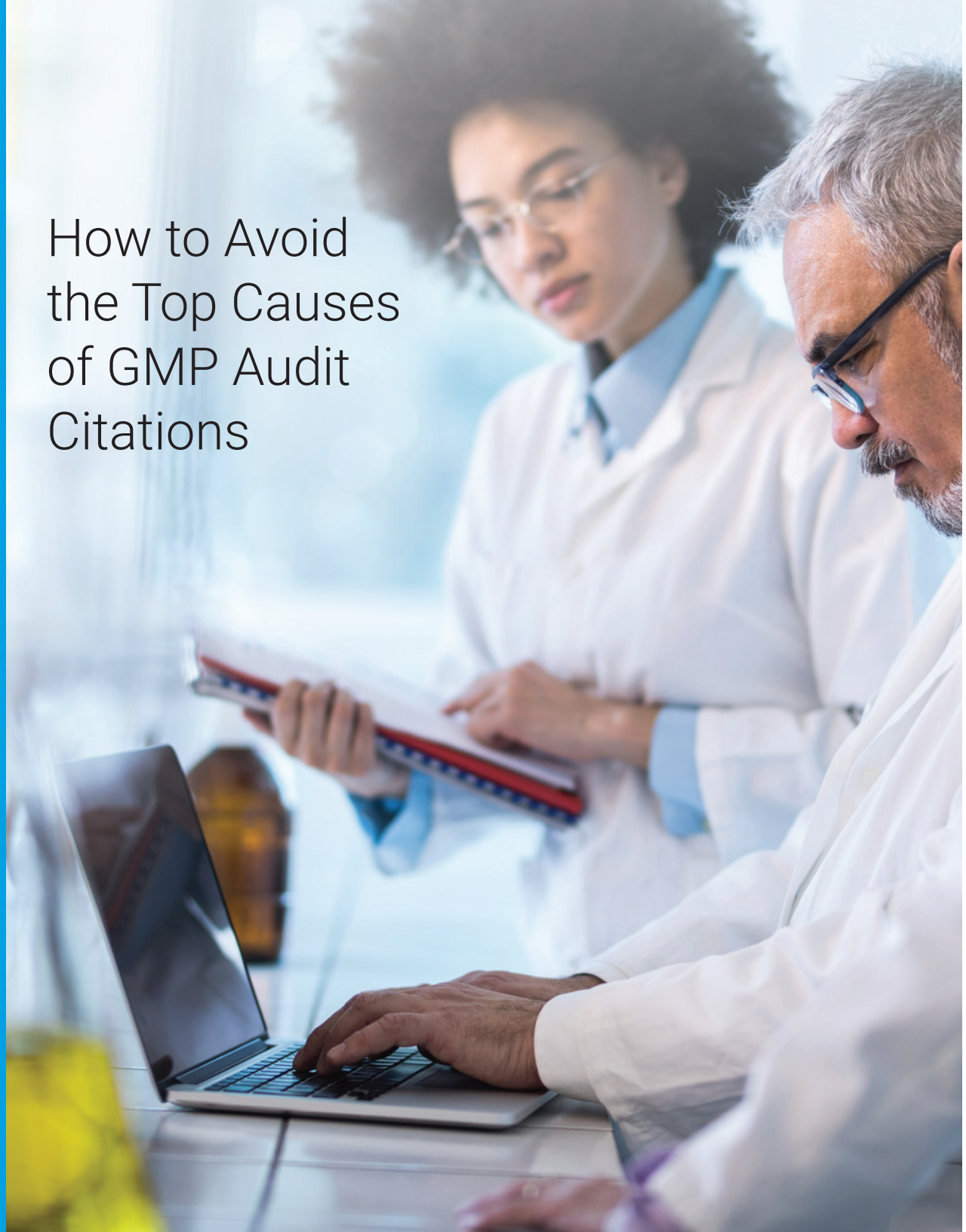
How to Avoid the Top Causes of GMP Audit Citations



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Introduction

Who audits medicine manufacturers?

The US Food and Drug Administration (FDA) is responsible for ensuring the quality of medicines that are supplied to the American market. They undertake inspection audits of drug manufacturing facilities worldwide to ensure that the drugs are being manufactured according to the current Good Manufacturing Practice (cGMP) standards. Most other countries have equivalent regulatory bodies and over 50 of them (including the FDA) are part of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). This scheme aims to develop, implement, and maintain harmonized GMP standards and inspection systems.

What happens during an audit?

A regulatory auditor will visit a drug manufacturing site to assess whether products are being manufactured according to the latest GMP standards. Sometimes, an auditor will specifically inspect the Quality Control (QC) laboratory on the site. The FDA publishes guidelines for auditors to use when inspecting a QC lab.

If an FDA auditor observes a problem during an audit, they list the problem on an FDA Form 483. A summary of the findings on these forms is published each year by the FDA.

What problems do FDA inspectors typically find when they audit?

The most recently published FDA inspection observation summaries are from inspections between 1st October 2016 to 30th September 2017.

The top five most common problems observed by inspectors at drug manufacturing sites were:

GMP standard reference	Short Description	Long Description
21 CFR 211.22(d)	Procedures not in writing, fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].
21 CFR 211.160(b)	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity.
21 CFR 211.192	Investigations of discrepancies, failures	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed.
21 CFR 211.100(a)	Absence of Written Procedures	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess
21 CFR 211.67(b)	Written procedures not established/followed	Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

As the list shows, three of the top five problems are related to documentation. As you are probably already aware, the documents in a site's Quality Management System (QMS) (or that are not there, but should be) are a major compliance risk. In this ebook, we address how to write documentation that works, helping you to avoid citations based on inadequacies of your QMS.

Quality Management Systems

A well designed and maintained Quality Management System can be a critical business asset. It can help achieve greater consistency in providing products and services and reduce mistakes. It can increase efficiency and make life easier for employees, management, suppliers, and customers.

