessment, screenings, and validation data for release methods must be conducted [9, 30, 34].

Recommended maximum acceptable concentration limits for the residues of metal catalysts or metal reagents that may be present in pharmaceutical products were issued earlier by EMA [29, 30]. Another classification of impurities, i.e., elemental impurities that the pharmaceutical industry needs to comply with is defined recently in ICH Q3D [9]. Comparison for these classifications of residues of metal or elemental impurities in pharmaceutical products defined by EMA and ICH was indicated as shown in **Figure 3**. Several significant difference of elemental safety concerns between EMA and ICH, such as Cr, As, Cd, Hg, Pb, etc., can be found.

3. Strategies to establish analytical methods and acceptance criteria of PRIs and DRIs

This chapter will be followed by a discussion of procedure to establish an analytical method and acceptance criteria of DRIs and PRIs.

Steps for the determination of potential degradation products, including a science-based risk assessment, can been addressed as below [11, 25]:

1. Stress studies of API.

2. Accelerated stability studies or kinetically equivalent shorter term stability studies.

3. Validation/verification by long-term stability studies of both the drug substance and formulated drug product.

An integrated scheme in accordance with the requirements of ICH for the establishment of analytical methods and acceptance criteria of PRIs and DRIs is proposed as demonstrated in **Figure 4** [2, 3, 17, 22, 39, 40].

In general, when an unknown peak was found, no matter it was found in a stress or stability studies of API or drug product, the first step is to distinguish the classification of unknown impurity belongs to. Different regulatory requirements of the

management for different kinds of impurities, i.e., PRIs and DRIs are required to apply. For instance, requirements of ICH Q3B(R2) and Q1A(R2) request that impurities present in API need not be monitored or specified in the drug product unless they are also degradation products. Due to the probability of degradation during storage period and are likely to influence quality, safety, and/or efficacy, degradation impurities must be included into the plan of stability studies [39]. Meanwhile, degradation impurities can ultimately determine the expiration, retest, or shelf-life periods of API and drug products, by evaluating the intersection of extrapolation-upper confidence limit and upper acceptance criterion of degradation product(s) [40]. Reporting threshold, identification threshold, and qualification threshold in the case of maximum daily dose ≤2 g/day of APIs administrated are illustrated in **Figure 4** [17].

Structure of impurities present in API at a level greater than (>) the identification threshold needs to be elucidated. An identified impurity content can be either

