29th July 2010

Charles Roosen (Mango Solutions) - Introduction

R Validation for Life Sciences

Andrew Ellis (ETH Zurich) - Desktop Publishing with Sweave

Dominik Locher (THETA AG) - Professional Reporting with RExcel

Validating R for Regulated Purposes

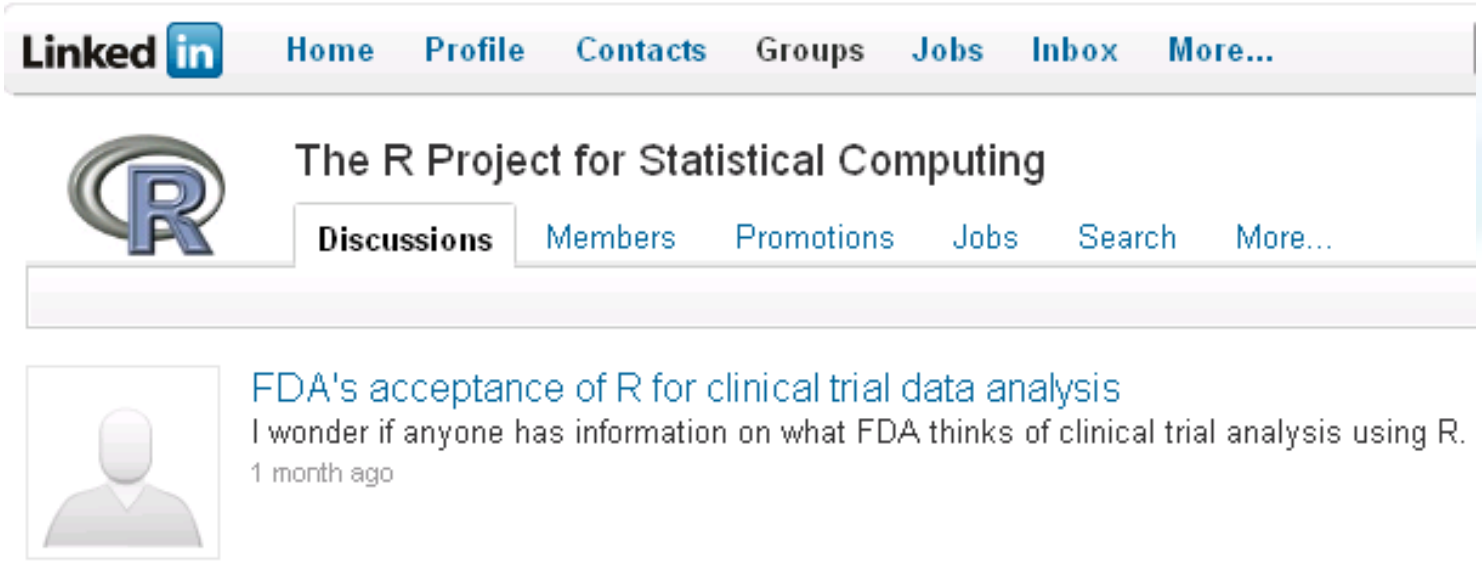
Sebastian Pérez Saaibi (ETH Zurich) - R Generator Tool for Google Motion Charts

A quick introduction

- Ian Francis
- Started as Analytical Chemist with GlaxoSmithkline
- IT Compliance and Validation for 12 years
- Living and working in Basel for last 2 years
- Fortunate to have the opportunity to work with Tony Rossini and Mark Schwartz updating the "*R: Regulatory Compliance and Validation Issues A Guidance Document for the Use of R in Regulated Clinical Trial Environments*" (*R-FDA)* for the R Foundation

Why am I here?

- In the past some people have thought R cannot be used for regulated purposes
- Just last month, Aug-2010….LinkedIn forum



- I do not see similar questions about SAS…
- Why is this…?
  - Regulatory requirements for “validation” cannot be met (too much testing)?
  - Open Source Model?