The ABCs of a Quality Management System

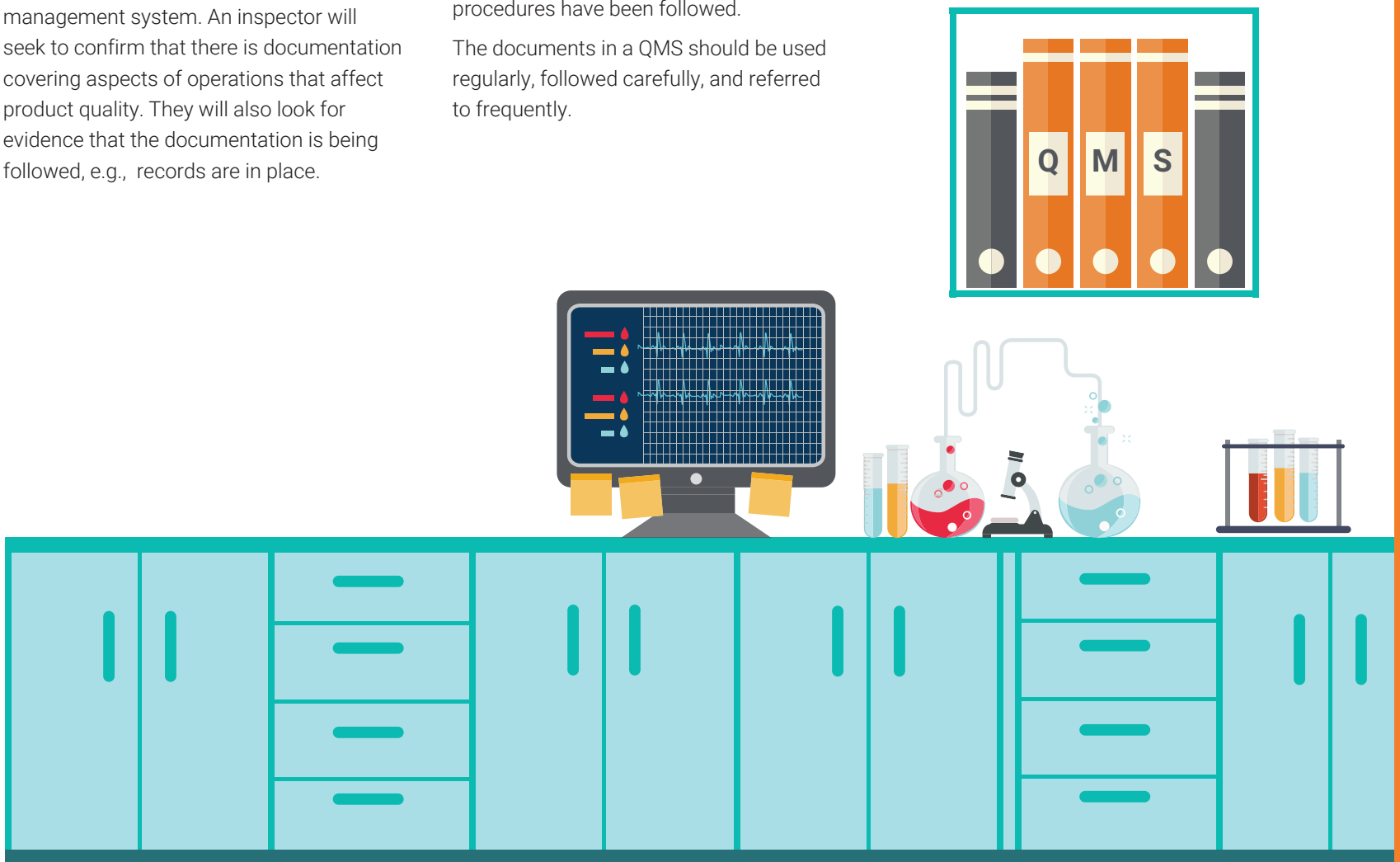
If you've worked in a GMP-regulated industry for a while, you'll be familiar with Quality Management Systems (QMS). They are the collection of documents that describe how things should be done within the company.

Often, the first thing an inspector will ask for are documents from the quality management system. An inspector will seek to confirm that there is documentation covering aspects of operations that affect product quality. They will also look for evidence that the documentation is being followed, e.g., records are in place.

There's a saying that *"If it isn't written down it shouldn't happen"* – meaning that you need to have documentation in place for all of your processes. The other part of the saying is *"If it isn't written down, it didn't happen."* – meaning that you need to have records or other evidence in place to show that written procedures have been followed.

The documents in a QMS should be used regularly, followed carefully, and referred to frequently.

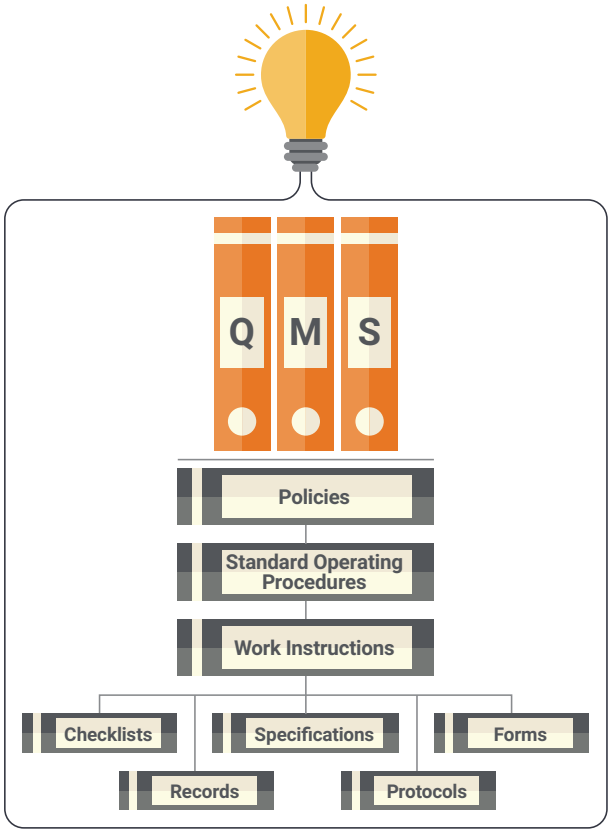
"If it isn't written down, it shouldn't happen. If it isn't written down, it didn't happen."