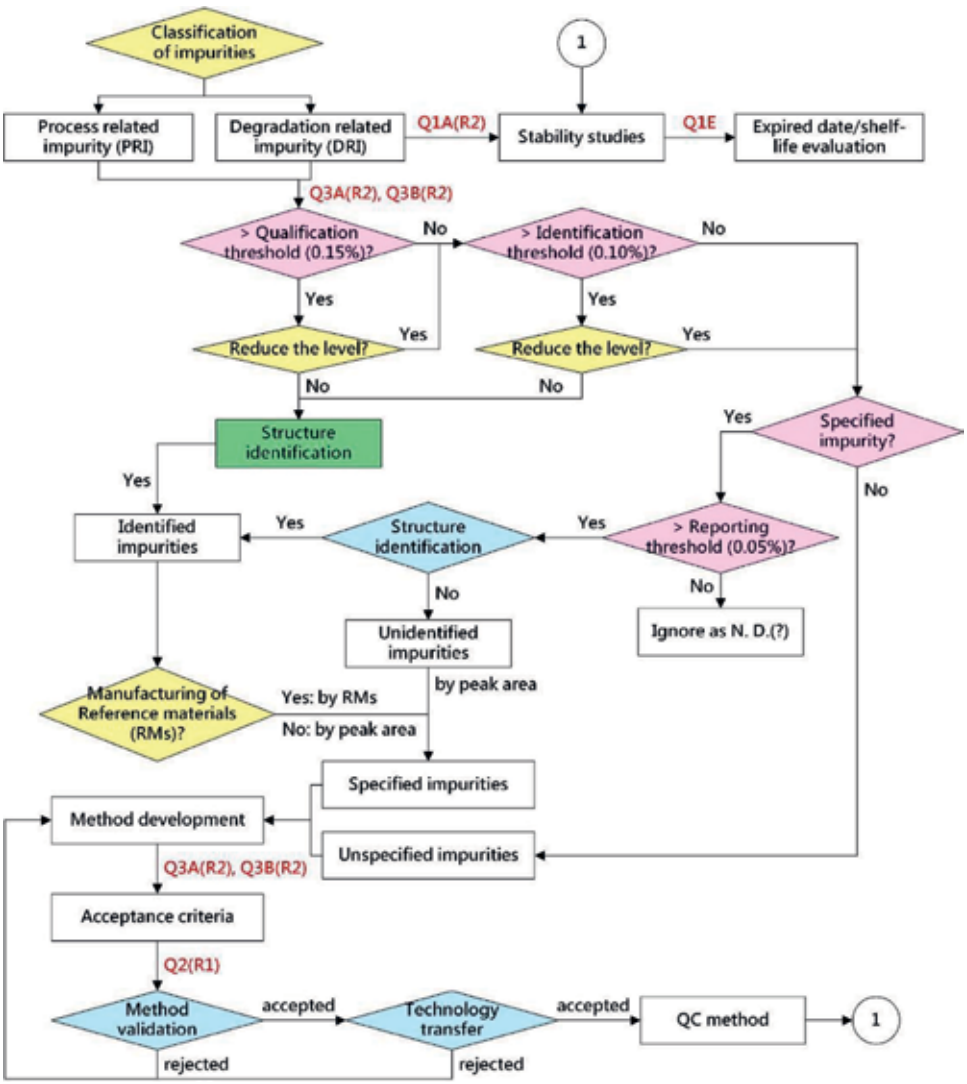

Figure 4.
Scheme to establish analytical methods and acceptance criteria of process-related impurities (PRIs) and degradation-related impurities (DRIs) according to the requirements of ICH guidelines [2, 3, 17, 22, 39, 40].

determined by interpolation with calibration curve of reference material or calculated using the peak area of the main component, i.e., API. In contrast, unidentified impurity content can only be determined using the peak area of API, no matter they are specified or unspecified impurities. Impurities with specific acceptance criteria are referred to as specific impurities, including identified and unidentified impurities [2].

Before conducting method validation, all of the impurities shall be verified by spiked or known addition to demonstrate they do exist under the "real" storage conditions such as accelerated or long-term storage conditions. Otherwise, it may not be necessary to examine specifically for certain degradation products if they are not formed under the "real" storage conditions [11, 25, 39].

The method for technology transfer to QC laboratory, i.e., receiving unit (RU) must be a well-validated and stability-indicating method. A method fails to pass the criteria of validation or technology transfer, investigation to clarify the root cause(s) and revalidation shall be initiated and conducted by the originating unit (OU) and approved by quality unit (QU).

4. Identification and validation of DRIs

4.1 Practice of kinetic study to distinguish PRIs and DRIs

Algorithms for the identification and verification of DRIs are proposed as indicated in **Figure 5**. Degradation reaction kinetics can be represented by a linear regression curve on an arithmetic or logarithmic scale [39]. Meanwhile, nature of degradation relationship is determined by the reaction kinetic constants and can be accordingly used to distinguish whether an impurity is DRI or PRI compound (**Figure 5**).

One example regarding how to distinguish PRIs and DRIs by kinetic study was illustrated as demonstrated in **Figure 6**. Analysis by HPLC revealed that some impurities were existed in one of our products. Kinetic study helps us to distinguish the type of impurities.

Plots of the impurity formation concentration ([A] or Ln[A]) versus time can obtain rate constant, i.e., the slope of a reaction in straight line as arithmetic (i.e., k_0) or logarithmic (i.e., k_1) scale. Furthermore, correlation coefficient (r) of linear regression analysis indicates a perfect positive correlation (r = 1) or conversely, there is no relationship between the two variables (r = 0).

The slopes and correlation coefficients of Pk#5, Pk#6, and Pk#7 indicated that they were not degradation-related products of API. But conversely, kinetic curves showed that Pk#1–4 and Pk#8 were degradation products. These results were also consistent with the findings of molecular weight results shown in LC-MS/MS (data not shown).

4.2 Unknown impurity structure elucidation using LC-MS/MS

As shown in **Figure 5**, the first step for structure elucidation is running full Q1 scans in both positive ion mode and negative ion mode to locate the m/z of parent peak. In this step, sample solution is typically introduced directly into mass spectrometer (MS) at a flow rate of 10 μL/min using a syringe pump. However, since dimer or oligomer may also be one of the potential impurities, range of Q1 scan shall be as wide as possible, e.g., to mass number of 1000–1200 at least.