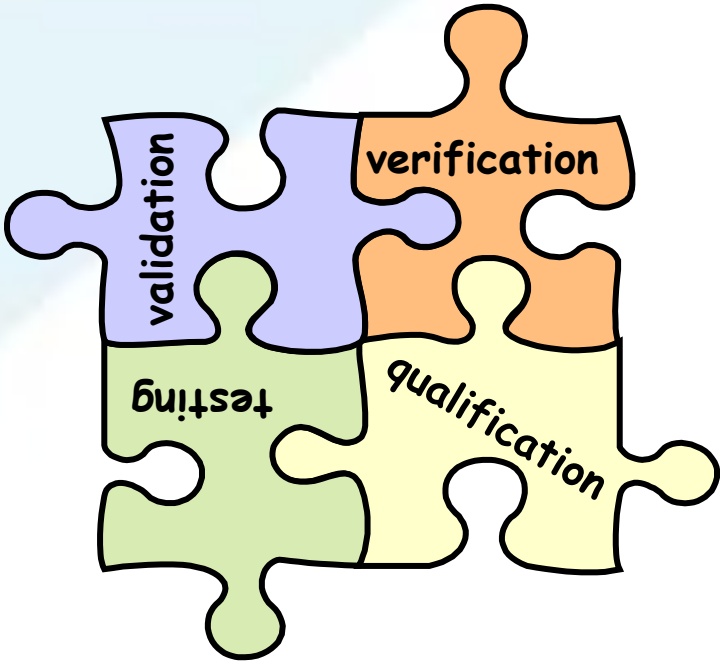
What is Validation?

- Different meaning depending on who you ask
- Here's what the FDA state…
  - Validation - Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

FDA GLOSSARY OF COMPUTERIZED SYSTEM AND SOFTWARE DEVELOPMENT TERMINOLOGY

What is Validation?

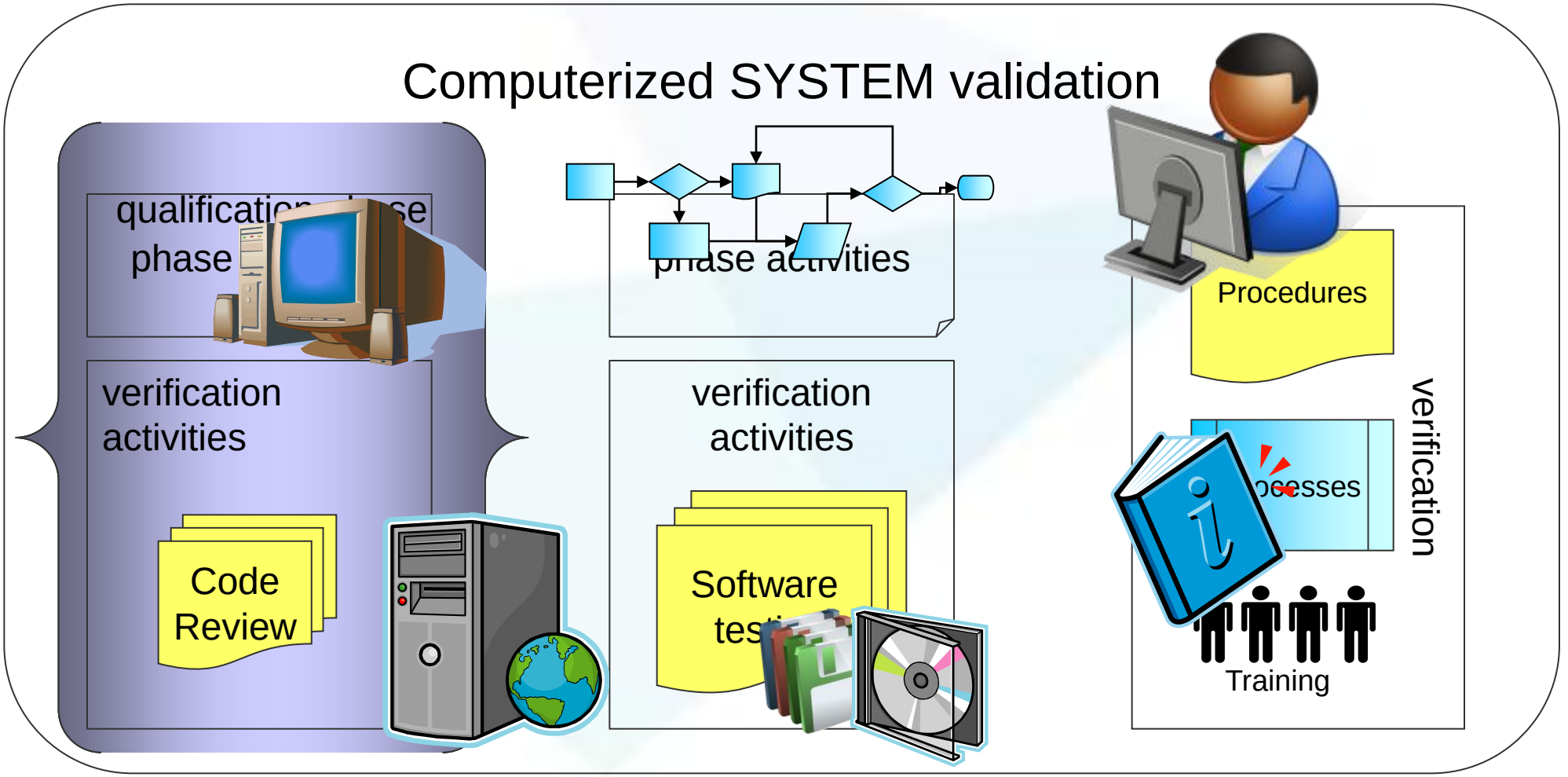
- Let us also say what validation is NOT
  - testing...OR... verification...OR...qualification
  - It is **all** these things and more….
- So what exactly do these terms mean?!?
- …**and how do they fit together?**