Document Hierarchy in a Quality Management System

Standard Operating Procedures (SOPs) are a well known document type. But they are only one of several different document types that exist within a quality management system. Here are some other common types that you'll encounter:

Document type	Purpose
Policy	A policy should describe the INTENT of the company in an area e.g. Staff training policy
Standard Operating Procedure	An SOP is a set of written instructions that document a routine or repetitive activity e.g. "Supplier selection". Major processes are documented in SOPs – with work instructions used to document the details of specific tasks within a procedure.
Work Instruction	A work instruction would be used where further detail is required to describe an activity which is related to the procedure. So, for the supplier selection, there might be a work instruction for conducting a supplier audit. The instructions in a work instruction are usually completed by one person at one time. A procedure might cover a longer period, with multiple roles performing tasks to achieve an outcome.
Specifications, checklists, forms, records, protocols	These lower-level documents collect the evidence that SOPs and work instructions have been followed. They'll usually be referred to from an SOP or work instruction, so will be linked to that 'parent' document in the QMS.



The typical document hierarchy in a quality management system.

There is often blurring between what is an SOP and what is a work instruction. Their definitions should be determined and documented by the company in the QMS. For example, you may decide to have the high level processes as SOPs and everything else as work instructions. It doesn't matter – as long as it's consistently applied.

Starting a New Document

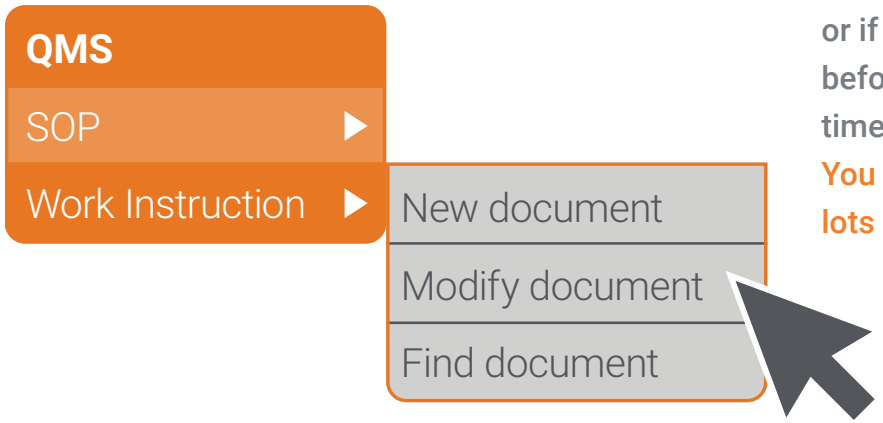
You may have a new piece of equipment or a process change has happened, and you need a new document to support the change.

What already exists?

Before you start writing, have a chat to the person responsible for the QMS. They will usually sit within Quality Assurance. They will be able to tell you if there's already a document in the QMS that you could modify to include the new content. They will also provide advice on the document type to use (SOP or Work Instruction). They may also show you how to find other documents that you should reference, such as an overarching policy or related SOPs. For example, you may be writing a procedure on how to perform an assay on a new lab instrument. You'll probably need to cross reference the SOP that covers the calibration and maintenance of laboratory equipment.

Gather your tools

If you write QMS documents infrequently, you'll need to check with the document control department about the correct template to use and the correct procedure to follow. These documents should be in the QMS. Read these documents so that you understand the QMS document creation process. There may also be documentation training that you can undertake before you start. Just knowing how to use MS Word correctly is very helpful. Most people use about 5% of its functionality! Using the built-in tools like stylesheets and auto-cross referencing will save you considerable time. They will also prevent a world of pain if you have to do major changes to your nearly-complete document.



QMS documents can breed uncontrollably and quickly become unmanageable. Always check to see if there's an existing document you can modify or if you can consolidate several documents – before you create a new document. It costs a lot of time and money to create and maintain a QMS.
You can make the problem a lot worse if you create lots of new documents.

How to Write SOPs that People Can Actually Follow

What's the Purpose of SOPs?

When you are planning and writing an SOP, it helps to remember the reasons why you are writing one. Obviously, regulatory-compliance is a big reason, but SOPs can have powerful impacts on many aspects of operations.

Poka Yoke

The Japanese system to mistake-proof your processes. A poka-yoke is a mechanism in a process that helps avoid mistakes. Its purpose is to eliminate product defects by preventing, correcting, or drawing attention to human errors as they occur. A USB cable has a poka yoke built into the connection. You can only insert a USB cable one way – this prevents the mistake of inserting a USB cable upside down.

Useful. Usable. Reliable

A QMS document should aim to be:

Useful

It tells the reader WHAT they need to know to perform a task or achieve an outcome.

Usable

The reader should be able to follow the document. It should be well structured and easy to read. Terms should be explained and not rely on previous knowledge. It is a GMP requirement that "Documents must have unambiguous contents. The title, nature, and purpose should be clearly stated. They must be laid out in an orderly fashion and be easy to check."

Reliable

The information in the document should be up-to-date and reflect the current process. It's a GMP requirement that documents are regularly reviewed and kept up-to-date. Documents that are part of a Quality Management System should have a review date. If there are changes to the process or equipment prior to the review date then the document should be updated at the time of the change.

SOP – <Title of SOP>					
Department	<department name>	**Document ID**	<SOP number>	**Revision**	XX
This document will be reviewed 3 years from date of issue/review				**Effective date**	DD-MM-YYYY

GMP documents should always include a review date, in this case, three years from the date of issue. All documents in your QMS must be under change control.

Balancing Compliance vs Usefulness

It can be tempting to put as little information as possible into an SOP. You know the people performing the procedure are very familiar with the steps and, with less in the SOP there's less chance of it not being followed exactly, right? Wrong. You must include enough information that the process can be reliably, and consistently performed by a suitably qualified person—this means someone who hasn't done the task for 20 years!

You need to balance including enough information that a person new to the job can follow the instructions vs including too much specific information that the reader doesn't really need.

