TOBACCO PRODUCT REGULATION

Building laboratory testing capacity

World Health Organization

TOGETHER LET'S BEAT TOBACCO
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Tobacco product regulation: building laboratory testing capacity.

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PREFACE

It is well established that tobacco use is a major public health problem. However, tobacco products are one of the few openly available consumer products that are virtually unregulated in terms of contents, design features and emissions. The majority of countries hesitate to implement regulations in this area, partly due to the technical complexity associated with tobacco product regulation. There has been a high demand from WHO Member States for resources consolidating information on tobacco testing and building laboratory capacity for countries, especially to facilitate the implementation of Articles 9 and 10 of the WHO FCTC[1]. This is to provide a useful, comprehensible and easy guide for regulators and policymakers on how to test tobacco products, what products to test, and how to use testing data in a meaningful way to support regulation.

The importance of laboratory testing is reflected in the WHO Framework Convention on Tobacco Control (WHO FCTC). Article 9 of the WHO FCTC defines obligations for Parties with respect to the testing of tobacco products, while Article 10 deals with the disclosure of information on the contents and emissions of tobacco products. The disclosure of product information takes two forms: 1) the disclosure of information by manufacturers to regulators, and 2) the disclosure of information from regulators to the public. Tobacco product testing is used to generate data necessary to support both forms of disclosure.

In 2006, the first Conference of the Parties (COP) to the WHO FCTC established a working group to elaborate guidelines and recommendations for the implementation of Articles 9 and 10 of the Treaty (Decision FCTC/COP1(15)). COP 2 extended the mandate of the working group and encouraged WHO's Tobacco Free Initiative (WHO TFI) to continue its work on tobacco product regulation (Decision FCTC/COP2(14)). In 2010, the partial guidelines submitted at COP4 were adopted. The partial guidelines currently contain recommendations for regulation to reduce the attractiveness of tobacco products. Recommendations to reduce the addictiveness and toxicity of tobacco products will be developed later. The working group was requested by the COP to continue its work to elaborate the guidelines in a step-by-step process, with updates on addictiveness and toxicity requested to be submitted to future sessions of the COP for consideration.

It is important to note that, contrary to claims by the tobacco industry, these guidelines are final and in effect. The regulatory measures advocated by the partial guidelines are to be treated as minimum requirements and do not prevent Parties from adopting more comprehensive measures.

[1] Participants of a WHO workshop on the How-to's of Establishing a Testing Laboratory in (April 2016, New Delhi, India) requested WHO to prepare a handbook on building laboratory capacity. Additionally, the WHO Tobacco Laboratory Network's sixth meeting (Maastricht, Netherlands, 9-11 May 2016) recommended the development of a primer informing governments and the public of WHO TobLabNet's activities in order to expand membership and build testing capacity globally.

WHO has continually supported Member States in developing laboratory capacity. In 2004, WHO TFI published a recommendation from the WHO Study Group on Tobacco Product Regulation (TobReg) on 'guiding principles to increase laboratory capacity to facilitate the implementation of Articles 9 and 10 of the WHO FCTC and to guide the initiation of tobacco product testing'. *(1)* The guiding principles provided advice to countries intending to develop such capacity and help in realising this objective. Over the intervening years, new knowledge has developed and progress has been made to support these efforts; these include establishing the WHO Tobacco Laboratory Network (TobLabNet) in 2005 and the Global Tobacco Regulators Forum (GTRF) in 2016. Therefore, it is appropriate to update the previous document and provide a practical guide for countries interested in developing or accessing tobacco product testing capacity to support their regulatory authority.

This document provides options for building laboratory capacity, which include developing a testing laboratory, using an existing internal laboratory, contracting an external laboratory, and making use of the support mechanisms available, including but not restricted to WHO TobLabNet. Finally, it provides practical, step-by-step approaches to implementing tobacco testing and is relevant even to countries with inadequate resources to establish a testing facility.

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GLOSSARY

Accreditation — the documentation by an independent body that a laboratory has the systems in place that should enable them to produce reliable results that have been adequately tracked and verified.

Accuracy — the nearness of a measurement of a quantity to the quantity's true value

CDC — U.S. Centers for Disease Control and Prevention

DAD — diode array detector

FID — flame ionization detection

Firewall — a system to ensure that data and information are protected so that public health and commercial interests are separate and not accessible to each other

GC — gas chromatography

HPLC — high-performance liquid chromatography

Labstat — a private commercial tobacco analysis laboratory, Labstat Incorporated, in Kitchener, Ontario, Canada

LC — liquid chromatography

MS — mass spectrometry

MS/MS — tandem mass spectrometry

NCEH — National Center for Environmental Health at the U.S. Centers for Disease Control and Prevention

OSH — Office on Smoking and Health at the U.S. Centers for Disease Control and Prevention

PAHs — polynuclear aromatic hydrocarbons are multi-ringed aromatic compounds varying from two rings (naphthalene) to much larger ringed structures (e.g. Indeno[1,2,3-c,d] pyrene)

Precision — a determination of how close measurement results are to each other if a measurement is made repeatedly on the same sample, typically using the same method

Quality control — a process which evaluates whether systems are operating within standard parameters on an ongoing basis

Ruggedness — ability of an analytical system to withstand deviations from the defined analytical method.

Selectivity — the ability to correctly identify that a substance is not present when it is indeed not present.

Sensitivity — the ability of a measurement to make accurate and precise determinations at low levels.

TCD — thermal conductivity detector

TFI — Tobacco Free Initiative of the World Health Organization

TobLabNet — WHO Tobacco Laboratory Network

TobReg — WHO Study Group on Tobacco Product Regulation

TSNAs — tobacco-specific nitrosamines [N-nitrosonornicotine (NNN), 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanatabine (NAT), and N-nitrosoanabasine (NAB)]

UV — ultraviolet

WHO — World Health Organization

WHO FCTC — WHO Framework Convention on Tobacco Control

Chapter 1

TESTING IN THE CONTEXT OF A COUNTRY'S REGULATORY AUTHORITY

Tobacco product testing is a valuable tool to support tobacco control and regulatory efforts, which can have a clear impact on population health. Tobacco product testing per se does not lower the levels of toxic and carcinogenic constituents in tobacco, or reduce the use of tobacco products which cause the exposure of both users and non-users to the harmful chemicals in tobacco product emissions. However, it can be an effective tool if the objectives and justifications are set out upfront on how data on design, contents or emissions will be used for regulatory purposes. How that tool is used is a critical factor in determining whether tobacco product testing is effective.

It should be understood from the start that obtaining data on design, contents or emissions alone is not an adequate reason to require tobacco product testing. It is critical that countries establish sound reasoning on how this information will be used because testing can be expensive, even if the manufacturers are required to fully fund the work, and a solid justification is important in order to defend against legal attacks or address legitimate questions posed by government officials. For the purposes of this document, the term "manufacturers" will be used to refer to tobacco product manufacturers, importers, or other companies that fall under a country's tobacco product regulatory authority and are responsible for marketed tobacco products.

The first step in developing a tobacco product testing programme is identifying the basis and justification for testing and reporting. In addition to providing an important justification, these considerations will point the programme in a direction that will be most beneficial and ensure that the effort provides data that can be used to effectively support tobacco control and regulation in that country. While there are some good examples of how other countries have approached the need for product testing, each country's experience is different. Identifying how information will be used at the national level is the foundation upon which all further action is built and the unique needs of the country must be the first consideration.

There are two ways to use laboratories in a tobacco regulatory scheme, depending on the way in which government regulatory agencies intend to require tobacco product testing. The first approach is for the government agency to oversee or carry out routine analysis of all products. Even in this case, requirements can be put in place so that the cost of these analyses are borne completely by the manufacturers (see Section 1.7 below), but this effort would require a significant logistical effort that

many countries may not want to undertake. Alternately, countries may choose to limit their direct involvement in testing to assessing the accuracy of data reported by manufacturers, using a random scheme for choosing a subset of brand/subbrands and analytes, and reanalysis by the government itself, or having other mechanisms in place to ensure this accuracy. As explained above, manufacturers can be required to fund this testing. This document is applicable to both approaches.

1.1 INITIAL CONSIDERATIONS

The first step in identifying what testing should be required is to carefully evaluate the government's powers to require testing. Every country's authorizing legislation is different and these differences must be considered when determining how best to use the testing data that will be obtained. For many countries, national tobacco control legislation can be guided by the treaty obligations under the WHO Framework Convention on Tobacco Control (WHO FCTC). Articles 9 and 10 of the WHO FCTC and their partial guidelines, set out the recommendations for Parties to the Treaty to adopt, while framing national legislation on tobacco product regulation.

1.1.1 Reason for the regulatory authority

The first question to ask is the primary purpose for creating the tobacco product regulatory authority. There are several reasons as follows:

- One common concern relates to the harm to children's health resulting from taking up tobacco product use. While many health consequences from tobacco use take a long time to manifest, the testing of tobacco product ingredients and emissions that have a particular appeal to children may constitute the highest testing priority .
- Other ingredients or design features could also be of high priority for analyses and would determine early decisions about such testing capability.
- The legislation may have been based on the rights of non-users not to be exposed to harmful chemical constituents. In this case, measurement of harmful emissions in second-hand smoke may be the most critical data from tobacco product testing. Measurement of chemical agents in second-hand smoke is more challenging than measurements in mainstream smoke, so, if this is a critical issue, laboratory decisions should consider the ability of laboratories to make these measurements.
- Another possible issue may be false advertising and other marketing statements by the tobacco industry. In this case, it is critical that testing capabilities be able to verify such claims.
- If there are claims that one product poses a lower risk, the ability of product testing to address these claims should be a central consideration.

There are other issues which may have been the primary consideration of legislation and these should also be considered when making testing decisions.

1.1.2 Scientific basis of the legislation

Another equally important aspect to consider is the scientific basis for the legislation. As decisions are made concerning what laboratory capability is necessary, it is important to consider whether the original decision and rationale were strongly supported by scientific data, whether it was driven by public health policy concerns or whether it was based on treaty obligations. If legislation was particularly based on scientific data, laboratory data that supports the legislation may be part of a critical defence of the decision taken by the regulatory authority. In this case, the data derived from laboratory testing must be unimpeachable. Tobacco regulatory authorities must ensure that the public release of data will strengthen legal arguments. In most cases in which there is a strong scientific rationale for regulating tobacco products, the choice of a well-established, experienced and accredited laboratory will prove indispensable in how the data is eventually used.

1.1.3 Public health concerns

From a public health viewpoint, regulatory agencies should consider identifying the major issues of concern. This will differ from country to country, and it is important that regulatory agencies determine what concerns are most important and can be addressed using laboratory data. For example, does the use of manufactured cigarettes cause the biggest tobacco-related public-health problem? This may be the case in many countries, but others may have a bigger public health concern about other tobacco products, such as the various forms of smokeless tobacco, waterpipes, *bidis*, *kreteks* or flavoured products. If these other products are the biggest public health problem, testing of manufactured cigarettes may be the most straightforward, but not the most effective choice for tobacco product testing, to aid effective regulatory actions. Another public health concern may be the introduction of new products. Whilst the overall impact of new products might at first be unclear, tobacco regulators will likely be asked about them. The ability to provide scientifically-based answers will demonstrate the usefulness of the testing capability. Focusing testing resources on the real source of public health concern will demonstrate a better rationale for requiring the testing and more readily achieve real improvements in public health.

Tobacco regulatory authorities should also identify the real objectives of the regulatory programme and how tobacco product testing can help. The specific objectives may be to ban certain products from the market, reduce prevalence of use, or reduce disease and death resulting from tobacco product use. Too often, decisions are based on what appears to be most readily accomplished and not whether this fits into an overall goal for tobacco regulation. When tobacco product testing is aimed at supporting the main strategic objective, it demonstrates its value and leads to better results.

1.1.4 Resonance with the public and decision-makers

It is also important to consider the data that would most resonate with the public and the authorities, and how such data can be made comprehensible. This is important because, as discussed above, tobacco product testing is only effective when coordinated with and used by the tobacco control or regulatory authority. For example, if addiction is a major public health issue, measurement of nicotine, the primary addictive component of tobacco products, may be the primary aim for laboratory capability. If the toxicity of the product and its impact on causing disease is the main issue, this would point to the measurement of toxic and carcinogenic substances, such as tobacco-specific nitrosamines (TSNAs) and polynuclear aromatic hydrocarbons (PAHs) in emissions. If tobacco control authorities need data showing that non-users are being exposed to second-hand smoke, this may be the most effective way to accomplish public health goals. If the data addresses a public health issue that is clear to the public and decision-makers, or can be made clear, the data is more likely to be used to substantially improve public health.

1.1.5 Legal requirements

Finally, a country's legal requirements and its possible impact on enforcement must be considered. Lack of certification or adherence to standards may impede admissibility, or reduce the weight to be attached to a laboratory report in court proceedings. Issues like chain-of-custody or participation in inter-laboratory validation (see Appendix 1) could be important considerations in the choice of laboratories to carry out tobacco product testing. It is most likely that tobacco manufacturers will use highly qualified laboratories and any compliance or enforcement proceedings taken against a manufacturer would need to match the qualifications of the scientific source to be credible. Government bodies should consider relevant rules of evidence in selecting laboratories to assist in enforcement and other proceedings. They may also work in collaboration with the ministry of justice, or some other judicial or legal administration, while developing the testing requirements to ensure that laboratory data are adequate as evidence for legal proceedings.