Carefully compare the difference of mass-to-charge (Δm/z) numbers between experimental and nominal values of parent (molecular) peak as well as their stable isotope distribution patterns and natural abundances. Previous study for the

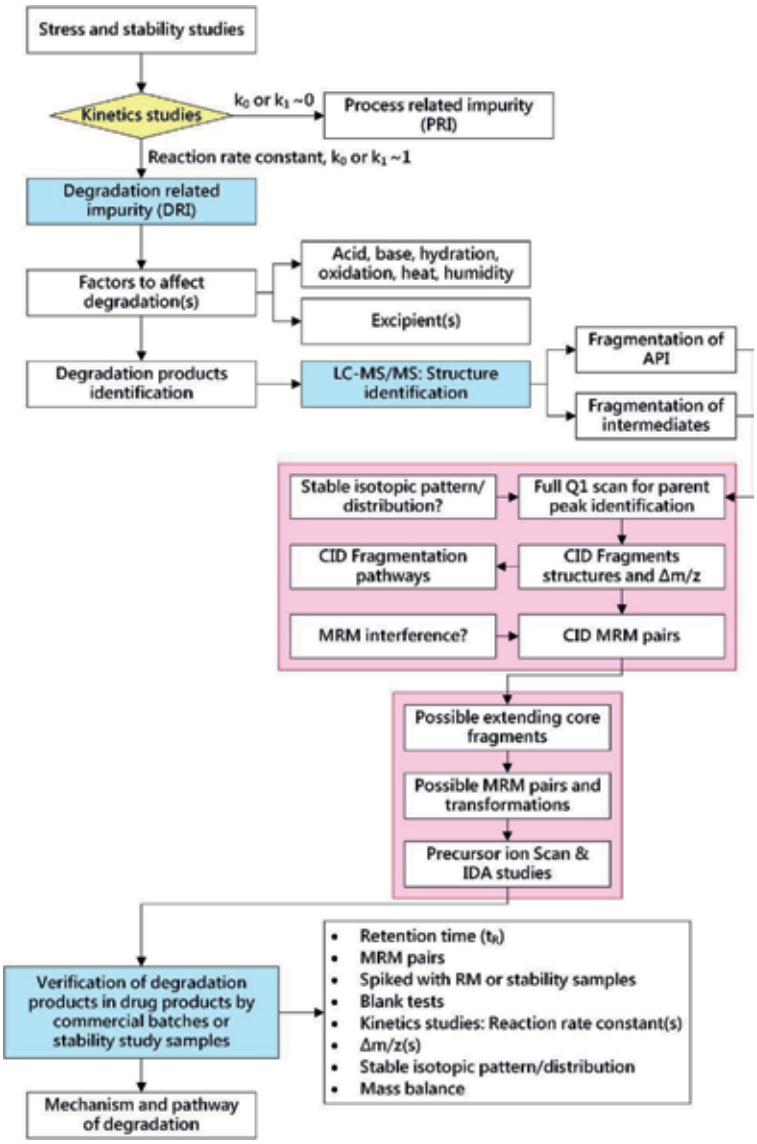

Figure 5.
Algorithms for the identification and verification of API-related degradation impurities (DRIs).

elucidation of degradation pathways of ethyl cysteinate dimer (ECD), a significant Δm/z value of −2 in Q1 scan between experimental result (m/z = 323.60) and nominal result (m/z = 325.46) of parent peak was found and indicating that an intramolecular disulfide (S-S) product, i.e., $[ECD_{S\text{-}S}+H]^+$, was the prominent form of ECD (not $[ECD+H]^+$) in aqueous solution before labeling of radioisotope, i.e., technetium-99m for i.v. injection (**Figure 7**) [25].

Repeat the product ion scans, precursor ion scans, and neutral loss scans of API to establish its collision-activated dissociation (CID) fragmentation database, including the optimal CID energies of each fragment and multiple reaction monitoring (MRM) pairs. Propose the promising structures of CID fragments and fragmentation pathways of API, accordingly. Provide the comparison of Δm/z results between experimental and nominal values for each peak, which is related to the fragmentation to verify the reliability of proposed fragments and fragmentation pathways [24, 25].