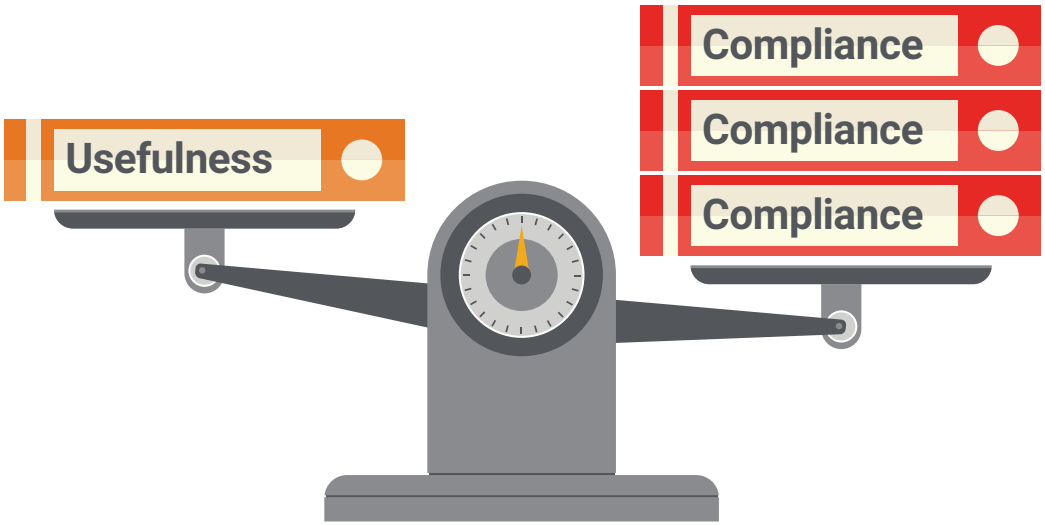
For example, if you were writing instructions on how to prepare a sample for analysis you could say:

Mix the sample with water.

Or

Get a 100 mL volumetric flask from the glassware cupboard in lab 3. Unscrew the sample bottle provided by the Receiving Department. Weigh 10 g of sample into the flask. Fill a 1 L conical flask with distilled, de-ionized water from the supply next to the sink on the western wall of the lab (it's the tap marked with the red label)… etc.

The first option is too little information and the second option has too much unnecessary information.



What to Include and What to Leave Out of Procedures?

Use the following guidelines to determine the level of detail to include in your documents:

Put this into your documents:

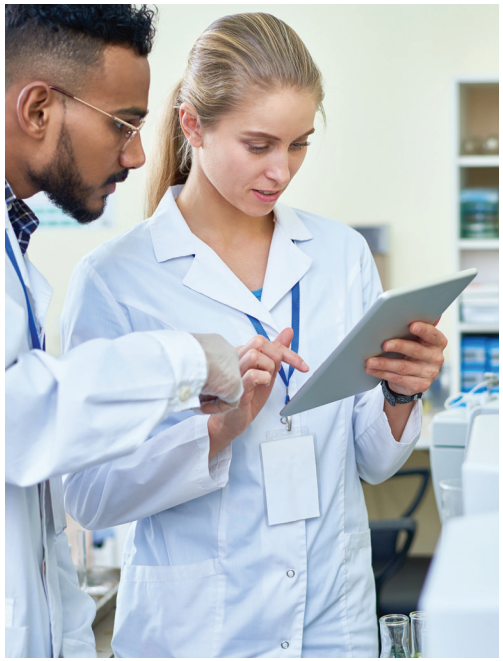
- ✓ If the information is likely to be referred to frequently, or is different from step to step then include it every time e.g. “Set the pump speed to 5 rpm”.
- ✓ GMP-critical information must be included. This is typically numbers and process-specific information such as time, temperature, instrument settings, quantity, and anything else that may affect product quality.
- ✓ Write the level of detail a new hire would need, to be able to complete the task (after they’ve been suitably inducted).
- ✓ Describe the records that must be kept to prove that the SOP has been followed.

Leave this out of your documents:

- × If the reader will only need the information once, then don’t include it. This usually includes information that would be provided during an induction process, e.g., where things are located.
- × Vague words like “appropriate”, “adequate” “approximately”, “regularly”. These nonspecific words are red flags to auditors as they indicate that you aren’t sure about your process.
- × Explanations of terms that someone with the education and experience to do the job would know. For example, if you’re writing a laboratory procedure for chemists you can assume that they know how common laboratory instrumentation works and what it’s used for.
- × Revision numbers of documents you are cross referencing should be left out as they change. Include only the document number and title.

If you are writing laboratory procedures, you can assume that the reader has the qualifications and experience needed to do the job. They will know what a pipette is and how to use one, so you don’t have to include those specific instructions in your procedure.

The Golden Rule: Know Your Reader



Spend time watching someone do the procedure you are documenting so that you fully understand your reader.

Before you start writing an SOP or Work Instruction, think about:

- Will your reader do this task often or will there be weeks or months between having to do the task again? This information will help you determine how much detail to include as they are likely to forget specific details if they do the task infrequently.
- Where will your reader be and what will they be wearing when they are reading the document? Will they have both hands in a glove box while they are doing the task? If so, then put all the information they need on one sheet of paper. This design will allow them to complete the task without having to pull their hands out to turn the page.
- Is it likely that English is not their first language or the reader will have low literacy skills? If so, keep the language in your document simple. For example, use 'Find out' instead of 'Determine' and avoid the use of short forms such as you're instead of you are.
- The education level and expertise of the reader. Are they a factory worker, lab technician, manager, or office worker? What would the reader already know about the task? How technically savvy are they likely to be? This information will determine the style of language you use and the level of detail you need to include.
- How often would someone completely new to the task use your document? This might be the case if there is high staff turnover. If this is likely, you may need to include more details as the reader will be unfamiliar with the task.
- What attitude would the reader be likely to have – enthusiastic, resentful, nervous? This should also influence the style of language you use.

If you don't know the process that you are documenting well, it's a good idea to watch someone doing it and ask lots of questions. You'll then know your reader a lot better.

A study commissioned by Pfizer found that using writing strategies to help low literacy readers increased usability for all users without reducing user satisfaction. Read the study.

Writing to Help Your Reader Learn and Retain Information

The human mind stores information in short-term memory and then either copies the information to long-term memory or forgets it.