How do these terms relate?

validation

testing verification qualification



Where can we get help?

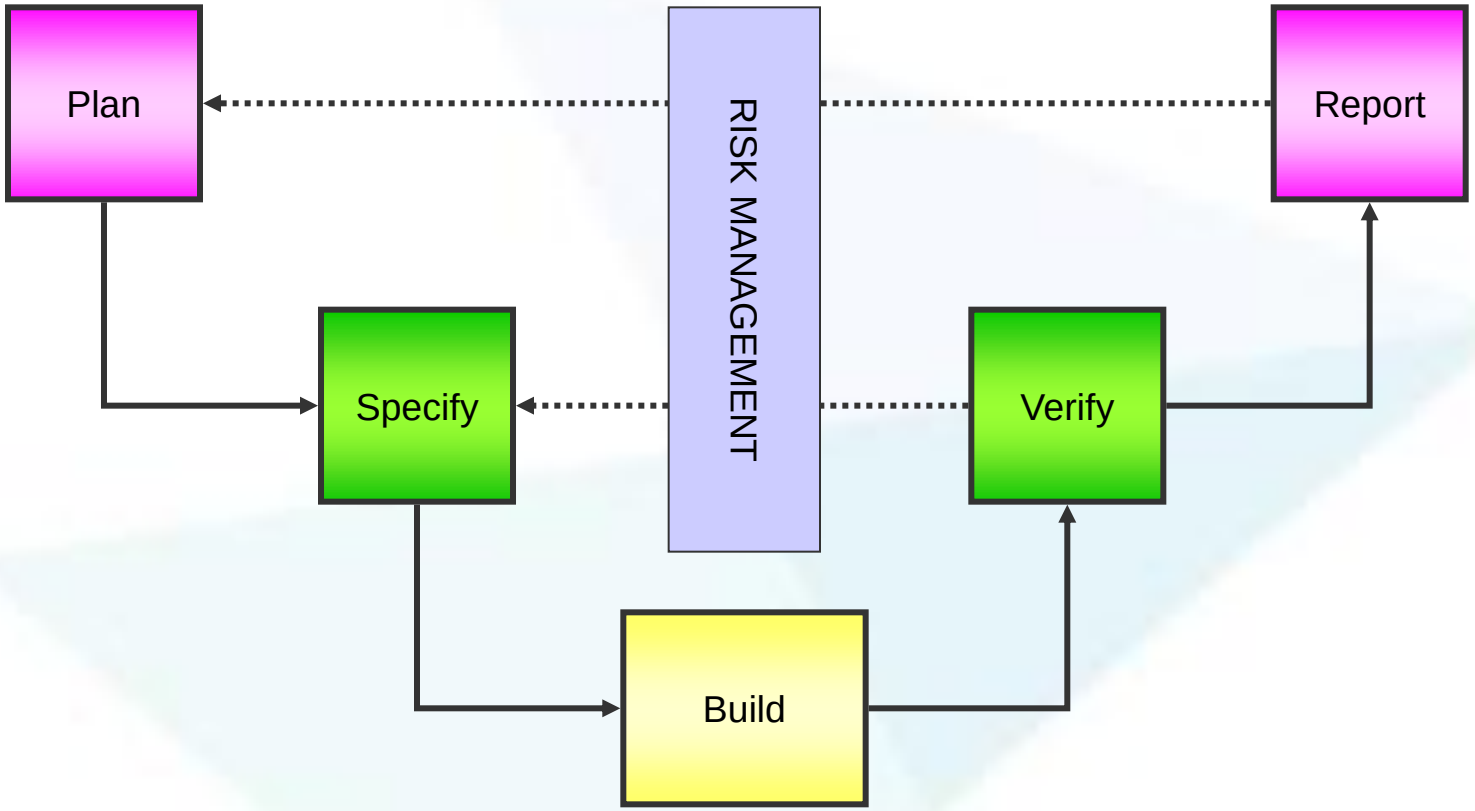
Lots of places…

AND MORE!!

What do these guidances say?

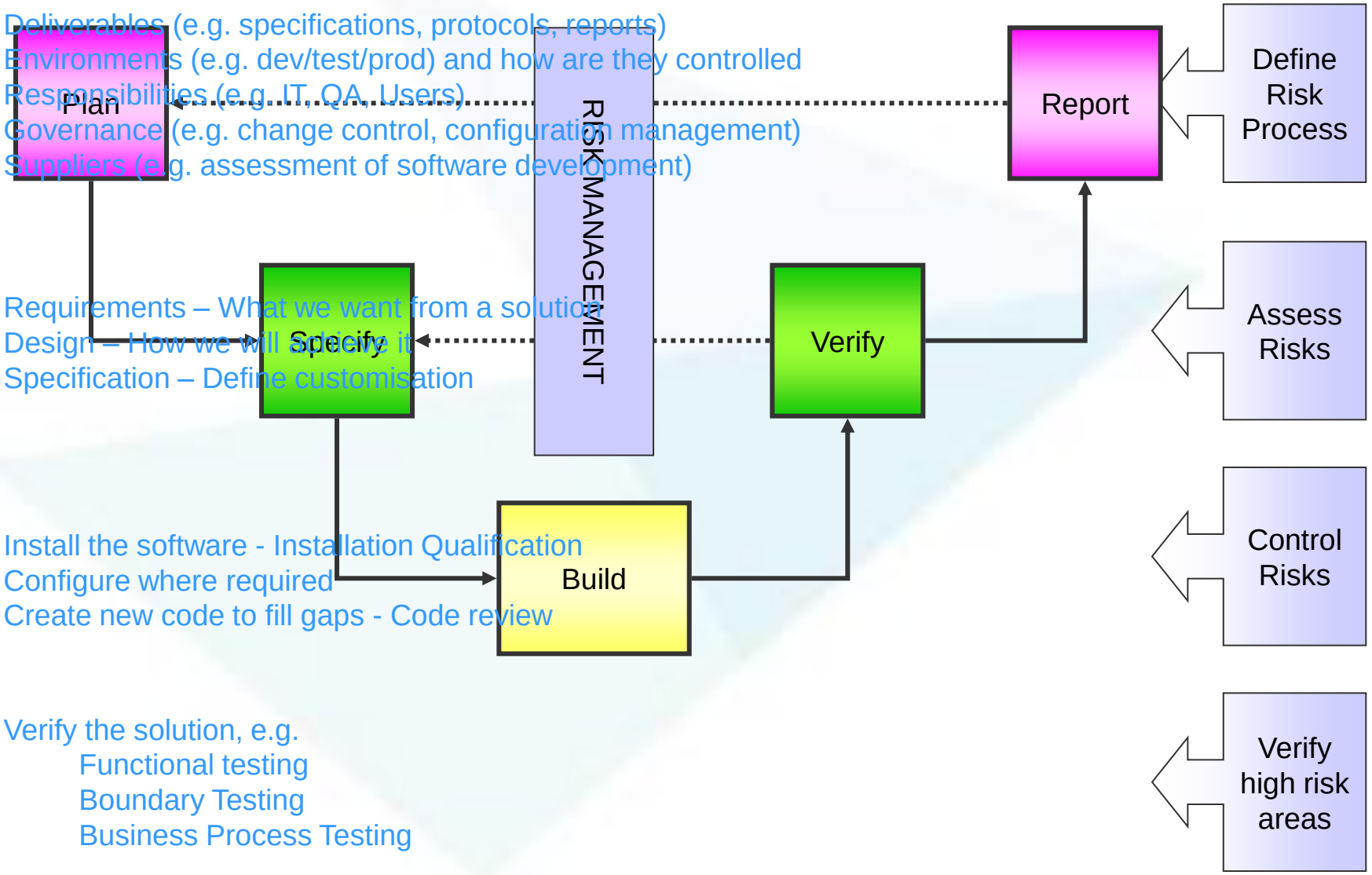
- *Do they talk about statistical analysis software?*
  - **NO**
- *Do they talk about <u>any</u> specific type of software?*
  - **NO**
- *So what DO they describe?*
  - **A generic methodology that can be applied to a wide range of software and hardware solutions.**
  - **Any specific approach should be based on minimising risk to products and consumers.**