1.2 HOW DATA CAN BE USED

Laboratory data provide an opportunity to avoid statements of opinion or anecdote by offering statements of fact that have a definitive basis in scientific determination. Without strong scientific data, the grounds for regulatory action will be more easily questioned and rebutted, and any action taken is less likely to accomplish its objective. While laboratory data do not guarantee success, scientific data strengthen every rationale and increase the likelihood that goals will be achieved.

Enforcement authority, which can be used to reduce disease and death from tobacco product use, differs from country to country. But the powers granted by a national government carry both risks and opportunities. Unfortunately, most tobacco reg-

ulatory agencies do not have adequate resources to make use of all of the data that might be made available. Stretching an organization too thin makes it less likely that goals will be achieved. So, it is critical that regulators assess what can be done with the powers and resources available and how to use them most effectively. Identifying how the data will be used should determine what data are collected and what requirements are placed on that data.

Some possible ways that countries might use testing data include the following:

- setting product standards
- limiting advertising claims
- educating the public
- informing future legislation
- marketing authorization
- developing scientific information to support research, and
- setting manufacturing standards.

1.2.1 Product standards

When a country has the regulatory authority, setting product standards can be a valuable regulatory tool in reducing disease and death resulting from tobacco product use. But because they can be so effective, these standards are likely to be challenged in the courts. To prepare for these challenges, supporting evidence must be derived from well-documented and peer-reviewed scientific evidence. Product standards used by national regulatory bodies include those aimed at both the addictiveness and attractiveness of tobacco products.

- In 2012, Brazil enacted a product standard banning the use of additives in cigarettes and other tobacco products sold there. *(2)* This was based on the impact of additives to encourage the use of products by young people and facilitating initiation of their use.
- In 2009, Canada enacted a ban on flavours, except menthol, in cigarettes and cigarillos. *(3)* The action was intended "to protect the health of Canadians", "to protect young persons and others", and "to enhance public awareness of the hazards of tobacco use". This ban was recently expanded to include menthol. *(4)*
- In 2009, France also adopted a law restricting the use of flavouring ingredients in cigarettes in an effort to reduce youth initiation of smoking. *(5)*

All these standards were based on laboratory data that demonstrated the presence of ingredients of concern in tobacco products. The choice of product standards should be driven by critical country-specific issues as discussed above.

1.2.2 Marketing/Advertising restrictions

Marketing/advertising restrictions have been used by several countries to make products less appealing. This can take the form of limiting direct marketing, such as statements of lower risk for certain products or indirect marketing appeal, such as the use of colours and imagery in packaging. For example, in 2001, Brazil was

the first country to ban misleading terms, such as "light" and "low-tar" on tobacco product labelling. *(5)* While laboratory data alone is unlikely to be sufficient to support action on marketing/advertising restrictions, it can be used as a factor in evaluating relative risk statements and to support action banning or restricting these statements.

1.2.3 Public education

Public education may be one of the most effective applications for using testing data by countries just beginning to establish a tobacco regulatory programme. The public, in general, is not scientifically knowledgeable. Users and non-users alike do not understand how the design, contents and emissions of tobacco products affect their health. Many do not understand that increases in exposure to harmful chemicals results from the process of growing, manufacturing and use of tobacco products. *(6, 7)* Improving that understanding with information from product testing can be a valuable way to inform users and discourage tobacco use. But it is important that information provided to the public is scientifically sound. Trust in the reliability of the government agency to provide accurate information is critical to countering false messages provided by tobacco product manufacturers.

Public education can be a valuable tool to help users make informed choices and for non-users to be aware of the dangers associated with exposure to emissions from tobacco products. This education can take many different forms. Experience in Canada has shown that the public has a weak understanding of numeracy and can be misled by placing machine-derived numbers on products. The Regulatory Impact Analysis Statement that was published with the amendment to the Tobacco Products Information Regulations (TPIR) states:

> Research has shown that the current format of the toxic emissions statements, which displays a range of values for six toxic substances, is generally not noticed by tobacco users and many people find them confusing. The proposed Regulations would replace the numerical values currently displayed with four text-based statements that provide clear, concise and easy-to-understand information about the toxic substances found in tobacco smoke. *(8)*

On the other hand, the public generally wants to avoid exposure to "chemicals" especially when these can be linked to adverse health outcomes. *(9)* So while care must be taken on how to make available information on toxic and addictive substances in tobacco products, this should be provided to the public in a meaningful manner.

1.2.4 Informing future legislation

It is likely that most countries' legislation to enact treaty obligations under the WHO FCTC was not comprehensive. Data derived from product testing provide information for future legislation. This future legislation could take many different forms and should be carefully considered based on the overall purposes of the tobacco

regulatory programme, as discussed above. If a product standard authority was not included in the original legislation, testing of tobacco products may be a valuable source of data demonstrating its value. Another example of additional legislation may be complete smoking bans in indoor public places, workplaces and public transport, as enacted in many countries in recent years. Since indoor smoking bans are largely driven by concern for non-smokers' exposure to second-hand smoke, the focus of this effort would be on the chemicals to which non-smokers are exposed. Product testing can identify and quantify the toxic and addictive chemicals that are emitted from using tobacco products to which these non-users are exposed.

1.2.5 Notification or marketing authorization

Some countries receive notification when a new product is introduced to the market, with some regulatory agencies specifying notification requirements in their national legislation or tobacco control laws. As part of this process, tobacco manufacturers may be required to provide detailed product information, including the ingredients used in the tobacco products marketed in the burnt and unburnt form, quantities thereof, their toxicity, as well as possible adverse effects. The use of testing to evaluate these products and ingredients can be a valuable use of the testing and reporting mandate under the WHO FCTC.

Most countries do not have authorization to determine, before marketing, whether a product can be authorized for sale. For those countries that do, this can be a very powerful regulatory authority, but it requires substantial internal resources. When that authority has been granted, product testing is an important factor in evaluating marketing authorization. Because companies want to be allowed to market their products, they are willing to provide a wealth of testing data as required. To properly use this data, regulatory authorities must have the dedicated scientific resources and expertise needed to evaluate data provided by the manufacturers.

1.2.6 Developing scientific information

Data generated from testing of tobacco products can be used to develop scientific information which may be valuable for others, such as researchers, to better understand the impact of the country's tobacco products on disease and death. Because of limited resources, issues related to trade secrets and the impact of regular design changes on tobacco product emissions, researchers are rarely able to fully evaluate the tobacco products that their test subjects are using. If this information can be obtained from the manufacturers and made available to researchers and other interested parties, it would be a valuable tool to improve the interpretation of the results of human research into a specific country's tobacco product use. These data can then be used to support many of the purposes listed above, including shaping future regulations.

1.2.7 Manufacturing standards

Manufacturing standards are another regulatory tool to address the harm caused by the use of tobacco products. Testing data can identify the variability of levels of chemical ingredients in production starting materials. For instance, tobacco-specific nitrosamines (TSNAs) are some of the most potent carcinogenic agents in tobacco products. *(10, 11)* But the levels of nitrosamines delivered to the user are highly dependent on the levels of carcinogens in the original tobacco used in manufacture and these levels vary widely depending on the tobacco. *(12)* By setting limits on the levels of chemical constituents in ingredients used in manufacturing or contaminants, such as heavy metals *(13)*, exposure of product users can be reduced. But these levels must first be determined by valid testing of tobacco products.

1.3 IDENTIFYING TOBACCO PRODUCTS TO TEST

Each country will have products that are best targeted for regulation. If resources to evaluate testing results are limited, which is generally the case, it may be best to identify highly significant products and consider these as a testing priority. The following discussion is not intended to eliminate any particular product from the testing requirement, but to suggest factors that regulators may consider when determining which products should be the highest priority.

There are three factors to be considered in evaluating which product to address as the highest priority:

1. which types of tobacco products are most prevalent in the market
2. which types of tobacco products are the most harmful to users
3. which tobacco products are most feasible to regulate?

1.3.1 Types of tobacco products most prevalent in the market

In order to have a substantial impact on reducing disease and death from tobacco use, it is important to address the type of product which has, or is likely to have, a large market share . If manufactured cigarettes are only used by a small fraction of the population, even major reductions in use will only have a minor public health impact. There are several sources of data that can be used to evaluate the prevalence of use of different types of tobacco products in a country. *(14)* Global surveys and similar efforts have identified the number of people using different types of tobacco products. Many of these surveys also break down use by gender and age. The prevalence of product use varies dramatically between countries. In Indonesia, *kreteks* (flavoured cigarettes) are prevalent, but these products have only a minor market share in most other countries. Smokeless tobacco use in India is very common, but the smokeless products being used are very diverse. Another example is the use of menthol cigarettes, which is widespread in some countries, such as the Philippines. So focusing regulatory product testing efforts on products other than manufactured cigarettes may be the best use of resources for some countries.

1.3.2 Types of tobacco products most harmful to users

Toxicity and the harm caused by tobacco products differ both within and between product classes. It is generally understood that, because of the high concentrations of very toxic and carcinogenic chemicals delivered to the lungs, combusted traditional products (i.e., cigarettes, cigars, *bidis*, *kreteks*, waterpipes, etc.) pose the most harm to users. The diversity of smokeless tobacco products poses further regulatory and testing challenges. But the toxicity of various products could vary depending on specific manufacturing practices and user behaviour. A product that is less toxic but used often may be a bigger concern than one that is more toxic but only rarely used. When choosing the tobacco products on which efforts should be focused, regulators should consider which products in their market present the most significant threat to health.

1.3.3 Tobacco products most feasible to regulate

Regulatory opportunity is the third factor to consider when identifying the tobacco products on which to focus initial product testing requirements. Depending on the specific authority given by the enacting legislation and the nature of the political climate, some actions may be easier to accomplish than others. As indicated above, new products being introduced into the marketplace that do not have a significant market share may be a more viable initial target than well-established products with strong stakeholder support. Generally, products that are manufactured in a limited number of facilities and not substantially altered by the user are more readily regulated than products made by a cottage industry. When products are made by hundreds of thousands of small manufacturers, enforcement of required testing could be so challenging that this should not initially be the highest priority when establishing new testing and reporting requirements. Regulators should consider the feasibility of successfully regulating an industry that is very widespread as part of their prioritization process. An example of this concern would be *bidi* manufacturing in India. *Bidis*, hand-rolled tobacco products, are widely used and present a significant health concern to users. But there is a large manufacturing sector for these products in private homes or very small shops. Enforcing testing requirements for these cottage-industry products in India would be very challenging and might not be the first priority for testing. After successes with other products, *bidis* may be later identified as a target. Also, the usefulness of data from manufacturers of tobacco products that are altered by consumers (e.g., adding lime to increase free nicotine levels) should be considered as part of the process for determining the products for which testing and reporting data should be the highest priority.

1.4 ANALYTES TO TEST

Several countries have developed lists of analytes – chemical substances measured using chemical analysis – to be tested. Canada was one of the first countries to identify lists of analytes to measure in mainstream smoke, sidestream smoke and

whole tobacco. *(15)* In 2007, Brazil also established a list of design properties, contents and emissions *(16)* to be tested. In 2012, the US Food and Drug Administration (FDA) published a list of 93 harmful/potentially harmful constituents in tobacco products and tobacco smoke. *(17)*

These lists can serve as a starting point for countries which intend to require testing and reporting of design properties, contents and emissions from tobacco products. But the decision concerning which analytes should be tested involves several factors and should be carefully considered.

The first factor is which analytes best meet the purpose of how data is intended to be used, as described in Section 1.2 above. Analytes should be chosen using a rationale to link the results of testing data with their use. For example, if the regulatory agency intends to communicate to the public or decision-makers the concern for cancer-causing chemicals in cigarette smoke, clear choices for testing would be TSNAs and PAHs (or benzo[a]pyrene as a surrogate for PAHs), since they are known carcinogens and have been linked to cancer in tobacco product users. Alternatively, testing of heavy metals for the purpose of setting product standards may not be a good choice, since heavy metals in tobacco are largely driven by levels in the soil in which the tobacco is grown and not by the manufacturing process. It is important to know if this is an issue in the products being marketed and if a standard can be used to reduce these levels. How testing data is to be used is a critical factor in determining which analytes to measure.

An equally important factor is which analytes are of most concern in the products identified in Section 1.3. The use of certain products and the health effects from their use should be considered when identifying the analytes to be measured in tobacco product contents and emissions. For example, measurement of carbon monoxide is an analyte of concern in combusted tobacco product emissions. But because smokeless tobacco is not burned when used, requiring measurements of carbon monoxide in traditional smokeless tobacco is both unnecessary and inappropriate. It is important that the analytes chosen be relevant to the products to be tested. Testing of constituents that are generated only by the burning of tobacco is not appropriate for testing of traditional smokeless tobacco products.

Thirdly, those analytes to be tested should have reliable methods for their determination. For the purposes of this document, reliability is considered to include the ability to produce accurate and reproducible results at appropriate detection limits with suitable sensitivity and selectivity. When first establishing a list of analytes to be measured in tobacco product contents and emissions, analytes that have already established, widely accepted, and sensitive analytical methods would be the highest priority so that results can be obtained as quickly as possible. Analytes for which no established methods exist can be added at a later date when the testing programme is more mature and the value of testing has been established.