Use these tactics so that information can be more easily committed to short-term memory:

Use 7 ± 2 items

You should keep the maximum number of items in a list to 9 or less. The number of steps in a procedure should not exceed 9 without being broken up into another section (use subheadings to chunk information).

Arrange information in related chunks, groups, or patterns

Try to group information into steps that are related to each other, rather than having unrelated elements.

Relate the information to something the reader already knows

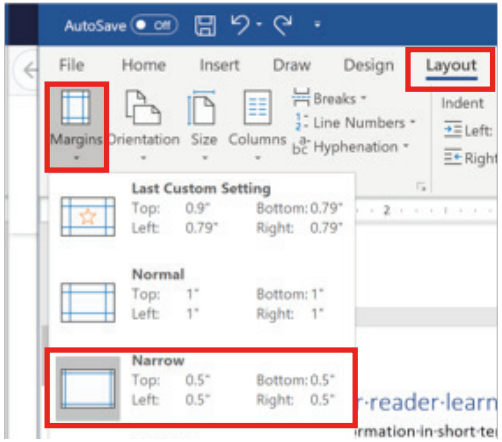
Using metaphors and similes, or drawing on knowledge that the reader will already have is a good way to help someone learn and remember. An example is using a traffic light simile when describing how to treat test results. Results in the 'red zone' need to be reviewed, while those results in the 'green zone' can be accepted as reported.

Use images and diagrams instead of words

Using screen captures of software screens instead of words is a great example of the use of images. Instead of saying: "Set the margins of the document to 'Narrow' by selecting that option in the Margins menu, under the Layout menu in Word…

You can say:

Set narrow document margins by selecting the menu option shown below:



Tips for Good Writing

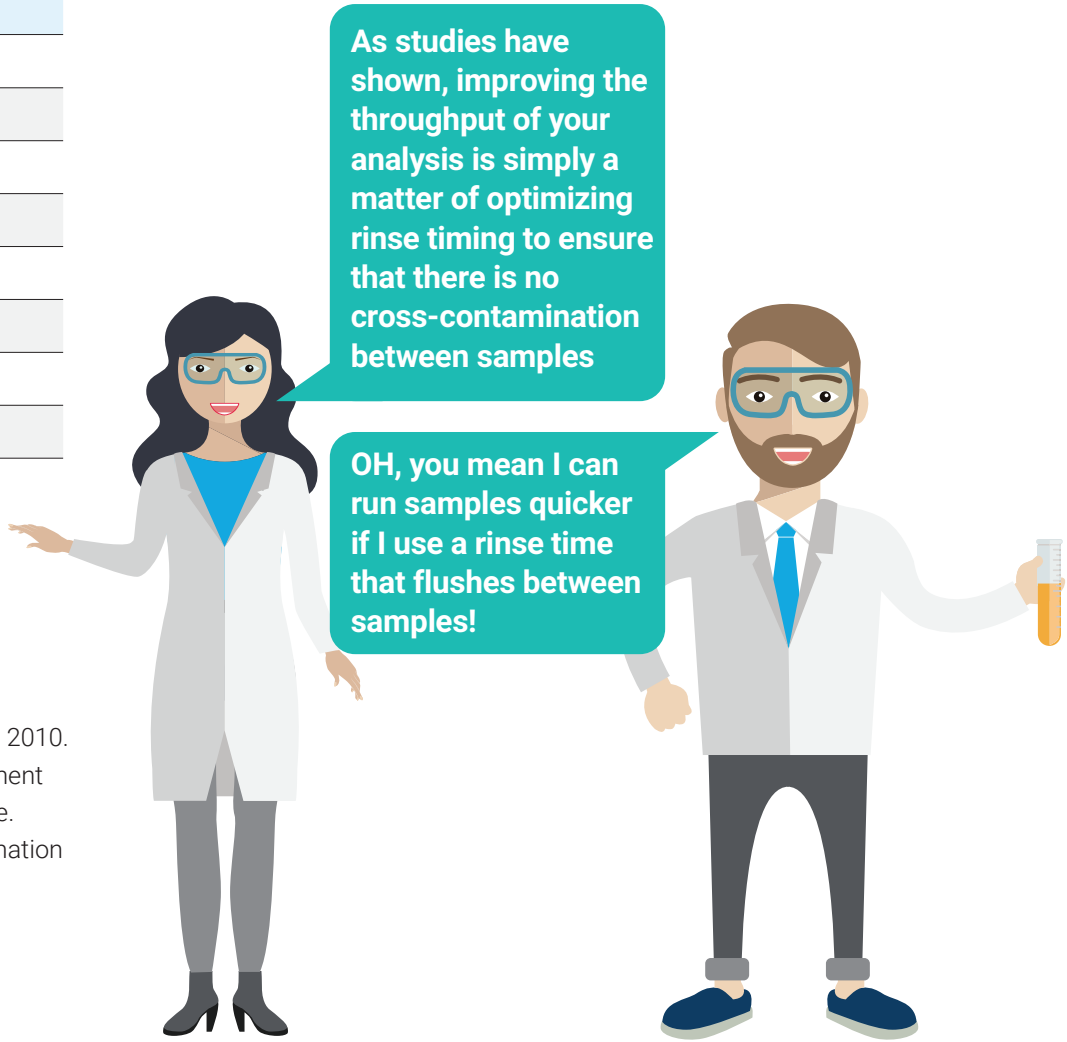
- Keep sentences short, aim for 15 to 20 words. Tip: Find out what level of education a reader would need to understand your writing. The online Flesh Kincaid test will assess a sample of your writing at www.online-utility.org/english/readability_test_and_improve.jsp
- Keep paragraphs short. Have only one topic in a paragraph and put the important information at the start of paragraph.
- Think about your main message for each step and don't bury it in detail
- After you've finished writing, go back and remove excess words. The classic culprits are 'however', 'therefore', 'thus' etc.
- Read your document aloud to find where improvements can be made.
- Use short, familiar words, rather than long words.
- Avoid jargon and clichés. Would a typical reader of your document understand the technical terms and acronyms you have included? For example, you understand that Apache is an open-source software system. Your reader might think it's a native American tribe.
- Acronyms can have a negative impact on communication. They break up the flow of the text and can be easily misinterpreted. You can use an acronym instead of the spelled-out term when the acronym is more widely understood. For example, USB, URL or NASA. If the acronym is not well known or known only by a specific group of people, then use sparingly. Always spell uncommon acronyms out in full, the first time you use them in a section that is likely to be read independently of other parts of the document. If your SOP or Work Instruction template has a definitions table, then put the definition of each acronym in the table.
- Avoid negatives (except when required for safety instructions). Say …use tubing Y for organics… instead of …do not use tubing X for organics.