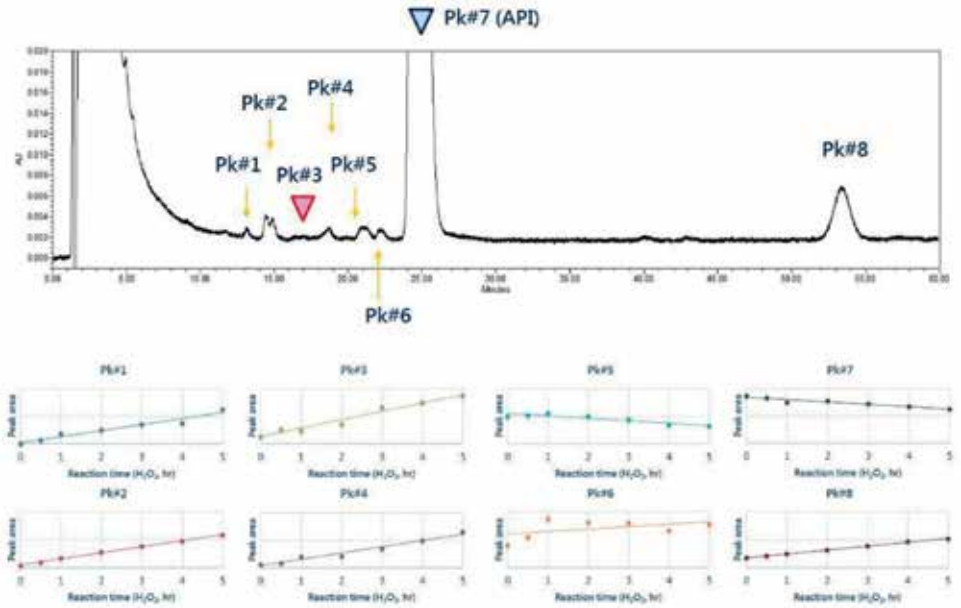

Figure 6.
Kinetic study of impurities formation by conducting stress studies to distinguish DRIs and PRIs.

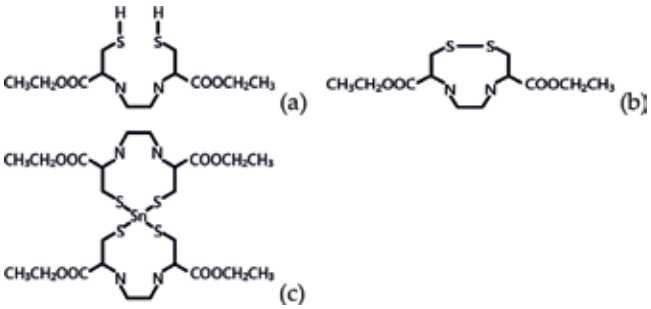

Figure 7.
Structures of (a) ethyl cysteinate dimer (ECD), (b) intramolecular disulfide (S-S) product of ECD, i.e., $ECD_{S\text{-}S}$, and (c) intermolecular dimer of ECD and reducing agent ($SnCl_2$), i.e., $Sn(ECD)_2$ (DP#4) [25].

Linear relationship within dynamic ranges for the quantitation of MRM pairs, i.e., correlation coefficients (r = 1) between precursor ions and product ions is another indication to verify high stability and reproducibility of fragmentation in CID conditions of tandem MS [24, 25].

Before using the MRM pairs for impurity scanning, interference of fragments generated from background, matrix, or contaminants such as plasticizers present in the solvents and mobile phase must be verified. Plasticizers, e.g., di(2-ethylhexyl) phthalate (DEHP) are one of the most common contaminants in organic solvents, including acetonitrile and alcohol [41].

Repeat the same procedures mentioned above in **Figure 5** to obtain a comprehensive information of fragments for any available intermediates and degradation products which are received from synthetic division, from contract manufacturing organization (CMO), from a stress study, or stability study sample conducted by the R&D team.

Steps for the determination of impurities related to degradation of API are illustrated as follows:

1. Step 1: According to the CID fragments of API, intermediates, or/and degradation products, a list of potential core fragments, which may be related to the unknown component(s) is proposed.