1.5 HOW THE TESTS ARE TO BE CONDUCTED

How analytes are tested is another important consideration when developing the requirements for laboratory testing. Different countries have approached this in different ways and there are limitations based on national laws and acceptable requirements. One issue is whether to allow the use of different analytical methods to measure the analytes in tobacco product contents or emissions, or require the use of specific methods. The requirement to use specific methods, as is done in Canada, has certain distinct advantages. One of the issues that will arise in tobacco product testing is data comparability at one time and over time. Data generated using different methods are not always comparable, even though they should be, due to differences in accuracy, sensitivity and selectivity. These issues are largely overcome when the same method is used because these differences are largely removed. But they may not be fully addressed because of inter-laboratory differences in carrying out these measurements (see Section 4.3). Inter-laboratory differences can be addressed to a large extent through participation in inter-laboratory comparison studies. But if possible, a better way to guarantee comparability is to require the use of the same analytical method by the same laboratory. This will maximize the comparability of data. WHO TobLabNet has developed and globally validated methods for testing of some priority tobacco products contents and emissions.

The disadvantages to this approach result from its rigidity. If the same method is required by legislation or regulation, it may be hard to adopt new more effective methods as science advances. The method that is specified will, over time, not keep up with the development of new and more sensitive, more reproducible methods which could benefit the interpretation of analytical data for public health purposes, at least until the legislation or regulation is updated. Also, the requirement to use a single laboratory, if allowed, would eliminate competition which can reduce costs and encourage the development of additional testing capability by initiating development of other labs. If allowed, the choice of methods and/or laboratories, the reliability of the method, and the reliability of the laboratory doing the testing must be fully evaluated before the data are accepted (see Sections 4.2, 4.3 and 5.3). This can require an extensive effort and needs expert advice. Requiring measurement of known standards can help. Regulatory agencies should consider these trade-offs when deciding which approach to take.

1.6 COMMUNICATING DATA TO REGULATORS

Requirements concerning the data to be communicated to regulators are as important as the choice of analytes and how they are to be tested. Regulators need to have information about how the measurements were made so that the quality and comparability of the data can be assessed and appropriate action taken. Analytical results alone, without the context of how they were determined, have limited use.

Regulators must decide the frequency of data to be reported on each brand/subbrand. Acceptable frequency may range from twice a year to once every two years. More fre-

quent measurements help evaluate variation between manufacturing runs but increase cost and the resources necessary to collect, compile and evaluate the data provided. The regulatory agency should weigh these factors before requirements are finalized.

There are some reporting requirements that are obvious. The undisputable identification of the product tested must be provided. This includes information on the brand/subbrand such that the specific product can be identified. As a minimum, subbrand information should include:

- the size of the article[2] (length and diameter for cigarettes)
- the number of articles or size of the package (e.g., 20 cigarettes, 3 ounces for smokeless)
- ingredients added, including flavours (e.g., menthol, strawberry, mint)
- tobacco cut size for smokeless (e.g., long cut)
- ventilation level for cigarettes, and
- any other designator that a manufacturer or a consumer would use to distinguish between products of the same brand name.

It is also critical that the levels determined along with the units of measure (e.g., mg/cigarette, mg/gram of tobacco) be reported. Finally, all analytical determinations made, the number of replicates and the overall mean among those statistically accepted data should be reported. It is important that all results, even those that were rejected, be included along with the reason for rejection so that the data that were reported can be properly assessed. Regulators should also specify the number of significant digits (typically three) that should be reported. Differences that may be significant between samples (e.g. 3.12 versus 3.45 mg/g) could be lost if too few significant digits are required (e.g. 3 versus 3 mg/g).

Additional supporting information that establishes the quality of the analytical measurement is highly recommended. The report to the regulator should include the method(s) used to make the analytical measurements and the method validation parameters (see Appendix 1). To properly assess the reliability of the data and understand if it can be compared to other data being reported and to previous data reported to the regulator, or in the peer-reviewed literature, it is necessary to know the method(s) that were used and their accuracy, reproducibility, sensitivity, and selectivity. Only then can a proper comparison be made. Additional data to be reported to the regulator which help demonstrate the quality of the results reported include quality control results demonstrating that the analytical system was operating properly when the measurements were made, and levels of known standard materials. The measurements of samples, the levels of which have been independently established, can be used to evaluate whether the levels reported are in line with scientifically-accepted results, and by implication whether the results reported on unknown samples are valid.

It is also important to include information about how the testing samples were selected. In addition, the location(s) from which the sample(s) was/were taken (e.g.,

[2] Article refers to the specific product used by the consumer. For example, for cigarettes, an article is the actual cigarette stick that is burned.

from the manufacturing line, storage room, retail location) and the shipping and storage conditions that the sample has experienced must be provided, as some analytes change under certain storage conditions. For example, under some storage conditions, the levels of TSNAs rise in some tobacco products. *(18)* Also, the pH of smokeless tobacco has been shown to change during storage, altering the levels of free nicotine. *(19)* In these cases, it is not appropriate to compare analytical results for samples stored for different times under different conditions. In order to reduce bias, the means of selecting samples should be specified. This could include a randomization scheme for samples that have been placed into the same storage room, a requirement for sampling from multiple manufacturing runs, blind selection of samples at retail, or other means. The randomization scheme should be designed so that the samples selected are representative of the products that are marketed. This is necessary to ensure that samples are not manufactured and sampled specifically for the analytical test but are representative of products sold to consumers.

1.7 COVERING COSTS

Regulatory agencies and governments should not bear the cost of testing and reporting. The manufacturer should bear all costs as a condition of doing business and having access to markets. This is standard practice for most industries (food, cosmetics, pharmaceuticals) and should also be applicable to tobacco product manufacturers. Covering the costs of testing can be accomplished by a direct transaction between the manufacturer and the testing laboratory. Though they may choose to do so, it is not necessary for regulatory agencies to act as intermediaries, receiving samples from manufacturers and sending these off for testing. This imposes a substantial logistical burden on the regulatory agency that is best borne by the manufacturer. But to ensure data accuracy and integrity, other safeguards as described in this document should be instituted.

Regulators may incur some expenses for their part in the testing programme. These include evaluation of the data reported, oversight of the testing and reporting system, enforcement activities, and analyses to check the authenticity of the reported results. There are several mechanisms that countries might use to ensure that these costs are also borne by the manufacturers.

Some countries may choose to impose user fees on manufacturers to cover government regulatory costs and to allow the marketing of tobacco products. User fees can be based on the number of brands/subbrands for a particular manufacturer in the market, or the market share of a particular product. A set amount should be established for the functioning of the regulatory agency, which can be broken down so that each manufacturer pays an appropriate share. Total user fees should not be formulated so that they decrease if the prevalence of product use decreases. Instead, if prevalence decreases, user fees per product sold should increase. This will serve an additional purpose in that per product prices will increase if prevalence decreases.

It is very important that the user fee structure does not oblige a regulatory agency to allow marketing or encourage an increase in tobacco product sales. For example, user fees should not be based on the total number of products sold, with user fees increasing as prevalence increases. This could cause a conflict of interest in the regulatory agency. The design of the user fee system should encourage reductions in tobacco product sales or, at a minimum, have no impact. It must not be designed so that it encourages an increase in overall tobacco product sales. When regulatory agencies evaluate whether to allow the marketing of products, the payment of a user fee based on this decision must be the same whether the decision is to allow or deny marketing. User fees must not be based on a positive decision to allow marketing of a product.

Fines can provide another source of revenue for regulatory activities, although it should not be the sole means of funding. Examples include monetary penalties for unlawful or non-compliant activity, including failure to report. This approach encourages compliance by manufacturers. A set fee for business activity not related to proportion of sales is another possible source of revenue to cover costs.

When using any of these funding mechanisms, a firewall should be set up between the manufacturer and the agency carrying out regulatory activities to prevent the manufacturer having undue influence. This can be accomplished by requiring the manufacturer to pay the appropriate funds into the national treasury, with the regulatory agency receiving a suitable appropriation. But national governments are often looking for sources of funds to support a myriad of activities, so any mechanism must be clearly described by law and ensure the continuous, certain and appropriate funding of regulatory activities.

1.8 IMPLEMENTATION

An important question when considering how to create a tobacco product testing programme is whether to implement everything at once, or step-by-step. When possible, a step-by-step approach is generally recommended. This allows the programme to start more quickly, since incremental steps can be taken to address obvious needs instead of having to anticipate every future possibility. In addition, it allows regulatory agencies to learn from initial mistakes and make adjustments. If an all-at-once approach is taken, it may be so burdensome to change direction that initial decisions may hinder the programme into the future.

Under certain circumstances, the situation may require an all-at-once approach. If the political conditions are such that a gradual approach is not possible, regulatory agencies may be required to start immediately. While this may be possible, there are significant hazards to this approach. Because of the possible pitfalls that agencies may encounter, there is a higher need for careful consultation with experts both before and during the process of creating the testing programme. Details of the various approaches to establishing laboratory capabilities are given in the next four chapters. See section 5.2 for a discussion of expertise available from TobLabNet.

Chapter 2

INTRODUCTION TO THREE POSSIBLE ROUTES TO A TESTING LABORATORY

Operating a laboratory and maintaining the necessary quality of laboratory measurements can be costly and resource intensive. Tobacco product testing laboratories require experienced staff who have successfully carried out analytical measurements that will be heavily scrutinized and challenged. Testing laboratories require effective laboratory information management systems that can efficiently process, evaluate and store large amounts of data. These requirements differ from the requirements of typical research laboratories because of the nature of the work and the intensity of the workload. Laboratories require expensive analytical equipment that must be maintained, serviced and replaced periodically. Modern laboratory instruments are very complex devices that require particular expertise to ensure they operate properly and meet specifications.

Laboratories must maintain day-to-day analytical reliability so that all results are consistent and accurate. Laboratories require external accreditation and quality monitoring to demonstrate the quality of results, their dependability and to demonstrate their fidelity when under the intense scrutiny to which they will be subjected. To accomplish all this, there must be a guarantee of regular and sufficient support of both funding and personnel resources for any laboratory to maintain its testing capability. Competence is developed over time and must be maintained so that it can be relied upon when needed. We suggest three approaches to creating laboratory capacity for the testing of tobacco products design, contents and emissions.

This chapter summarizes these approaches, and subsequent chapters provide further detailed information on this capacity.

2.1 CONTRACTING WITH AN EXTERNAL LABORATORY

There are several experienced, independent tobacco testing laboratories around the world that are not affiliated with the tobacco industry. TobLabNet was set up to encourage the development of such laboratories and to better assure the quality and consistency of measurements. Laboratories, such as these, generally take two forms: independent commercial tobacco product testing laboratories and government-owned/operated tobacco product testing laboratories.

If they have been in operation for a substantial period of time, independent commercial tobacco product testing laboratories have certain advantages. They should already have capabilities that have been adequately tested and verified, and have experience participating in inter-laboratory comparisons. They already have experienced scientists and technicians on staff and the equipment needed to carry out a range of analyses. They will be accustomed to testing and reporting on a contractual basis and prepared to provide results under those conditions. They will already have developed IT systems and should already participate in an external quality assurance programme. For a regulatory agency ready to have testing done, these laboratories can quickly respond and provide results in a timely manner. But in general, they are limited to their own menu of testing capabilities. It may be possible for them to develop new capabilities, but this would take time and they would need assurances that developing and validating a new method would be commercially beneficial. So a country-specific test may not be an immediate priority.

Some independent commercial tobacco product testing laboratories also make measurements on a contractual basis for the tobacco industry. This may concern some countries regarding their adherence to Article 5.3 of the WHO FCTC. In these cases, countries should require assurances of a firewall[3] to protect public health from commercial interests and to ensure confidentiality and independence of results. Laboratories that perform product testing for both the industry and regulatory agencies should not be automatically rejected, but evaluated to ensure their integrity, lack of bias and confidentiality.

There are also a substantial number of government-owned and operated tobacco product testing laboratories. TobLabNet continues to successfully work with several government-owned tobacco testing laboratories around the world to encourage the development of capabilities and provide a mechanism for inter-laboratory validation (see Appendix 1). Thus there are very effective and reliable government laboratories that understand the importance and objectives of regulatory testing of tobacco products and that face many similar challenges to those encountered in starting a new programme. These laboratories have many of the same advantages as working with independent commercial tobacco product testing laboratories, including experience, IT systems, quality assurance programmes and established capabilities. In addition, working with another country's regulatory agency can be a big advantage for a country that is just starting a programme.

For example, this interaction can provide a natural consultation relationship between new and experienced programmes. If a new regulatory agency is making unsuitable decisions (e.g., testing of the incorrect analytes in emissions), government agencies are more likely to provide advice in place of carrying out an inappropriate measurement. This could be a major advantage for a new tobacco regulatory programme. The biggest disadvantage of working with an established government laboratory is that they have their own statutory requirements and priorities. So they are not as likely to be available to carry out measurements in the time frame

[3] A system to ensure that data and information are protected so that public health and commercial interests are separate and not accessible to each other.

desired. They may be delayed by other priorities and their management is likely to require that their own priorities take precedent.

The third option for external laboratories is those owned and operated by the tobacco product manufacturers themselves. These should be avoided under any circumstances since there is an inherent conflict of interest.