What are the basics of all these methodologies?



Disclaimer: This is not intended to imply or endorse a waterfall lifecycle!!

What does this mean in practice?



R Validation Example

- A pharmaceutical company based in Basel, using R for statistical modelling and clinical trial analysis, asked for a validation strategy for R…

Plan

- Defined a Validation Plan – based on the approach outlined earlier
- Include a risk assessment documenting that Part 11 controls do not apply
- Describe the server environment/windows desktop that R will be installed to ands how that area is “validated”; describe how the IT group will be involved, e.g. by doing installs, controlling software (SCM), backup/restore
- Include a supplier assessment (a regulatory expectation) based on *R-FDA* document

Specify

- Define a set of user requirements
- Included non-functional requirements, such as security and availability
- Mapped requirements to functions based on package licenses (not all R packages are freely available (e.g. ~850 out of ~1200)
  - e.g. UR: the system can perform ANOVA
  - DS: Packages dae, GAD, granova, maanova, TANOVA

R Validation Example

Biop

Build

- Review of existing qualification for infrastructure
- Installation to controlled test and production environments
  - List the packages to be installed; Steps for installing packages, can refer to “R Installation and Administration” document
- Use built-in R verification routines (*make check)*

Verify

- Define test strategy based on package risk
- Risk dimensions include;
  - Frequency of use, complexity of function, what the output will be used for, and risk of input error
- Functional testing only of high risk packages
- Why?
  - Balance between the need to test and the time / resource available
  - Cannot “test in” quality; more testing does not increase quality of code
  - Certain level of testing already performed by developers

Summary

So can we use R for regulated work?

- Of course...the FDA use it themselves!

- Open Source does not mean uncontrolled
- Quote...