Keep It Simple

A common writing mistake is using long, complicated words instead of simple ones.

Here are some examples:

The complicated word	The simple equivalent
Terminate	End
Utilization of	Use
Optimum	Best
At this stage	Use
On the other hand	Alternatively
Accomplish	Do
Accrue	Add or gain
Adjacent to	Next to



Helpful plain English tips

The US Government introduced the Plain Writing Act in 2010. This requires all US federal agencies use clear government communication that the public can understand and use. The www.plainlanguage.gov website has helpful information about writing to be understood.

Active vs Passive Voice

When writing instructional documents, always use active voice, not passive voice. Passive voice tends to use more words and isn't as clear as active voice.

Here's how to tell the difference between active and passive voice:

This is active voice

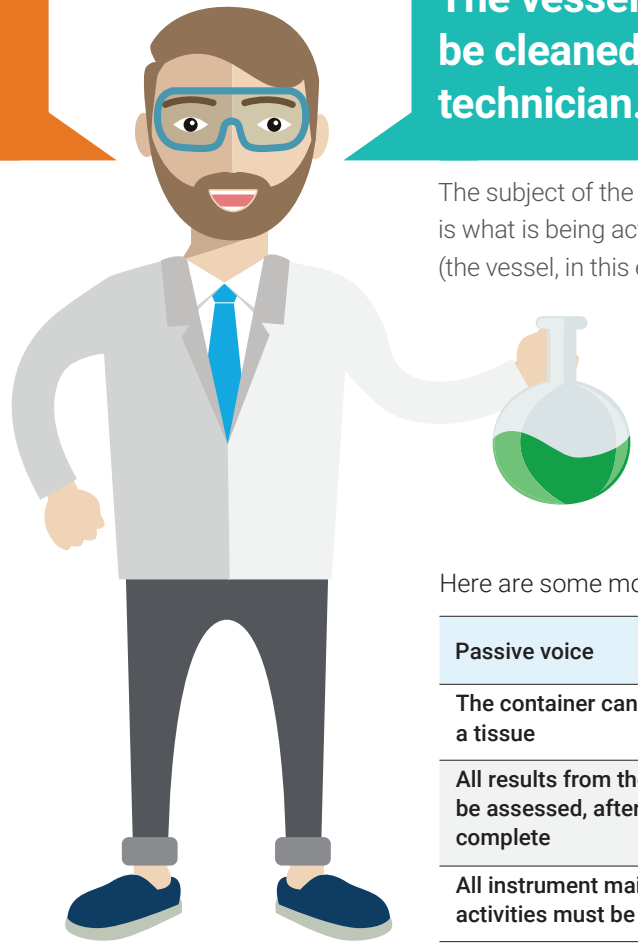
The technician cleans the vessel.

The subject of the sentence is the person taking the action (the technician in this example)

This is passive voice

The vessel should be cleaned by the technician.

The subject of the sentence is what is being acted upon (the vessel, in this example)



Here are some more examples

Passive voice	Active voice
The container can be wiped with a tissue	Wipe the container with a tissue
All results from the analysis must be assessed, after the analysis is complete	Assess all results after the analysis
All instrument maintenance activities must be recorded	Keep records of all instrument maintenance

Avoid this Common Mistake

Each bullet point or step in a procedure should have the same structure and address the same topic. A common mistake is something like this:

Set up the instrument by:

1. Unpacking the box.
2. Remember to notify Engineering to add the new instrument to the asset register. This will ensure it is included in routine maintenance activities.
3. Do the auto testing that comes with the instrument.
4. The instrument serial number should be entered into the LIMS system.
5. Run a standard reference material to confirm the accuracy of the instrument.

Compare that structure to this:

Set up the instrument:

1. Unpack the box.
2. Notify Engineering of the new instrument.
3. Perform the autotest function.
4. Enter the instrument serial number into the LIMS system.
5. Run a standard reference material to confirm instrument accuracy.

The later example has a *parallel* structure. All the steps start with matching forms of verbs; unpack, notify, perform etc. Any information that does not directly relate to the task is not included, e.g., why Engineering need to know about the new instrument.

Consistency is a Good Thing

Using the same term to describe an action or object reduces the mental load on the reader. It's a common mistake to call something a slightly different name in a document. The reader then must think "Is this the same thing as last time?".

Here's an example.

1. Fill a conical flask with water and heat it to 60 °C.
2. Weigh 125 mg of the supplied sample.
3. Place the sample in the vessel.

The reader will be thinking "is the *vessel* the same as the *conical flask* in step 1 or do I need to get something else?"

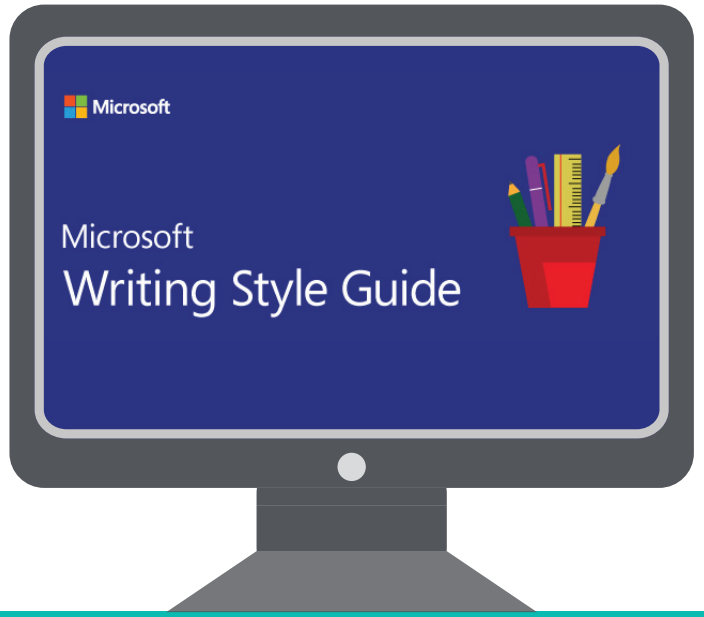
Another common mistake is to describe onscreen actions in slightly different ways. Here's an example:

	Inconsistent	Consistent
1	**Put in your name**	Enter your name
2	**Enter your password**	Enter your password
3	**Select the Conc module**	Click the Conc module
4	**Input the concentration of the calibration standards into the appropriate fields**	Enter the concentrations of the standards

In the inconsistent example, a different word is used to describe the same action – entering data into software fields e.g. put, enter, input. Always use the same word to describe the same action or object.

The Microsoft Writing Style Guide

Is it a check box? A radio button? An option? This free guide provides details on how to refer to Windows controls and how to write in a way that's natural, simple, and clear. You can access it here: docs.microsoft.com/en-us/style-guide/welcome/

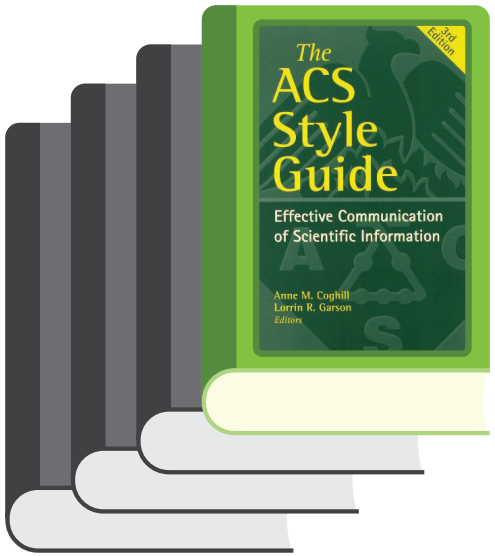


Tips and Tricks to Maintain Consistency

If you are writing a long document or a series of documents on the same topic, it can be hard to maintain consistency. What you called the "adjustment handle" morphs into being called the "tuning lever" later in the document. Sometimes you've written the names of menu items in bold text and other times you've written them in bold italic. It gets confusing for you and even more confusing for the reader. Inconsistency has a negative impact on the readability of a document.

Here's how to maintain consistency:

- **Create a cheat sheet.** The sheet should include the 'official' names of equipment, products, departments etc. If you are writing documentation to support a new product introduction or some other major change, then it's a good idea to develop this cheat sheet with the whole project team. All documentation will then be consistent across the organization. Print it out and refer to it as you write.
- **Use a writing style guide.** Ask the department/person responsible for documentation if there's a recommended writing style guide to use. These books are like dictionaries for writing style. They provide guidance on how to present common information like dates, places, and numbers. Writing style guides also cover punctuation and grammar and include a wide range of other writing guidelines. There are several well known style guides: The Chicago Manual of Style, Strunk and White The Elements of Style and some governments have their own, such as the Australian Style Manual. There's even The ACS Style Guide for presenting scientific information, published by the American Chemical Society.
- **Use AutoText in Word.** You can set up a series of words and terms in MS Word. When you type a few characters, Word will fill in the rest. Cool huh? This ensures that you are always consistent when you use those words/terms and it saves time. Here's how to set up AutoText: https://support.office.com/en-us/article/automatically-insert-text-0bc40cab-f49c-4e06-bcb2-cd43c1674d1b



The American Chemical Society publishes a style guide to promote the effective communication of scientific information.

Consistency with regulations, and across a Quality Management System

Consistency with regulations

It's important to use the same words and terminology in your SOPs that are used in the regulations. For example, a common mistake is to use the term corrective and *preventative* action, whereas the FDA refers to corrective and *preventive* action (CAPA). It can be easy to just adopt the terminology used within your company – which may be a modified version of the official term in the regulations. An inspector will understand what the official term means. Check the regulations and use the same terms as used in those.

Consistency across documents

If the process you are documenting in an SOP has outputs that are the inputs for another process then you should consult with the owner of the subsequent process. Make sure consistent terminology flows across the documents. Even if it's not the same department doing the second process, it will create confusion if that department refers to the input of their process as the "elemental analysis results" and you've called the same results the "toxic metals results".

Using Tables to Improve Readability

Tables are ideal for procedures that include a series of numbered steps. Here's an example of how presenting information in a table makes it easier to follow.

Before

1. Click the CONTACT PERSON tab and fill the Last name and the First name. For Country Type fill 'UE'. After you have filled the First name click on FURTHER DATA. A new screen will appear.
2. Fill only the First four fields (Profession, Position, Nationality, and Age Group) then press ENTER. Then go to the Last name and double click. Add the details of Gender & Marital status.
   At the bottom of the page add the Person and Communication details. Once that is done click on back. Then go to SALES AREA DATA. Under SALES fill the CUSTOMER GROUP number: 07(wholesale)/01(retail).
3. Under PARTNER FUNCTION fill in the NUMBER column with the number of the Employee - E.g.107335 (employee number for Nahi Azzi). ENTER

After

Step	Instruction
1	Select [CONTACT PERSON] tab and fill the Last name and the First name.
2	Enter UE for Country Type.
3	After you have entered the First name, select [FURTHER DATA]. **Result:** A new screen will appear.
4	Fill only the First four fields (Profession, Position, Nationality and Age Group) then select [ENTER].
5	Go to the Last name and double click. Enter Gender and Martial status details.
6	At the bottom of the page enter the Person and Communications details.
7	Select [BACK].
8	Go to SALES AREA DATA. Under SALES enter the CUSTOMER GROUP number: • 07-wholesale • 01-retail
9	Under PARTNER FUNCTION enter the NUMBER column with the number of the Employee. **Example:** 107335
10	Select [ENTER].