2.2 USING AN EXISTING INTERNAL LABORATORY

For this discussion, we are assuming that a country has an experienced laboratory that is already doing testing for other purposes. For example, the country may conduct environmental or pharmaceutical testing and has previous experience of compliance testing and reporting. There are certain advantages and disadvantages to this approach.

For a laboratory already testing other consumer products, the development of internal capabilities to test tobacco products will have a foundation upon which to build. One of the biggest challenges in developing an effective laboratory where none existed before is hiring of staff with valuable expertise who understand how to carry out valid and legally-defensible measurements. In addition, much of the laboratory equipment, IT systems and quality assurance programmes will already be in place and can be adopted for tobacco product testing purposes. Such an approach will be cheaper and quicker than creating a tobacco-testing laboratory from scratch. There may also be other advantages to using this approach. If funding is inadequate for the current laboratory to be as effective as desired, additional funds from tobacco testing could help. This would be a major advantage for laboratories which are often provided with limited government funding.

On the negative side, tobacco testing is likely to require new equipment and expertise. For example, smoking machines and expertise in their use are limited to combusted tobacco product testing; environmental or pharmaceutical testing laboratories will not have this equipment or experience. Thus, acquiring this capability will still require some significant start-up time and costs. But if planned correctly, this could be a second stage in laboratory development if there are specific priorities (e.g., cigarette tobacco content or smokeless tobacco testing) that do not require this capability. In addition, as with the situation described above, developing tobacco product testing capabilities in an existing laboratory may result in priority conflicts. For example, a drug testing laboratory is likely to already have fully assigned staff and equipment. Rarely do laboratories have significant excess capacity. So a natural conflict will occur at times when both programmes need results quickly. It would be wise to specify clearly how such conflicts will be addressed before final agreement is made.

If there are research laboratories available that may add tobacco product testing capabilities, be aware that the nature of the work and the scientific approach are not the same. The work of a laboratory that tests products for compliance or reporting

purposes has requirements that are different from those of a research laboratory. In general, research laboratories would need to increase IT infrastructure, put more robust quality assurance systems in place, seek accreditation, and be prepared to provide forensic evidence in order to be successful as a compliance laboratory. By contrast, an existing internal compliance laboratory should already be accustomed to generating results that can be used for compliance or legal purposes. A Case Study with a pre-existing tobacco testing laboratory using other facilities to support additional tobacco product testing capabilities is described in Section 4.3.

2.3 DEVELOPING A DEDICATED LABORATORY

The final option to be considered is developing a dedicated government tobacco product testing laboratory without sharing resources. This approach has some considerable advantages. Having a dedicated testing laboratory means that the priorities of testing capacity and developing new testing capability will be driven by tobacco regulation priorities. Thus the priorities for use of available capacity can be set by a single management structure. It is also possible to use any excess capacity as a means of generating additional revenue to support the laboratory's operations.

On the other hand, developing a laboratory that can generate completely reliable results will require significant commitments of time, funding and human resources. This may be alleviated somewhat if there are current laboratory facilities or even facilities and staff that can be reassigned to a new mission. If not, this could require construction or remodelling of physical structures. Laboratories require special air handling, power requirements (such as uninterruptible power supplies) and other physical facilities that are not typically present in office, retail or commercial buildings. This may mean building new facilities or conversion of current facilities. It may be challenging to maintain adequate support to develop a laboratory that requires years of construction and outfitting, especially when government has other budgetary priorities. Maintaining support for testing capabilities among government decision-makers is likely to require data to demonstrate the value of this significant investment; delays could result in loss of support. While this is certainly a viable option, several countries have been unsuccessful when trying this approach. Their lack of success has been largely the result of delays in construction and changes in government priorities as administrations change.

This advantages and disadvantages described above are summarized in Table 1 and described in more detail in the chapters that follow.

Table 1. Advantages and disadvantages of approaches to developing laboratory capability

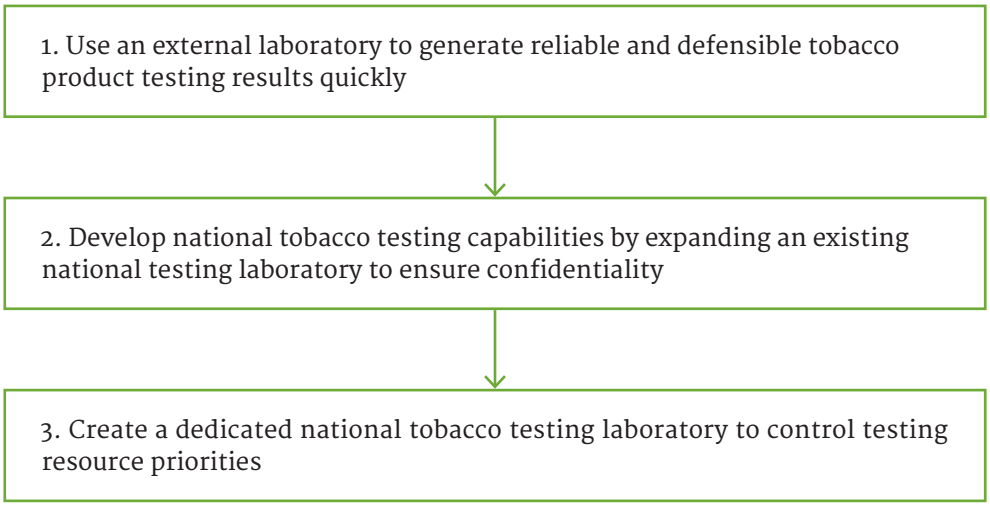
Laboratory type	Pros	Cons
External laboratory – commercial	• Internal measurement expertise not required • Lower start-up costs • Faster start-up than developing new capabilities • Broad capabilities • Immediate access to experienced scientists • Recognized validity of results	• Availability not guaranteed • Reliability must be regularly assessed • May be more expensive long-term • May be limited to methods available in that laboratory • Less flexibility to develop new methods
External laboratory – government	• Developing new internal expertise may not be required • Less expensive start-up costs • Faster start-up than developing new capabilities • Immediate access to experienced scientists • Recognized validity of results • Encourages consultation with regulatory agencies from other countries	• Possible delays in generating results • Reliability must be regularly assessed • May be more expensive long-term • Less flexibility to develop new methods • May have limits to capability and capacity
Existing internal laboratory	• Some expertise available • Improved overall efficiency through resource sharing • Lower start-up costs • Faster start-up than creating a new lab • Pre-existing and reliable IT and quality systems • May help stabilize funding for both programmes	• Availability depends largely on other priorities • Must purchase some tobacco-specific equipment (e.g. smoking machine) • Must develop some expertise (e.g. smoking machine operation) • Will require some start-up time and costs
Dedicated internal laboratory	• Guaranteed availability • Can generate revenue through outside work • Can develop capability as needed • Complete flexibility of priorities	• Broad capability is expensive • Large start-up costs • May require building facilities • Will require significant start-up time • Must obtain expertise • Government support and funding level may fluctuate

For countries beginning a testing programme, starting with an experienced external laboratory is recommended (See Fig. 1). This serves several purposes, of which the three most important are listed below:

1. It allows the testing to be started quickly while support is strong.
2. It provides data quickly to help support the rationale for carrying out tobacco product testing long-term.
3. It lifts the burden of laboratory development and data quality from regulators, allowing them to concentrate on other critical issues.

If there is a significant sample load and support remains strong, a regulatory agency may consider an agreement with another government-owned and operated testing laboratory within the country to carry out tobacco testing. If the external contract is maintained, this will allow a step-wise transition with no loss of capability, but expanded capacity. Finally, if sample throughput supports it, consideration may be given to build and outfit a dedicated national tobacco testing laboratory. But this should only be done if it is evident that there is an adequate volume of testing and administrative support continues to be strong. As discussed above, going directly from no capacity to a dedicated national tobacco product testing laboratory has not proven to be a viable approach.

Fig. 1 **Suggested approach to building testing capabilities**



Chapter 3
CONTRACTING WITH AN EXTERNAL TESTING LABORATORY

3.1 LABORATORY SELECTION CRITERIA

There are several important considerations when attempting to identify an external laboratory with which to contract. The emphasis given to each of these in making a final decision will vary from country to country, but all may be considered. It is worthwhile to investigate each of these considerations before making a final decision.

3.1.1 Experience in tobacco analyses

This is critical and possibly the most important factor. The primary reasons, as listed above, for working with an external laboratory are based on specific experience in performing tobacco product analyses. Choosing a laboratory with limited experience contradicts the advantages of using an external laboratory. As has already been described, tobacco analyses has its own requirements, procedures, equipment and standards, and a laboratory with years of experience in this field and a demonstrated track record will substantially reduce start-up costs and time.

3.1.2 Equipment capabilities

Analytical chemistry is constantly evolving to develop procedures and equipment that are more accurate, reproducible, selective and sensitive. While improved sensitivity is not necessary when analyte levels are high, many ingredients and emissions in tobacco products are at levels that challenge the ability to detect and accurately quantify. Modern analytical equipment is steadily improving detection and quantification limits such that these improvements may be critical for answering specific tobacco regulatory questions. Evaluation of an external laboratory should include an assessment of the breadth and sophistication of analytical instrumentation. In order to address immediate needs, laboratories should include, at a minimum, the equipment listed in Table 3. Countries should also consider which of the equipment listed in Table 4 and any additional equipment that may be needed for country-specific analyses. Any laboratory to be considered must include gas chromatography (GC)-flame ionization detection (FID) and liquid chromatography (LC)-diode array detection instrumentation. It is an advantage to also have LC-tandem mass spectrometry. In addition, the degree to which automated sample preparation apparatus

are used will help reduce human error. It is expected that tobacco manufacturers will have access to the most advanced instrumentation available and when comparing data in a compliance, enforcement or legal setting, it is best to know that the instrumentation used is the most advanced for a particular purpose. Decisions should be based, wherever possible, on state-of-the-art analyses.

3.1 3 Staff qualifications

An experienced and capable staff is the most valuable commodity in a laboratory. While advanced equipment can be purchased, staff must be trained and experience requires time to develop. Experienced laboratory analysts and instrument operators are necessary for making reliable analytical measurements on any commodity, but especially so for tobacco products because of the particular requirements. When assessing a laboratory, an evaluation should be made of the number and length of time that staff members have been performing analytical measurements as a whole, and tobacco product analyses in particular. In addition, a system for regular training of new and experienced staff should ensure they are competent and evaluated before they start independent analyses and to make certain that they keep up with advances in the field.

3.1.4 Breadth of capabilities

Even if the initial range of analyses is limited, it is likely that, at some point, the situation will change and there will be the need to perform new tests. A laboratory that only has limited capability may not be able to perform new analyses when needed for regulation. In that case they will require significant start-up time to develop capabilities and verify new measurements. If those capabilities are already present, this start-up time would be minimal. In addition, a laboratory with a wider breadth of capabilities is likely to be of higher quality. Capable scientists are always looking for new challenges or ways to improve. A laboratory that allows staff to grow in their jobs attracts and retains better-qualified scientists.

3.1.5 Excess capacity

In order for testing results to be useful for regulatory purposes, they must be accurate, reproducible, sensitive, and selective (see Section 4.3 below). But, they also must be timely. If a laboratory is not able to provide results when needed, the critical opportunity may have passed, and these data may no longer be relevant or have the most impact. Capacity is not only the sample throughput when all systems are operating as expected, it also offers flexibility. For example, a tobacco smoke testing laboratory that has only one smoking machine cannot process any combusted product emission samples if it is being repaired. A facility that has duplicates of all critical equipment and backups for all staff members can continue to function when unexpected events occur. Capacity should be included in an overall laboratory assessment.

3.1.6 Proven track record

Advanced equipment, trained staff and excess capacity do not ensure that laboratories can produce and report reliable results within deadlines. Timeliness can also be a function of the institutional culture and the effectiveness of management. Laboratories should be able to provide references or records showing that reliable results can be regularly produced and reported on time. It is worthwhile, if possible, to obtain a list of previous customers and contact some of them randomly to evaluate the ability of the laboratory to produce results, as promised.

3.1.7 Accreditation

Accreditation is the documentation by an independent body showing a laboratory has the systems in place that should enable them to produce reliable results that have been adequately tracked and verified. There are international and national laboratory accreditation bodies and accreditation standards such as ISO 17025 that effectively carry out this function (see Section 4.2). Any laboratory generating results for compliance and enforcement purposes should be accredited. Any laboratory that is not should immediately be removed from consideration. Even so, it is important to keep in mind that accreditation alone does not guarantee valid results. It is possible for laboratories to be accredited and not be able to produce adequate results.

3.1.8 Ability to add new methodologies

As discussed above, there will be times when a specialized analysis is needed that was not previously anticipated and for which there are no current methods. A good example is the introduction of a new product type or product modification likely to generate new emissions. In that case, a laboratory may need to develop and validate a new method in a relatively short time. Laboratories should be able to give examples of carrying out this process from previous instances. Because this could require substantial development efforts, the costs for new methodology analyses will likely be higher than for a routine measurement.