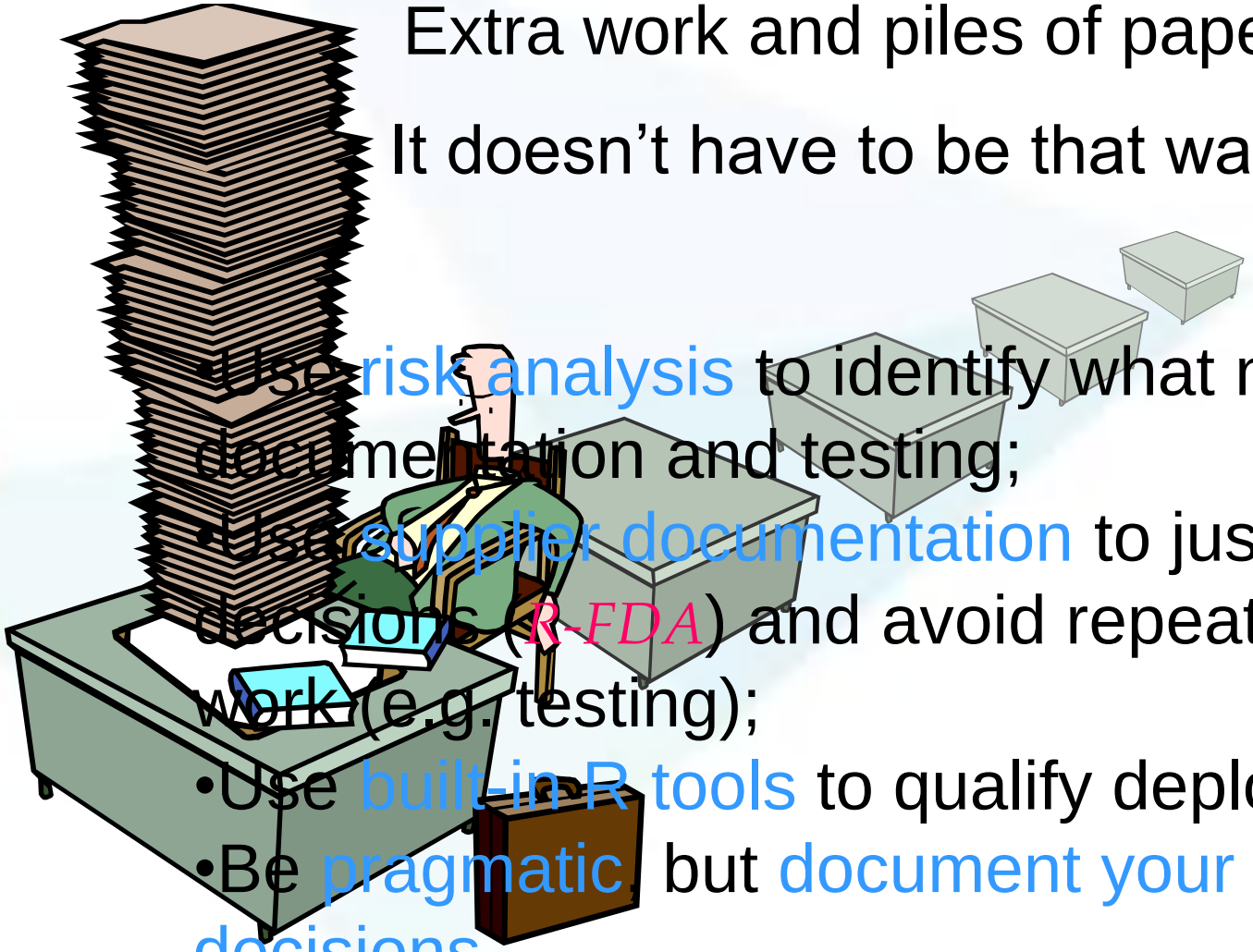
"At Novartis, we've got the open source version set up with appropriate processes and guidances for usage for health authority work. It's not a problem, just a matter of getting the details right….the critical problem is the packages, ascertaining and accepting risks inherent in that code.

And more critically, knowing that it's a whole process you are validating, not a piece of software. So it's just a matter of getting the risks and components of what you are doing identified and put together.

(no software can be validated unless it "is" the process -- qualified, yes, but despite … claims by commercial companies looking for a cheap slogan, "we have validated software!", they can't deliver it in the regulatory sense)."

Anthony Rossini, LinkedIn response, 02-Sep-2010

What does it all mean…?



Extra work and piles of paper?!

It doesn't have to be that way.

- Use risk analysis to identify what needs documentation and testing;
- Use supplier documentation to justify decisions (*R-FDA*) and avoid repeating work (e.g. testing);
- Use built-in R tools to qualify deployment;
- Be pragmatic, but document your decisions.

Thank you for your time

Ian Francis

Life Sciences IT Compliance and Validation

BIOP AG

ian.francis@biop.ch

Statistics | Programming | Medical Writing | Programme Management | Clinical Data Solutions