2. Step 2: Predict a set of potential/extending MRM pairs in line with the list obtained in step 1 and then coupled it with the relevant (bio-) transformations under the storage conditions of APIs/drug products for conducting MS/MS scans.

3. Step 3: Conduct the precursor ion scans together with function of information-dependent acquisition (IDA), where CID is automatically performed on the two highest intensity MS peaks to find the possible precursor ions containing core fragments established in step 2.

4. Step 4: Perform the reliability assessment by analysis commercial batches or long-term/accelerated stability samples to verify the identification results of step 3.

One preliminary study was illustrated as shown in **Figure 8** can be used to detail the algorithms of **Figure 5**. Core fragment of m/z 243 was found in the MS/MS study of API. In the meantime, four potential extending core fragments, i.e., m/z 183, m/z 185, m/z 197, and m/z 199 were obtained by the MS/MS studies of intermediate and degradation product (Step 1).

A total of five potential core fragments, coupled with the experience accumulated by degradation products that may be produced by similar chemical structures and prediction of relevant (bio-) transformations reactions under storage conditions, such as oxidation (+O, +2O), dehydration ($-H_2O$, $-2(H_2O)$), remove of carbon dioxide, and remove of acetic acid, a set of MRM pairs for scanning is established (Step 2).

Conduct the precursor ion scans by coupled with the IDA function for automatic performing collision on the two highest intensity MS peaks in the targeting regions of HPLC (Step 3). (Note: IDA is a build-in function of API 4000 QTrap (AB Sciex) for conducting an automatic collision on the highest intensity peak(s) scan.)

4.3 Verification of degradation products (step 4)

In addition to the methods mentioned above, i.e., kinetic study and difference of mass-to-charge ($\Delta m/z$) between experimental and nominal results, three other evaluation methods to verify the reliability of the identification results are available: including verification by real samples, by stable isotope distribution patterns, and by mass balance.

1. Verification by real samples

Investigation results of unknown degradation product(s) must be verified by the "real samples", i.e., commercial batches or long-term/accelerated stability studies samples. Verification of reliability is achieved by comparison the difference of retention time (t_R), MRM pairs, and stable isotope distribution patterns between real samples and stress study samples. If it is available, purified or enrichment sample of impurity can be spiked into a real sample for further verification.