3.1.9 Information technology systems

Accuracy is a fundamental requirement of analytical measurements. Accuracy can be maximized by using the right analytical methods and instrumentation carried out by trained and experienced staff. But errors can occur whenever the analytical process involves manipulation of data. This is a particular challenge whenever numbers are transcribed by hand. The less hand transcription of numbers, the fewer errors. Laboratory information management systems (LIMS) are common throughout the laboratory testing community and are considered a necessity for testing and reporting. A laboratory without a LIMS should be dropped from further consideration. The more automation, the lower the chance of human error, but there also needs to be a process for checking that the LIMS works properly. A LIMS that tracks samples and

processes data from sample receipt to report preparation is highly desirable. But, checks also need to be built into the quality assurance programme that regularly validate these systems.

3.1.10 Quality assurance programme

Quality assurance combines a well-defined quality control programme with an overall mindset of quality. Quality control evaluates whether systems continuously operate within standard parameters. Quality assurance ensures that the systems were designed correctly and are operated appropriately. A quality assurance programme involves training as described above, management review of compliance with laboratory standards, and regular review of results before they are reported. An effective quality assurance programme is critical for data reliability.

3.1.11 Participation in inter-laboratory validation

It is very likely that any results generated will need to be compared to results from other sources. These may be results generated historically by other laboratories or in other countries. It is also important, from a legal standpoint, to show that data from a particular laboratory is comparable to data from other laboratories. Inter-laboratory validation exercises occur on an international basis and go by several names including round-robin and inter-laboratory comparison. In these exercises, the same samples are analysed by multiple laboratories and sometimes using multiple analytical methods. Results are compared to determine what is the consensus mean between all laboratories and the deviation of each laboratory from the mean. Participation in round-robin inter-laboratory validation can help address an area of uncertainty that could be critical in the use of the data for public health regulatory purposes. Another substantial advantage of participation in round-robins is that, if there are high priority analyses and a laboratory is fully occupied or instruments are not operational, other laboratories can be utilized with an assurance of data comparability.

3.1.12 Cost of analyses

Cost may seem to be a major consideration, but it is one of the least important in deciding which laboratory to use. If tobacco product manufacturers are paying the cost of analyses, this should not be a critical issue for the regulatory body but should be noted as part of the overall assessment.

3.1.13 Other customers

There may be a conflict of interest within the laboratory with analyses performed for other customers, such as tobacco industry clients. As discussed, above in section 2.1, there are ways to address these concerns, but they should be considered as a factor when making a final decision.

3.1.14 Location

The proximity of the laboratory to the country requesting analyses is primarily a question of logistics, but can also be a matter of import law. The most critical factor is whether there are reliable means of transporting samples from the site of collection to the laboratory efficiently. Since samples will most likely be shipped through a common carrier, this is typically not a major barrier, but the process and length of time required should be evaluated beforehand. Samples that are not adequately stored during shipping may be altered and that could raise questions about data integrity.

Some countries have restrictions on tobacco imports and transferring such products across national borders can be problematic. But there can be allowances for products sent for testing purposes only. It is advised that this issue be clarified before deciding to use a laboratory in another country. It should also be considered that a laboratory that is close in proximity may be easier to visit for inspection purposes than one located far away.

The form below (See Fig. 2) provides a convenient means to organize a laboratory rating. The factor under weighting should be adjusted based on the specific country's requirements. A possible set of weights is provided, but should be adjusted as appropriate. These weights were based on factors which the author believes would enable a laboratory to be most successful in carrying out accurate testing of a wide range of analytes in tobacco products. The score should be determined for each laboratory. Then the product (weighting multiplied by the score) calculated and the sum added on the bottom line.

Fig. 2 Laboratory Rating Sheet

Laboratory Name _____

Factor	Weighting (1-10)	Score (1-10)	Product (weighting x score)
Experience in tobacco analysis	10		
Equipment capabilities	8		
Staff qualifications	8		
Breadth of capabilities	6		
Excess capacity	6		
Proven track record	8		
Accreditation	8		
Ability to add new methodologies	6		
Information technology systems	6		
Quality assurance programme	8		
Participation in inter-laboratory validation	8		
Cost of analyses	2		
Other customers	4		
Location	4		
Total (sum of above)			

3.2 WHO TOBLABNET

The WHO Tobacco Laboratory Network (TobLabNet) is a network of government, academic and independent laboratories designed to strengthen national and regional capacity in the testing of tobacco product contents and emissions. *(20)* In April 2005, the WHO Tobacco Free Initiative (TFI) established WHO TobLabNet based on the aims and objectives of Articles 9 and 10 of the WHO FCTC and the recommendations of the WHO Study Group on Tobacco Product Regulation (TobReg). TobLabNet is a primary source of laboratory support, methods development, and scientific information in the areas of tobacco testing and research for national governments to fulfil their requirements and needs related to the WHO FCTC.

Originally, there were 25 laboratories from 20 countries representing all six WHO regions who agreed to be a part of WHO TobLabNet. Over the years, the participation of laboratories in method validations has varied depending on national priorities and availability of resources. The current list of participating laboratories is given in Table 2.

The goal of WHO TobLabNet is "to establish global tobacco testing and research capacity to test tobacco products for regulatory compliance, to research and develop harmonized standards for contents and emissions testing, to share tobacco research and testing standards and results, to inform risk assessment activities related to the use of tobacco products, and to develop harmonized reporting of such results so that data can be transformed into meaningful trend information that can be compared across countries and over time". *(21)*

To accomplish this, laboratories work together and support each other in collaborative projects guided by various lead laboratories. WHO TobLabNet works actively to provide advice to national governments seeking to develop and improve tobacco testing laboratories as a means of increasing capacity and ensuring consistency.

WHO TobLabNet carries out work requested by the Conference of the Parties to the WHO FCTC through the WHO FCTC Secretariat, under the auspices of WHO, for accomplishing objectives set out under the WHO FCTC. Recently, this work has involved method development, validation and verification for measuring high priority contents and emissions in commercial cigarettes and other tobacco products. In addition, round-robin testing of the methods by various laboratories have been used to measure the inter-laboratory reproducibility of these methods. The current list of constituents and their status is found in Table 3.

Governments seeking information on establishing mechanisms for tobacco products testing are advised to contact WHO TobLabNet for advice and guidance. Based on the availability of resources, WHO TobLabNet may be able to provide training and support capacity building of laboratories looking to begin tobacco testing or expand current capabilities, both within the network itself and for laboratories looking to become a part of the network in the future.

Table 2 List of Tobacco Laboratory Network (TobLabNet) member laboratories

WHO Region	Country	Laboratory
Regional Office for Africa (AFRO)	Burkina Faso	Laboratoire National de Santé Publique
Regional Office for the Americas (AMRO)	Canada	Labstat International ULC
	Costa Rica	Instituto Constaricence de Investigación y Enseñanza en Nutrición y Salud (INCIENSA)
	Mexico	National Institute of Public Health
	United States of America	Centers for Disease Control and Prevention
		Alcohol and Tobacco Tax and Trade Bureau (TBB)
		Battelle Public Health Center for Tobacco Research
		Virginia Commonwealth University
		National Cancer Institute
Regional Office for South-East Asia (SEARO)	India	Directorate General of Health Services
	Indonesia	National Agency of Drug and Food Control
Regional Office for Europe (EURO)	Albania	Institute of Public Health
	Bulgaria	Tobacco and Tobacco Products Institute
	Finland	National Supervisory Authority for Welfare and Health
	France	Laboratoire National de Métrologie et d'Essais
	Germany	Federal Institute for Risk Assessment (BfR)

	Greece	General Chemical State Laboratory of Greece
	Ireland	State Laboratory
	Italy	European Commission, Joint Research Centre
	Lithuania	National Public Health Surveillance Laboratory
	Netherlands	Laboratory for Health Protection Research of the Dutch National Institute for Public Health and the Environment
	Russian Federation	All-Russia Research Institute of Tobacco, Makhorka and Tobacco Products
	Spain	Agrarian and Food Laboratory
	Switzerland	L'Institut universitaire romand de santé au travail (IST) Lausanne
	Ukraine	L.I. Medved's Research Center of Preventive Toxicology
Regional Office for the Eastern Mediterranean (EMRO)	Lebanon	American University of Beirut
	United Arab Emirates	National Laboratory & Research Center
Regional Office for the Western Pacific (WPRO)	China	China Centers for Disease and Control and Prevention
		Institute of Tobacco Safety and Control
	Japan	National Institute of Public Health
	Republic of Korea	Ministry of Food and Drug Safety
		Korea Centers for Disease Control and Prevention
	Singapore	Health Sciences Authority
	Viet Nam	National Institute of Occupational and Environmental Health

Table 3 Current TobLabNet Method Development Status

Method	Analytes	Matrix	Analytical Method	Status
Nicotine	Nicotine	Tobacco	GC/FID[a]	Validated
Ammonia	Ammonia	Tobacco	Ion chromatography/ conductivity detection	Validated
Humectants	Propylene glycol Glycerol Triethylene glycol	Tobacco	GC/FID (GC/MS)[b]	Validated
TNCO	Tar, nicotine, carbon monoxide	Smoke	GC-FID (nicotine) GC-TCD[c] (water for tar calculation) Non-dispersive infrared analyzer (for CO)	Validated
TSNAs	N-Nitrosonornicotine (NNN) 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) N-Nitrosoanatabine (NAT) N-Nitrosoanabasine (NAB)	Smoke	HPLC/MS-MS[d]	Validated
BaP	BaP	Smoke	GC/MS	Validated
VOCs	Benzene 1,3-Butadiene	Smoke	GC/MS	Validated
Carbonyls	Formaldehyde Acetaldehyde Acrylaldehyde	Smoke	HPLC DAD[e]	Validated

[a] Gas chromatography/Flame ionization Detection

[b] Gas chromatography/Mass spectrometry

[c] Gas chromatography/Thermal; conductivity detector

[d] High-performance liquid chromatography/Tandem mass spectrometry

[e] High-performance liquid chromatography/Diode Array Detector

3.3 AGREEMENTS AND LEGAL/ETHICAL ISSUES

As stated above, national regulatory agencies should consider their specific legal and ethical issues when planning to contract with an external laboratory. These should be understood and resolved before an agreement is signed and before analyses are performed. It is very important that the data obtained by regulatory agencies be adequate for their purposes; all requirements related to data quality for the use of the data should be clearly described in any agreement.

The first consideration when entering into an agreement with an external laboratory is ensuring the laboratory's independence from the tobacco industry. Article 5.3 of the WHO FCTC urges Parties to protect tobacco control policies from "commercial and other vested interests of the tobacco industry". WHO TobLabNet applies strict membership criteria which excludes laboratories that are totally or partially owned by a tobacco company, or laboratories with persons in senior management positions employed by or affiliated with the tobacco industry. Laboratories that receive funds from the tobacco industry must additionally demonstrate independence. These conflict-of-interest requirements ensure that public health objectives of testing policies are never compromised.

Another consideration is the legal requirement for introducing testing data as evidence in legal proceedings or as the basis for regulatory action. For example, it should be understood from the start that the laboratory has the required accreditation and evidence of data quality that are needed to use the data in taking action. Chain of custody may be a critical element in assuring that the data is from analyses of the materials intended to be tested. An assurance of sample integrity can be a critical factor in the legal acceptance of data.

Certain laboratories may consider background information related to the analyses that are performed as proprietary. Detailed descriptions of laboratory methods, quality control results, findings from method validation, or information on the results of round-robins could be considered private and not for release. If this information is needed as part of regulatory evidence, it should be clear from the outset that the laboratory must make this information available. Discovering otherwise, after the analyses have been completed, would greatly restrict the effective use of the data.

Another pre-contract consideration is the reporting of analysis results. Laboratory measurements typically involve multiple replicate analyses on each sample. In other words, in order to improve accuracy, account for the variability in a commercial product made from an agricultural product such as tobacco, and to evaluate reproducibility, multiple measurements are made and these are averaged to arrive at the final result. Typically, this may include anywhere from three to 20 replicates for a single final result. The number of replicate analyses to be made is a balance between sample availability, cost (more replicates cost more) and data quality (more replicates reduce random variability).[4] The regulatory agency should consider how best to balance the requirements of the data use versus the cost of the analyses. When choosing laboratories, the number of replicates typically carried out should be part of the overall consideration.

[4] More detail on this subject can be found in Appendix 1.

In the report provided to the customer, laboratories can report all of the replicates or can report the final average. Regulatory agencies should require the reporting of all replicates so that the data quality can be fully assessed and the appropriate statistical analyses can be carried out as suitable for the particular application. This should be included in the agreement with the laboratory so that the required information is retained and reported.

When using an external laboratory, it is important to understand if and when those data are available to parties other than those requesting and funding the analyses. Laboratories should have adequate firewalls so that business agreements with other involved parties including tobacco product manufacturers do not influence the analyses for the regulatory agency. Regulatory agencies should investigate whether laboratories have a potential conflict of interest before agreeing to use them. In addition, regulatory agencies should be aware of public access or freedom of information laws, which might impact access to the data by interested parties. These laws may not influence whether a regulatory agency carries out testing using a particular external laboratory, but they should be aware of issues that could arise.