Tips for Using Tables

- If a table is likely to be more than one page long, turn on the *Repeat Header Rows* option in Word. This will automatically add the header row to the table on each page it appears on.
- Every column should have a heading
- Check where page breaks split tables. You don't want a user to perform a step and then find out they should have considered something else when they read the next page.
- Include the word 'Continued…" at the end of a page when a table continues onto the next page.
- Use a 'Role' column if the responsibility for tasks changes for more than 50% of the steps in the procedure.

Step	Role	Description
1	QC	Xx
2	QC	Xx
3	QC	Xx
4	QC	Xx
5	QC	Xx

Step	Description
1	QC must: • Xx • Xx
2	The Initiator must: • Xx • Xx
3	QC must forward all documentation to QA. For final review.

- Use 'If…Then' sub-tables if there are alternative options for a step in a procedure.

Step	Action
1	Prepare the sample for analysis. **If the sample has total dissolved solids…** / **Then…** < 10 ppm / Go to step 2. > 10 ppm / Digest the sample by following SOP-13245-003
2	Dilute the sample x 5 with distilled water.

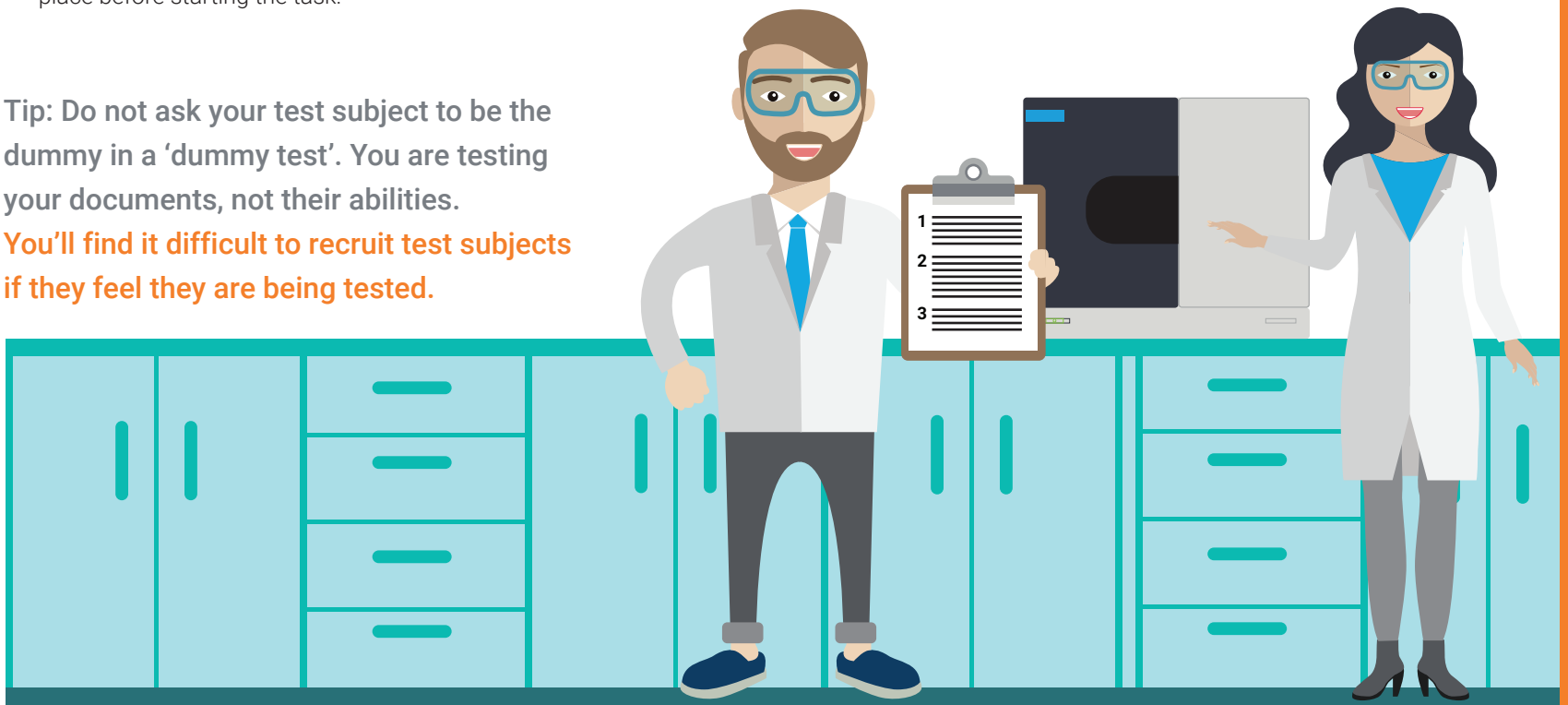
Usability Testing

The best way to find out if your document is usable is to test it. Sure, you could just use your document to do the task yourself, but you are now too familiar with the document and won't see where misunderstandings could occur. Usability testing your documents is a great way to learn how people read and follow instructions. It will improve your writing and make your documents so much better.

To test your document, do this:

1. Find someone who has the skills and experience to do the task but is unfamiliar with it. Preferably, choose someone new to your organization.
2. Print two copies of your document – one for you and one for the other person, who we'll call the 'tester'.
3. Set up any equipment or supplies that would normally be in place before starting the task.
4. Ask the tester to follow the instructions in the document to complete the task. Ask the tester to verbalize what they are thinking during the process. Most people find this difficult to do, so you might have to prompt them. If you see that the tester is not sure what to do, ask him/her questions such as "What are you looking for?" or "What do you think you should do now?" You are trying to find out what is confusing them, not helping them to complete the task.
5. Resist the temptation to help them do the task. As much as you'd like to rip that mouse out of their hand and do the job yourself, that isn't the aim of the test. Give the tester the opportunity to ask questions, just as they would if they were really doing the task.
6. Make notes on your copy of the document during the test. Note where they went wrong, what they found confusing.

Tip: Do not ask your test subject to be the dummy in a 'dummy test'. You are testing your documents, not their abilities.
You'll find it difficult to recruit test subjects if they feel they are being tested.



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U.S. and Canada
1-800-227-9770
agilent_inquiries@agilent.com

Europe
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Asia Pacific
inquiry_lsca@agilent.com

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