2. Verification by stable isotope distribution patterns or natural abundances

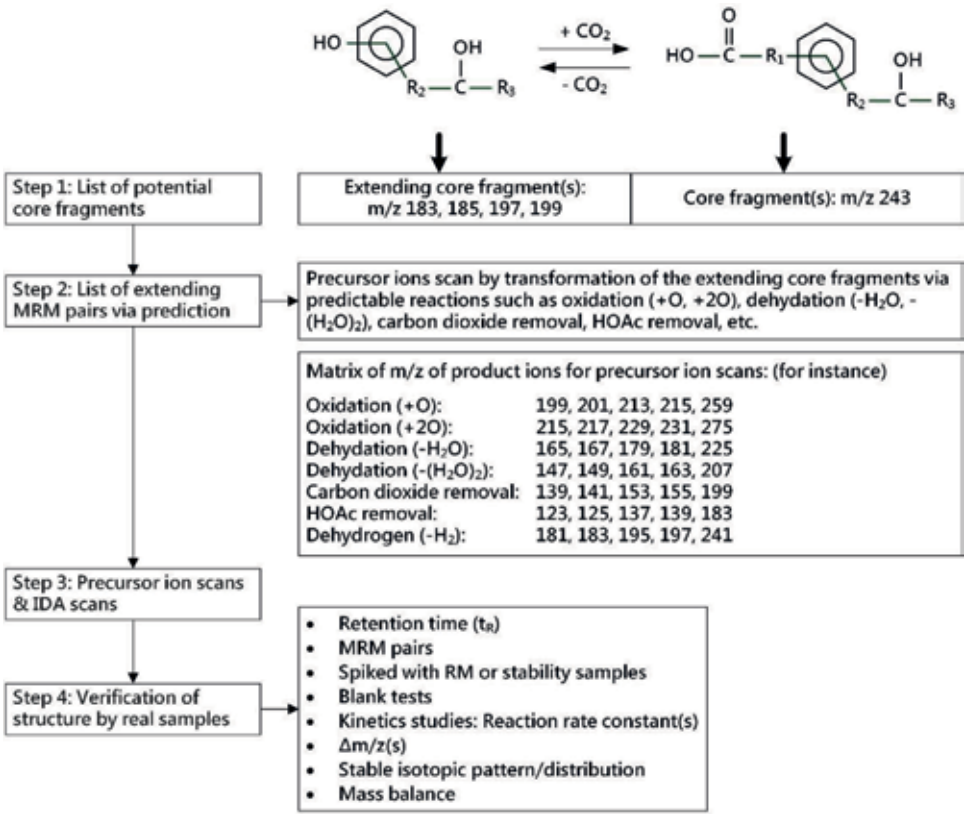

Figure 8.
Step for the establishment of potential extending core fragments, conduct of product ions screening with transformation/IDA function, and validation/verification.

Each element, like a fingerprint, has its own unique stable isotope distribution patterns and natural abundances. Occasionally, stable isotope distribution patterns or natural abundances are available as a unique tool for structure characterization.

Ten, two, and two of uncommon patterns in the MS spectra as shown in **Figure 9(a)–(c)** were clearly indicated in our structure identification of ethyl cysteinate dimer (ECD) cold kit, (R)-N-methyl-3-(2-bromophenoxy)-3-phenylpropanamine (MBPP), and methoxyisobutylisonitrile (sestamibi, or $Cu(MIBI)_4$), respectively. These uncommon patterns were attributed to the contribution of stable isotope distributions of tin (Sn), bromine (Br), and copper (Cu), respectively.

When 7 major (or actually total 10) peaks are shown in the MS spectra, it may strongly mislead the works of structure elucidation as shown in **Figure 9(a)**. However, if it is available to know the presence of some special elements may present in impurity.

If it is able to presuppose that some special elements may contain in the structure, then it will be easier to elucidate the MS spectra. In other words, when pattern of MS spectra is significantly different from the normal CHO distribution, it may also indicate that a special element exists on the structure.

By comparing the natural abundance of 10 stable isotopes of tin and simulation MS spectra of a promising molecular formula, a series of metal complexes of tin can be verified. In the case for study of impurities in ECD kit, it was an ultimate and effective way to identify all of impurities containing Sn, i.e., DP#4, DP#5, DP#6, DP#6′, DP#6″, DP#7, DP#7′, DP#7″, and DP#8 [25]. Similar case was found in