Even when it is understood that the analyses will be funded by the industry, there are at least three options for the reporting of results: government only, government and industry simultaneously, or industry only, which then provides data to the government. From a reliability standpoint, reporting results from the laboratory straight to the government is preferable if that accords with the requirements defined in the statutes or regulations that require these reports. This is possible either through reporting results to the regulatory agency alone, or simultaneously to the regulatory agency and the manufacturer whose products are being evaluated. Reporting directly to the government agency helps to reinforce to the laboratory that the regulatory agency is the end user of the results and a decision-maker concerning where analyses may be performed. Simultaneous reporting is the most likely acceptable option for all parties involved because of lack of trust. But reporting by the laboratory to the manufacturer, which then provides these data to the regulatory body, should be avoided since that provides an opportunity for data manipulation and creates unnecessary uncertainty.

3.4 SAMPLE LOAD ESTIMATES

Laboratory capacity is a significant consideration when choosing a laboratory because timely results are critical for providing data to decision-makers when issues are ripe for action. But excess laboratory capacity does come with a cost. For a laboratory to be prepared for a large sample load or unexpected requests, they must have access to excess equipment and staff. These resources must be supported even when not in use, so overhead costs increase. It is very important that regulatory agencies provide good estimates of anticipated sample load so that laboratories can be prepared ahead of time to provide a timely response. Poor estimates of sample load or timing of sample delivery causes delays in results reporting or wasted resources, the cost of which must be passed on to the customers.

In order to best optimize available resources, sampling and analysis requests should be spread over the entire year and not just at one time of year. There are several efficient ways of doing this. Manufacturers can be required to submit samples at different times of the year, perhaps spreading this out over all four quarters. Or manufacturers could submit one quarter of their brands/subbrands for analyses each quarter of the year. This spreads the laboratory workload, allows a more efficient use of resources and helps to control the cost of each analysis.

When choosing laboratories, it is important that evaluation is based on capacity and the ability to meet specified time frames. Some consideration must be made for unforeseen circumstances, and this should be considered when estimating sample reporting expectations. Regulatory agencies need to consider how soon results will be required after submission and whether there may be a need for special priority requests. This should be included in an agreement when contracting with a laboratory.

3.5 COSTS

The cost for tobacco product contents and emissions analyses can be high relative to other regulatory activities. No matter whether manufacturers submit samples directly to the laboratory or if the samples are first submitted to the regulatory agency and then submitted to the laboratory, all costs must be covered by the tobacco product manufacturers. If a manufacturer believes that the cost of testing is excessive, they can choose not to market their products or reduce the number of brands/subbrands sold in a particular market. In either case, a reduction in the number of brands/subbrands sold in a country could result in a reduction in overall tobacco product use and an improvement in public health.

Depending on the analysis to be performed, the matrix (tobacco or smoke), the equipment used, and the number of replicates, the cost of each individual analytical test in each individual brand/subbrand can range from hundreds to thousands of US dollars. Measurements in smoke are generally more expensive than measurements in tobacco because the process of generating and collecting smoke using an appropriate regimen adds an additional step to the analytical process. Some analyses can be performed using a variety of analytical equipment. For example, analysis of benzo[a]pyrene in mainstream smoke may be made using infrared spectroscopy, gas chromatography with mass spectrometry, high-performance liquid-chromatography (HPLC) with fluorescence detection, HPLC with mass spectrometry (MS), or HPLC with tandem MS. When a lab can perform adequate cross-method validation, use of alternative methods with other analytical instrumentation may be possible. The cost of purchasing and maintaining this equipment varies so that the cost of the analysis will be different. There may be certain critical benefits (sensitivity and selectivity) to using more sophisticated and sensitive analytical equipment, but the use of higher cost equipment when not needed should be avoided. Analytical measurements should be evaluated for their fitness for use before agreeing to carry out a higher cost analysis.

In certain cases, multiple constituents can be measured simultaneously using the same analytical method. For example, most analytical methods for TSNAs measure all four of these compounds using the same method. The cost is not substantially lower if only one of the TSNAs is measured. The case is the same for some PAHs, heavy metals, aldehydes, and many volatile organic compounds. So the overall cost of testing and reporting is less dependent on the number of constituents reported, but rather the number of analytical methods that must be performed to make the measurements.

3.6 CASE STUDY – CANADA

Canada provides a good example of a country that has successfully used an external laboratory for research purposes as well as method development in support of tobacco control. In the late 1970s, Health Canada started contracting the services of an independent laboratory[5] (not affiliated with the tobacco industry) to test the contents and emissions of various tobacco products on the Canadian market. In the 1980s, after having identified the need to measure a larger selection of analytes in the contents and emissions of tobacco products, Health Canada called upon the same independent laboratory to develop laboratory methods, work which continued throughout the 1990s and led to methods covering 20 analytes found in the contents and 40 in the emissions of tobacco products. *(22)*

The *Tobacco Reporting Regulations*, which came into force in 2000, incorporate these as "Official Methods", which manufacturers must use for reporting to Health Canada. *(23)* As per section 4 of the regulations *(22)*, tobacco product manufacturers must report results using a laboratory that is accredited under the International Organization for Standardization standard ISO/IEC 17025, entitled *General Requirements for the Competence of Testing and Calibration Laboratories*. Typically, independent laboratories are retained by the manufacturers to meet their reporting obligations. Health Canada continues to use independent laboratories as needed to support analytical development projects.

The use of a single analytical laboratory with a defined set of analytical methods has a clear advantage. When measurements are made by the same laboratory using the same methods, uncertainty is significantly reduced and there is increased confidence in the direct comparability of all results. The disadvantage to this approach is the dependence on a single laboratory. For example, if that laboratory ceased operations, there would be challenges in moving the necessary analyses to a different laboratory. Also, there may be concerns about sample analysis capacity if only one laboratory is used. If only a single laboratory is identified, it would be prudent to have the laboratory provide a backup plan describing what steps could be taken to mitigate any loss of capacity and ensure continuity of operations.

[5] Labstat in Kitchener, Ontario, Canada (http://www.labstat.com/servicesoverview.html)

3.7 STEP-BY-STEP PROCESS

1. Do your own internal research.
    a. Identify a reasonable first set of analyses for your tobacco testing that would address your country's priorities.
    b. Identify the analytical requirements for the intended use of the data.
    c. Determine the estimated initial workload (number of samples over what period). This may be determined by the number of brands/subbrands being marketed and the frequency and schedule of testing.
2. Discuss your approach with another country's regulatory agency that has experience with tobacco product testing.
3. Evaluate available laboratories.
    a. Check the requirements listed above and rank available laboratories.
    b. Evaluate the ability of laboratories to meet analytical accuracy, reproducibility, sensitivity and selectivity requirements to identify satisfactory laboratories.
    c. Use estimates of capacity requirements to identify acceptable laboratories.
4. Discuss particular needs and requirements for expected sample workload, turnaround time, reporting requirements, etc. with the identified laboratory.
5. Finalize any required contractual agreement.
6. Communicate to the manufacturers, if appropriate.
    a. what needs to be tested and when?
    b. which labs are acceptable?

Chapter 4

USING AN EXISTING INTERNAL TESTING LABORATORY

In certain cases, a national government may already have laboratories to test non-tobacco consumer goods. These may be test purity or to verify levels of therapeutic drugs in pharmaceuticals, cosmetics or imported goods. There may also be laboratories to test environmental samples such as air or water. The existence of government testing laboratories for other consumer goods or environmental samples provides an opportunity to readily develop government tobacco testing capabilities.

A tobacco regulatory agency may find that government organizations that already operate testing laboratories are willing to collaborate to expand their capabilities and include some tobacco design, content and emissions testing as part of their analytical portfolio. Because they are likely to be already overworked and underresourced, this may require some careful persuasion by highlighting the advantages that this could bring to their activities. Explaining how expanding to include tobacco would benefit their current programme could help to convince them.

There are several advantages to working together with current government testing laboratories, when possible. The existing laboratory is likely to have equipment, supplies, trained personnel and quality assurance and information systems in place. Equipment alone is expensive to obtain and maintain when establishing a laboratory. Analytical equipment can cost as much as hundreds of thousands of US dollars per item and maintenance and repair is an ongoing requirement. If the current laboratory already has the equipment in place and has budgeted funds for repair and maintenance, those costs will be already covered, and additional analyses for tobacco products will not increase these costs substantially.

Laboratory personnel are a critical asset. It can take years to get the training and experience to develop an effective analyst. While it may be possible to hire experienced analysts directly, this can be a significant challenge because of their limited availability. If a laboratory already has experienced analysts, as would be the case for an existing testing laboratory, the time required to train them to carry out methods for analysis of tobacco products will be significantly less. If it is a priority to generate results quickly to illustrate the value of tobacco product testing, collaborating with an existing laboratory is a much better approach than creating a laboratory from the ground up. The value of experienced analysts cannot be overemphasized. The knowledge and experience of staff carrying out the analyses is the most critical factor in determining whether reliable results can be produced efficiently.

Similarly, the use of an existing laboratory allows the testing programme to start in a restricted way, if needed. When building a laboratory from the ground up, considerations must be made about the size of the laboratory and projected resources many years in the future. Thus initial design considerations must allow for the expected increases in capabilities and capacity. Invariably, this leads to overbuilding at the start of the programme with significant unused space. This may be challenging for a programme that is just beginning. By using existing laboratory facilities, tobacco testing can start at a limited level and then grow in a controlled manner as the programme expands.

Another significant advantage to this approach is that it can provide an additional source of funding for an existing laboratory. Laboratories invariably have to balance their instrument capacity and the number of staff with the expected workload and funding. Periodic variations in sample load are always a challenge for laboratory management. By expanding the sources and amount of funds flowing to the laboratory, variability in sample load can be better balanced. This is an important advantage that can be presented when discussing this approach with the current laboratory management. While there will be some increase in resource requirements, additional funding streams could help to address the highs and lows of sample analysis requests and funding.

In addition to smoothing out the laboratory funding stream, additional funding can support the purchase of additional equipment, hiring of new staff and expansion of other capabilities that would not be otherwise possible. Most of the analytical equipment for use in analyses of tobacco product contents and emissions can be used for other work. So if allowed, tobacco funding may be used to upgrade analytical instruments, which can then also be used for analyses of environmental samples or pharmaceuticals and other consumer goods. This would provide a significant advantage to the current laboratory. To the degree that synergism is possible, both programmes will benefit.

There are some disadvantages to this approach. Because of their current programmatic responsibilities, the current programme will likely view tobacco analyses as a lower priority, at least at first. It is imperative that priorities be discussed and an agreement put in place that clarifies how differences are to be resolved and how the two programmes will work together to meet all requirements. Otherwise, this could be a significant issue.

In addition, there will be some analytical requirements for tobacco products testing that have no counterpart in analysis used in other testing programmes. The most obvious example of this is the need for the equipment and controlled temperature and humidity facilities required for the smoking of combusted conventional tobacco products. Existing laboratory management may hesitate to acquire these new capabilities. This should be discussed beforehand and an estimated timeline and plan clarified to prevent misunderstandings in the future.

4.1 REQUIREMENTS (LABORATORY EQUIPMENT, STAFF, OVERALL COST) – HOW TO IDENTIFY THE RIGHT LABORATORY

Requirements will be directly dependent on the initial analyses identified as the highest priority. If these analyses cannot be performed with available equipment, the benefits of using an existing testing laboratory will be limited. But much of the analytical equipment that is listed (in Table 3 above) should be available in a typical analytical laboratory.

A first step when assessing existing laboratories to which it may be appropriate to add tobacco analysis capabilities is to do a comparative analysis of available analytical equipment. A list of equipment that may be commonly found in a testing laboratory and used for analyses of tobacco product design, contents and emissions is given in Table 4. This list is broader than that presented in Table 3 and there are some duplications in this table because some analytes can be measured by more than one analytical instrument.

Previously, WHO identified useful equipment for developing a tobacco testing laboratory. *(24)* This list can be used when evaluating the instrumentation in an existing government laboratory to assess which existing laboratory might be best equipped and which equipment may still need to be purchased for particular tobacco testing applications depending on a country's priorities.

There is some additional equipment that will likely need to be purchased in order to carry out tobacco-product-specific analyses. This equipment should be considered in the overall plans for laboratory development.

- Smoking machine (w/non-dispersive infrared analyzer for carbon monoxide (CO)), approximately US$ 200 000
- Environmental chamber, approximately US$ 30 000

Section 3.1 above describes criteria for choosing an external testing laboratory. Except for experience in tobacco product testing, these criteria also apply when evaluating an internal laboratory that tests other regulated materials. The rating spreadsheet (Fig. 1) can also be used to identify those aspects that will need to be considered in this case. In particular, and in addition to the equipment available, when assessing the suitability of an existing testing laboratory, the following should also be evaluated.

- Adequate bench space.
- Effective information technology systems that can be used to track samples, limit data transcription and efficiently report and archive results.
- A quality assurance programme that meets accreditation requirements.
- Environmental control (temperature and humidity) that meets both current and anticipated instrument requirements.
- Adequate electrical systems that meet expected requirements by instrument manufacturers and ensure satisfactory instrument uptime.
- Well-trained, experienced staff who have a documented history of producing reliable analytical testing results.

Table 4 Analytical equipment for a tobacco testing laboratory

Instrumentation	Purpose	Approximate cost (US$)
Freezer(s)	Storage of samples	1,000
Analytical balance	Weighing of samples, "tar"	10,000
Pressure drop apparatus	Cigarette ventilation	40,000
Ion chromatography/ conductivity detection	Ammonia in tobacco	50,000
Continuous flow colorimetric analysis	Hydrogen cyanide in smoke	60,000
Chemiluminescence nitrogen oxide analyser	Nitrogen oxides	50,000
GC/FID	Nicotine in tobacco/smoke	100,000
GC/Thermal energy analysis	TSNAs in tobacco/smoke	150,000
HPLC/UV detection	Carbonyls in smoke	100,000
HPLC/Fluorescence	BaP, Phenols in smoke	100,000
GC/MS	Nicotine, VOCs, Carbonyls, PAHs, flavouring compounds, aromatic amines in smoke	150,000
HPLC-MS/MS	TSNAs in tobacco/smoke	250,000
Atomic absorption spectroscopy	Metals in tobacco/smoke	50,000
Inductively coupled plasma–atomic emission spectroscopy	Metals in tobacco/smoke	70,000
Inductively coupled argon plasma–mass spectrometry	Metals in tobacco/smoke	200,000

Note: These costs are only approximate and may vary substantially depending on country-specific differences

Volatiles: benzene, 1,3-butadiene, acrylonitrile
Carbonyls: acrolein, formaldehyde, acetaldehyde, crotonaldehyde

Metals: arsenic, cadmium, chromium, lead, mercury, nickel, selenium

4.2 ACCREDITATION

All analytical labs should be accredited by an international or national body. The standard for laboratories is ISO/IEC 17025. *(25)* This applies to all forms of testing laboratories: drug laboratories, environmental laboratories, tobacco product laboratories and others.

ISO 17025 addresses general lab competencies and management. It evaluates whether laboratories have the systems and protocols in place to document methods, staff qualifications and training, measurement verification and error minimization. It is broad enough to allow for laboratories that use standard methods, widely-accepted methods and laboratory-developed methods.

ISO 17025 does not and is not designed to evaluate whether methods used by a laboratory are accurate, reproducible and sensitive enough to make measurements fit for a particular application. For example, it is not intended to evaluate which analytical method is the most appropriate for a particular analysis. This is generally done through intra- and inter-laboratory verification. Thus accreditation is a necessary, but not sufficient factor in accessing laboratory competence.

Because of the general nature of the ISO standards, they are considered a minimum requirement for laboratories, but are not sufficient for demonstrating that a laboratory is able to provide accurate and reproducible analytical results. This is only proven through a complete quality assurance programme as described in Section 3.1.

4.3 CASE STUDY - SINGAPORE

A good example of a laboratory that uses pre-existing government laboratory capabilities is the Cigarette Testing Laboratory (CTL) in Singapore. The CTL, together with the Pharmaceutical Laboratory and Cosmetics Laboratory, make up the Pharmaceutical Division at the Health Sciences Authority of Singapore. Established in the late 1980s, the CTL was tasked to test for tar and nicotine in mainstream cigarette smoke in support of tobacco regulatory compliance. It later expanded its scope to deal with toxicants beyond tar and nicotine by utilizing existing analytical facilities in the pharmaceutical and cosmetics laboratories. This approach allowed the laboratory to expand its capabilities at marginal additional cost.
Besides assisting capacity-building for other countries through training as part of the WHO TobLabNet, the laboratory also supports tobacco testing initiatives from countries requiring testing facilities to support their tobacco regulatory framework. These countries include: Fiji, Brunei, Tonga, the Solomon Islands and Samoa. This effort, which utilizes available testing laboratory facilities to build capacity and support tobacco regulatory compliance, provides a good model for other countries.

4.4 STEP-BY-STEP PROCESS

1. Do your own internal research.
    a. Identify a reasonable first set of analyses for your tobacco testing that would address your country's priorities.
    b. Identify the analytical requirements for the intended use of the data.
    c. Determine the estimated initial workload (number of samples over what period). This may be determined by the number of brands/subbrands being marketed and the frequency and schedule of testing.
    d. Identify the instrumentation (See Table 4) that is needed to carry out the analyses
2. Discuss your approach with another country's regulatory agency that has experience with tobacco product testing.
3. Visit other government laboratories that are already doing consumer product testing.
    a. Check the requirements listed above and rank available laboratories.
    b. Evaluate ability of laboratories to meet analytical accuracy, reproducibility, sensitivity and selectivity requirements to identify satisfactory laboratories.
    c. Use estimates of capacity requirements to identify acceptable laboratories.
4. Negotiate with other government organizations, as appropriate, to obtain agreement to collaborate on testing.
5. Discuss particular needs and requirements for expected sample workload, turnaround time, reporting requirements, priority conflicts, etc. with the identified laboratory.
6. Finalize any required contractual agreement.
7. Communicate to the companies:
    a. what needs to be tested and when?
    b. which laboratories are acceptable?

Chapter 5

DEVELOPING A TOBACCO-EXCLUSIVE TESTING LABORATORY

For the following discussion, an exclusive tobacco testing laboratory means a laboratory within a government system that does not share resources (equipment and personnel) with other programmes although it may be housed in the same physical facility. Developing an independent government tobacco testing laboratory can be a significant challenge unless starting with an existing laboratory capability, because the time and funds required can be considerable. It can also be challenging to maintain administrative support to see the project through to completion. Several countries have attempted to build independent laboratory facilities without expanding current capabilities, but to date these have been unsuccessful. Organizations that have been able to establish exclusive tobacco testing laboratories have typically built these capabilities on the foundations of another laboratory testing programme, to the point that they are self-sustaining and independent (see the example given in Section 5.4).

5.1 REQUIREMENTS (INFRASTRUCTURE, LABORATORY EQUIPMENT, STAFF, OVERALL COST)

The facility footprint, equipment, and resources required depend on the expected scope of the testing programme. Making a clear thoughtful strategic determination of these requirements early in the process is a critical step and will greatly impact whether the entire programme is successful long-term. This cannot be overemphasized.

Organizations expecting to establish a laboratory with broad capabilities must anticipate the expected space requirement. Previously, TobReg gave recommendations for the facilities for a tobacco testing laboratory in 2004. *(1)* This document provides the following recommendations for a testing laboratory (See Table 5):

Table 5: Space requirements of a testing laboratory

Type of area/ accommodation	Minimum surface area (m^2)	Expanded laboratory surface area[a] (m^2)	Conditions
Preparation laboratory	20	60	Water and drainage required. Metals analysis will require a separate "clean room"
Smoking laboratory	20	60	Contains smoking machine(s). Air-conditioned and humidity-controlled (22 ± 2 °C and 60 ± 5%).
Instrument room	30	80	Air-conditioned; specialized instruments will require additional ventilation and other specific environmental controls.
Offices	20	40	
Storage	15	25	
Common area	15	25	
Utility room	15	40	
Total	135	330	

[a] An expanded laboratory would include the necessary equipment for performing all recommended analyses of chemical constituents.

This space-requirement description is only an estimate based on what is typically expected for testing needs. A programme not intending to carry out as many analyses would need less space and a programme that intends to perform more analyses would need more. It is highly recommended that, before programmes make final space decisions, they visit a currently operating tobacco testing laboratory to better understand the anticipated requirements.

The list provided in Table 4 identifies the basic equipment that may be needed for furnishing the analytical capabilities of the laboratory to carry out the analyses identified as a high priority. Additional equipment as described in section 4.1 may be needed for an expanded laboratory. In addition to the equipment listed in Table 4, standard laboratory equipment may be required.

A well-qualified and trained staff is necessary for successful tobacco product testing. For many of the analyses, specialized training will be necessary. As with floor space and equipment, the number of staff will depend on the expected number of analytical methods to be supported and the number of samples expected for analysis over the course of a year. In the same document cited above *(1)*, TobReg also provided an initial recommendation for staffing based on a typical laboratory performing testing on 150 brands/subbrands per year. TobReg recommended the following:

- one smoke laboratory manager;
- two-to-three smoke technicians, who should be familiar with the operation/maintenance of the smoking machine(s);
- two-to-three analytical chemists, who should have extensive knowledge of instrumentation; and,
- one quality control manager to supervise and control data and methods, and who should be well versed in statistics and data reporting.

The staffing should be increased proportionally if a higher sample load is expected. This is the minimum and does not include administrative staff or other non-technical staff who may be needed to provide support for laboratory operations.

5.2 INFORMATION TECHNOLOGY (IT) SYSTEMS

An effective and efficient IT system is critical for reducing errors and reporting results in a timely manner. The importance of IT systems is often overlooked by those unfamiliar with testing laboratory requirements. A significant part of background discussions with existing testing laboratories should include a discussion of the capabilities and requirements of current IT systems. An IT system for a laboratory should, at a minimum, include capabilities to:

- allow for logging in new samples
- enable scheduling of samples to be analysed based on changing priorities
- track samples through the analysis process
- allow for automatic data calculations where appropriate (most analytical equipment has internal systems that schedule, process, and assist analysts in analysing the raw data, but these systems must be compatible with the overall IT system)
- evaluate quality control results independent of the analyst
- reschedule analysis of samples that did not meet QC requirements
- report final results
- archive all data
- backup all data.

5.3 DATA VERIFICATION

Systems and processes must be put in place that allow for careful data verification before any data is reported. For experienced external laboratories or laboratories already in place for testing related to other regulatory programmes, systems should already be in place. For a newly established independent internal laboratory, systems will need to be developed.

5.3.1 Analysis of quality control materials

Quality control materials are samples introduced into every analytical run to ensure that systems are operating properly. There are well-established principles to assess quality control materials. *(26)* When results determined from the analyses of quality control materials deviate from a statistically acceptable range, results are rejected and investigations of the analytical systems are necessary.

5.3.2 Systematic checks of accuracy and reproducibility

Accuracy and reproducibility of analytical methods should be established before any method is used for analysis as described in Appendix 1. But changes in equipment, or other conditions, can cause these initial results to no longer be correct. Periodic checks of accuracy, by analysing known reference materials, and reproducibility, by performing duplicate analysis, should be performed to confirm that systems are continuing to operate within the original conditions and the initial measures are valid.

5.3.3 Long-term trend analysis

Long-term deviation of analytical results can be hard to identify because of the nature of these trends. Other quality assurance systems that are designed to monitor on a shorter time frame may not identify long-term deviation. Systems should be in place to ensure that long-term drift of data is identified and corrected.

5.4 CASE STUDY – CDC

In 1994, the Office on Smoking and Health (OSH) at US Centers for Disease Control and Prevention (CDC) approached staff of the laboratory of the National Center for Environmental Health (NCEH) to provide support in meeting certain regulatory requirements for review of information provided to OSH by the tobacco industry. Thus a clear mandate for testing was established. At that time, the laboratory already had a dedicated staff with 10 years of experience in using advanced analytical instrumentation applied to biomonitoring to evaluate exposure to users and non-users of tobacco products. Laboratory buildings were already in place with required environ-

mental control and an uninterrupted power supply. In addition, service contracts for the equipment were in place with replacement parts on site to enable quick repairs. The laboratory already had an extensive quality control programme and statistical and IT support. Finally, there was a strong support structure in place that was not dependent on quick results but understood the need for a strategic approach.

Several staff from the NCEH laboratory visited the private commercial tobacco analysis laboratory, Labstat Incorporated, in Kitchener, Canada. The staff graciously explained all of the requirements (environmental controls, equipment, staff, etc.) needed to outfit a successful tobacco testing laboratory. This allowed the staff of the NCEH laboratory to understand what other requirements were necessary to successfully develop the laboratory capabilities to test tobacco products. The laboratory purchased an environmental chamber, a smoking machine and particular tobacco product design testing equipment that were specific to tobacco analysis. This specialty equipment complemented the more general laboratory equipment needed to make analytical measurements. In a short time, the NCEH tobacco laboratory acquired equipment, laboratory space, and resources separate from the remainder of the NCEH laboratory so that equipment was no longer shared between programmes but was dedicated to tobacco product testing and research.

Several specific critical events, including the Philip Morris recall of 1995 *(27)*, occurred over the next few years that provided opportunities for the NCEH laboratory to demonstrate the value to the overall tobacco control programme at CDC. Since then, the laboratory has grown in size so that it has extensive capabilities and provides analytical support of the CDC mission and tobacco product research for the US FDA. The laboratory also serves as a training laboratory and works with FDA's own Southeast Regional Laboratory to develop and validate new methods for compliance testing.

The CDC tobacco laboratory was derived from capabilities that were already present. But the laboratory no longer shares equipment and personnel with other programmes. This process happened over a matter of years, allowing the laboratory to establish itself with only a minimal original investment. It also allowed the laboratory to grow as requirements and funding became available.

5.5 STEP-BY-STEP PROCESS

1. Do your internal research.
    a. Identify a reasonable first set of analyses for tobacco testing that would address your country's priorities.
    b. Identify the analytical requirements for the intended use of the data.
    c. Determine the estimated initial workload (number of samples over what period). This may be determined by the number of brands/subbrands being marketed and the frequency and schedule of testing.
    d. Identify the instrumentation (see Table 4) needed to carry out the analyses.
2. Visit other laboratories that are already doing tobacco product testing to better understand the requirements of tobacco product testing.
    a. Identify space, equipment and human resource needs.
    b. Identify specialty equipment and training that will be needed.
3. Secure administrative assurance of long-term support and funding to create and sustain a laboratory capacity.
4. Work in close consultation with an established tobacco testing laboratory.
    a. Develop laboratory facilities as needed.
    b. Hire experienced staff.
    c. Purchase analytical equipment
5. Send staff for training at established laboratories.
6. Operationalize a limited number of laboratory methods above.
7. Carry out intra-laboratory validation of methods by evaluating analytical accuracy, reproducibility, sensitivity and selectivity.
8. Participate in inter-laboratory validation exercises or exchange samples for analysis with experienced laboratories.
9. Expand capabilities by repeating 5–8 above.
10. Communicate to the companies:
    a. what needs to be tested and when?
    b. which laboratories are acceptable?