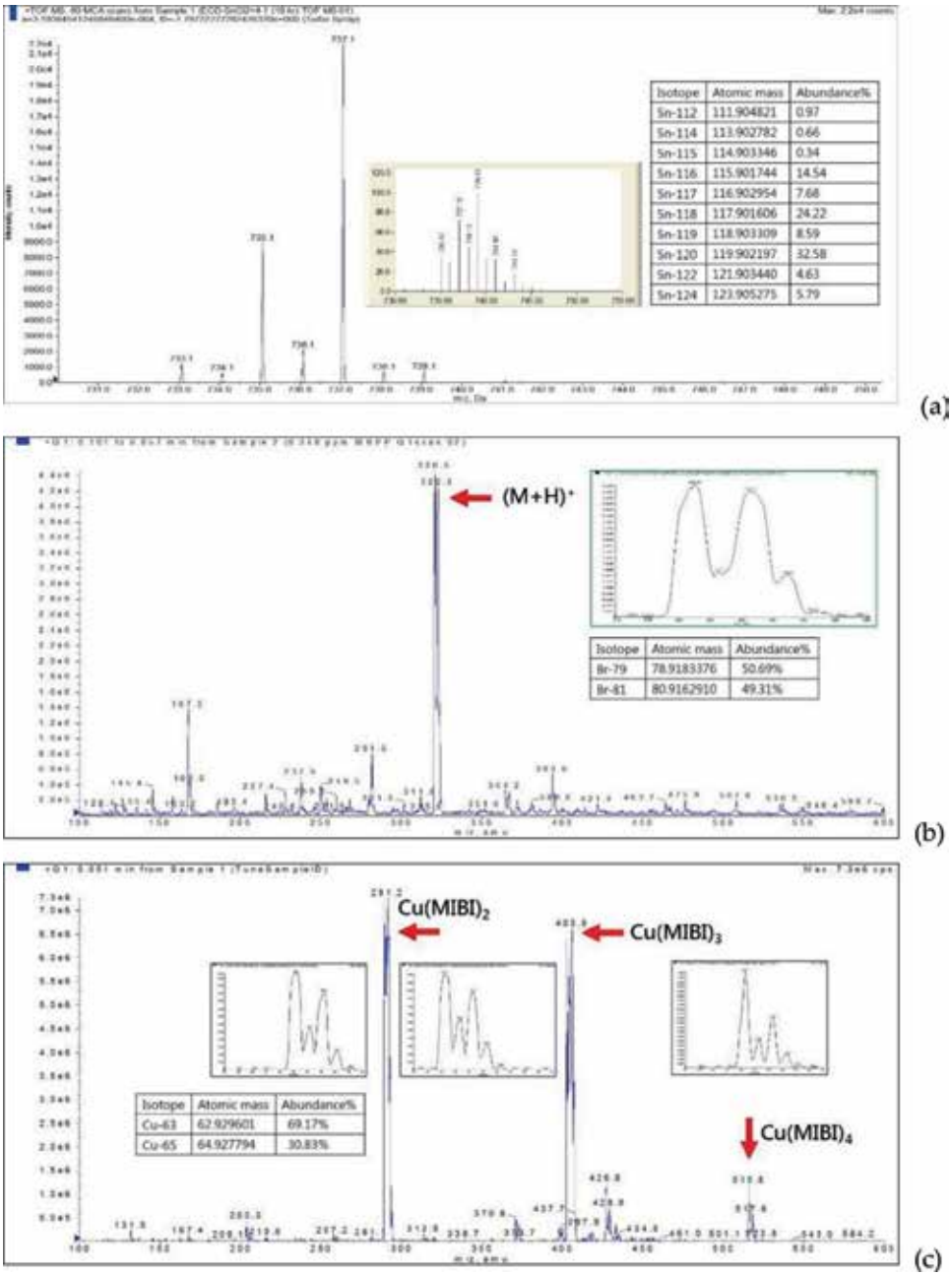

Figure 9.
Stable isotope distribution patterns and simulation of mass spectra of (a) $Sn(ECD)_2$ (DP#4), (b) (R)-N-methyl-3-(2-bromophenoxy)-3-phenylpropanamine (MBPP), and (c) methoxyisobutylisonitrile (sestamibi).

the structure determination of sestamibi as shown in **Figure 9(c)**. Coordination number (CN = 4) and core metal (Cu) in sestamibi can be clearly verified.

3. Verification by mass balance

When performing a stress study of API, one should determine content of API on each day by using a daily and freshly prepared calibration curve of API reference material, and interpolated within the validated dynamic range. The mass balance is

calculated by summation of the API and total impurity content. It is a tool to justify whether there are impurities unseparated (i.e., same retention time) or undetectable (e.g., without UV-visible chromophores). This topic and several major problems to cause poor mass balance have been detailed by Nussbaum et al. [42]

5. Conclusions

Management of impurities related to APIs in pharmaceutical products must be implemented in strict compliance with the regulatory requirements of pharmaceutical industry due to their quality and safety concerns. An integrated scheme in accordance with the regulatory requirements to establish analytical methods and acceptance criteria of process-related impurities (PRIs) and degradation-related impurities (DRIs) was presented, accordingly. Meanwhile, procedures for the identification and validation/verification of API-related DRIs were proposed. Validation or verification methods to evaluate the reliability of structure identification such as kinetic reactions, stress and stability studies, comparison of retention time(s) and $\Delta m/z$ between experimental and nominal values of targeting peaks, compatibility of MRM pairs with "real samples," stable isotope distribution patterns, and mass balance were demonstrated. Applying of the processes proposed in this article will help to ensure the reliability and quality of the impurity analytical results.

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Quality management (QM) practices are the basis for the successful implementation and maintenance of any QM system. Quality control (QC) is identified as a QM component. Therefore, QM effectiveness is dependent on the QC strategy. QC practice is more or less complex depending on the type of production. The book is focused on new trends and developments in QM and QC in several types of industries from a worldwide perspective. Its content has been organized into two sections and seven chapters written by well-recognized researchers worldwide. Several approaches are debated based on sample traceability, analytical method validation, required parameters, class of exponential regression-type estimators of the population means, determination of impurities, viewpoints, and case studies.

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