Chapter 6

RESOURCES: WHO TOBLABNET MEMBERSHIP (CRITERIA, ADVANTAGES, AND PROCEDURES)

WHO TobLabNet laboratories can serve as a vital resource for any regulatory agency that is considering developing testing capabilities through any of the mechanisms described above. When considering how a laboratory can fit into a tobacco regulatory programme, visiting a WHO TobLabNet laboratory can be a valuable opportunity to see how other countries have approached this challenge.

WHO TobLabNet member laboratories can provide very important information about space requirements, environmental (electrical requirements, air conditioning, water quality, etc.) requirements, analytical instrumentation and staffing needs. By visiting a WHO TobLabNet member laboratory, government regulatory agents can see first-hand how laboratories are designed and discuss with WHO TobLabNet members their lessons learned and the steps that can lead to success.

Typically, the purchase of advanced analytical equipment includes some training by the manufacturer/supplier/vendor. This training usually consists of the basics of operation and maintenance of the instrument and using the software. But this training will not be specific enough to enable staff members to perform measurement of the design, contents and emissions of tobacco products. As time allows, WHO TobLabNet members can provide training for analysts in how to make tobacco product-specific measurements to complement any instrument manufacturer/supplier/vendor training.

To be most effective, training should take place after equipment has been purchased and installed and the analyst has had some hands-on operating experience. If an analyst is trained before equipment is installed, the training experience will be much less effective because they will not be able to ask more practical questions based on experience operating the instrument. Training may be done in the developing or newly established laboratory, or in a WHO TobLabNet laboratory.

The advantage of training in the developing/newly established laboratory is that whatever systems are set up will be present when the trainer leaves. But the analytical equipment must be installed and operational to make efficient use of the training time. Staff who take part in training should be the analysts who will actually be operating the equipment. Managers or officials who are not performing the day-to-day operation of analytical equipment are not appropriate for training. They will not be able to effectively communicate the lessons learned due to the technical nature of the information.

Requests for training can be made to staff of WHO TFI who can suggest laboratories that might be appropriate. WHO TFI is also developing a series of online training modules on the use of available WHO TobLabNet standard operating procedures to measure priority toxicants in cigarette tobacco filler and in mainstream cigarette smoke under ISO and intense smoking conditions. Further information will be available on the WHO TFI website as soon as the training platform is launched.

As an international laboratory network, WHO TobLabNet can serve as a valuable source of activities that help develop and demonstrate the abilities of member laboratories to make valid measurements. One example of this is the testing of a limited number of sample materials by two or more independent laboratories and/or two independent analytical methods. For example, if a laboratory is operationalizing a known method or developing a new method, carrying out measurements in more than one laboratory on shared samples can help demonstrate that accurate results are being reported.

In addition, inter-laboratory activities can be a valuable source of validation for participating laboratories. These include periodic round-robin exercises which are carried out either by direction of the WHO FCTC or developed as a work product by WHO TobLabNet. Previous round-robins have resulted in published documents which are available on the TFI website. *(28)*

WHO TobLabNet holds regular meetings of network members to encourage information exchange and planning for future joint projects. This can be valuable for new laboratories and can serve as a forum of addressing questions and comparing experience. The criteria for WHO TobLabNet laboratory membership are listed on the WHO TFI website *(28)* and are also listed below:

- the place the institution occupies in the country's health, scientific or educational structures;
- evidence of work in conjunction with the tobacco control community active within that country or geographic region;
- not be unduly influenced by relationships with organizations or entities with a significant financial stake in the outcome of the measurements;
- the quality of its scientific and technical leadership, and the number and qualifications of its staff;
- the institution's ability, capacity and readiness to contribute, individually and within networks, to TobLabNet programme activities;
- experience with tobacco product testing or research or demonstrable intent to obtain capacity for tobacco product testing or research, e.g., commitment to train personnel and upgrade equipment;
- the institution's prospective stability in terms of personnel, activity and funding;
- the technical and geographical relevance of the institution and its activities to TobLabNet programme priorities;
- the working relationship which the institution has developed with other institutions in the country, as well as the at the inter-country, regional and global levels; and,

- the scientific and technical standing of the institution concerned at the national and international levels.

In addition, in order to prevent conflicts of interest, additional membership criteria *(29, 30)* are listed below:

- The laboratory should not be totally or partially owned by a tobacco company, however, laboratories that are owned or run by a national government that also owns or runs the national tobacco industry are allowed.
- Laboratories that receive funds from the tobacco industry in the form of fee-for-service must demonstrate independence from the tobacco industry. For these organizations, a conflict of interest form is required.
- If a publicly-traded company, the tobacco industry should not have more than a 10% share of the total stocks.
- The laboratory should not have any member of the Board of Directors, or someone in a senior management position, who is employed by a tobacco company, which includes consultancy positions, among others. This also includes non-compensated consulting or advice to a tobacco company that may create a conflict by carrying the promise of future work.
- The laboratory may have tobacco companies as customers, but not its sole customers.

SUMMARY

Tobacco product testing capability can be a valuable tool for countries trying to reduce the death and disease resulting from tobacco use by regulating the product. For the Parties to the WHO FCTC, the regulation of tobacco product contents and emissions (Article 9) and the regulation of tobacco product disclosures (Article 10) are among the key measures with the potential to contribute to reducing tobacco product demand. Although it is not an answer by itself, it can be used to inform and build on other regulatory activities, such as product review, product standards, packaging and labelling regulations, public education or as information to inform legislative decision-makers.

The approach to developing testing capabilities should be carefully considered strategically and based on clearly defined objectives. Those objectives will vary from country to country and can only be defined by considering individual national goals. This preliminary groundwork will pay off multiple times over by effectively using limited resources to achieve the maximum benefit.

While it may be possible to build a laboratory from the ground up, countries that have tried this strategy have not been successful. It is recommended that countries either contract with laboratories that are already testing tobacco products or build capabilities from existing laboratories with experience in testing other consumer products like pharmaceuticals, or environmental samples. This approach has been shown to be successful in several countries and provides the best opportunity for accomplishing a country's objectives.

WHO TobLabNet was developed to support existing capabilities and to assist in developing new national tobacco product testing capabilities. There are numerous ways that WHO TobLabNet can help in laboratory development and countries interested in developing new laboratories should contact WHO TFI, who can put them in contact with appropriate WHO TobLabNet laboratories and coordinate activities to support the development of a testing programme. This contact should be made as early in the process of developing a laboratory as possible.

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Appendix 1.
INTRA- AND INTER-LABORATORY VALIDATION

A1.1 INTRA-LABORATORY METHOD VALIDATION

All laboratory methods must be carefully tested and a determination made that they meet requirements for how the data is to be used. Because different uses may have different requirements and therefore different equipment needs, the data requirements should be assessed before the laboratory decision process.

Accuracy is the nearness of a measurement of a quantity to the quantity's true value. Accuracy is primarily impacted by systematic error or bias. An analytical measurement may have an analytical bias and thus the result determined may be higher or lower than the actual true value. Accuracy is typically assessed by either testing the agreement with levels of materials with known values or testing the closeness among various testing regimens that are independent and should not have the same bias. In either of these cases, the closer the values that are determined are to the known level or consensus level, the more accurate the particular measurement under consideration. A lack of accuracy cannot be overcome by taking more measurements. In a common analogy, if a series of arrows were shot at a target, accuracy would be the closeness of the average of the various arrows to the centre of the target.

Precision is a determination of how close measurement results are to each other if a measurement is made repeatedly on the same sample, typically using the same method. Precision is primarily influenced by random error which causes the results to be inconsistent. Precision is typically assessed by making multiple measurements of the same material and then statistically determining the variability of the results compared to each other. Because precision is primarily determined by random error, the impact of a lack of precision on the accuracy of a measurement can be addressed, to some extent, by taking more measurements. The more measurements that are taken, the closer the average of these measurements will be to the value determined using the method. But calculated precision can be influenced by which steps in the method are included in the precision determination process. For example, results determined using replicate instrument analysis of the same sample after the sample preparation steps are completed will typically be more reproducible than data determined on samples that pass through both the sample preparation steps and the analytical measurement process; both parts of the analytical method can introduce random error. In the same analogy above, if a series of arrows are shot at

a target, precision would be the closeness of the various arrows to each other even if the average taken together are not close to the centre of the target.

Sensitivity is the ability of a measurement to make accurate and precise determinations at low levels. Stated another way, it is the ability of an analytical system to detect an analyte if it is present. Sensitivity is impacted by the entire analytical process including analyte extraction, clean up, concentration, and analysis. Sensitivity can be represented by the limit of detection which is typically defined as three times the standard deviation of repeated measurement of a blank sample. Alternatively, it can be described by the limit of quantification which is defined at 10 times the standard deviation of repeated measurement of a blank sample. Sensitivity may be enhanced by improvements in any or all of the analytical steps; advances in instrumentation can provide substantial improvements.

A companion concept to sensitivity is selectivity or as it is also known, specificity. Selectivity is the ability to correctly identify that a substance is not present when it is indeed not present. Selectivity is primarily impacted by the presence of contaminants in a sample that have properties that are close enough to the analyte of interest to not be distinguished from the analyte of interest. Selectivity can be typically improved by better sample preparation methods and by more advanced instrumentation.

Ruggedness is the ability of an analytical system to withstand deviations from the defined analytical method. Deviations can include a wide range of phenomenon from errors in weighing materials to changes in instrument operation from one maintenance action to the next. For a proper assessment of ruggedness, the most likely deviations should be assessed in order to understand how these deviations will impact the final results. A proper ruggedness evaluation will identify those aspects that have the most impact on the measurement and should be most closely monitored.

A1.2 INTER-LABORATORY METHOD VALIDATION

Inter-laboratory validation is important if data from one laboratory is to be compared with data from another. Also, if a laboratory wants to establish that their results agree with results that have been determined by others, an inter-laboratory validation is essential. There are several available programmes for assessment of inter-laboratory validation. A widely-accepted approach to assessing the data is found in ISO 5725-1 and ISO 5725-2. *(1, 2)* The inter-laboratory validation process consists of a single source providing equivalent samples to a series of laboratories. These samples are analysed using individual methods under the operating conditions in each laboratory and results reported back. All results are then evaluated to determine the repeatability and reproducibility of the results. By definition, the difference between two single results found for matched cigarette samples by the same operator using the same apparatus within the shortest feasible time will exceed the repeatability, r, on average not more than once in 20 cases in the normal,

correct application of the method. Single results for matched cigarette samples reported by two laboratories will differ by more than the reproducibility, R, on average no more than once in 20 cases with normal, correct application of the method. The Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) has carried out several inter-laboratory validations to support efforts of the tobacco industry. *(3, 4)*. WHO TobLabNet has also carried out a series of inter-laboratory validation which are described in section 3.2.

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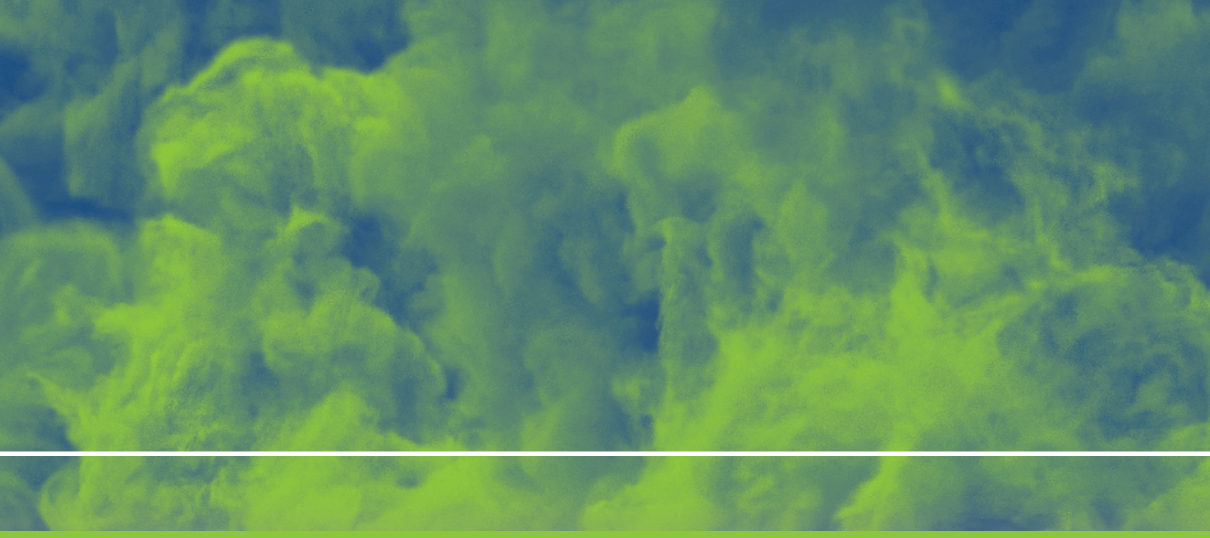

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