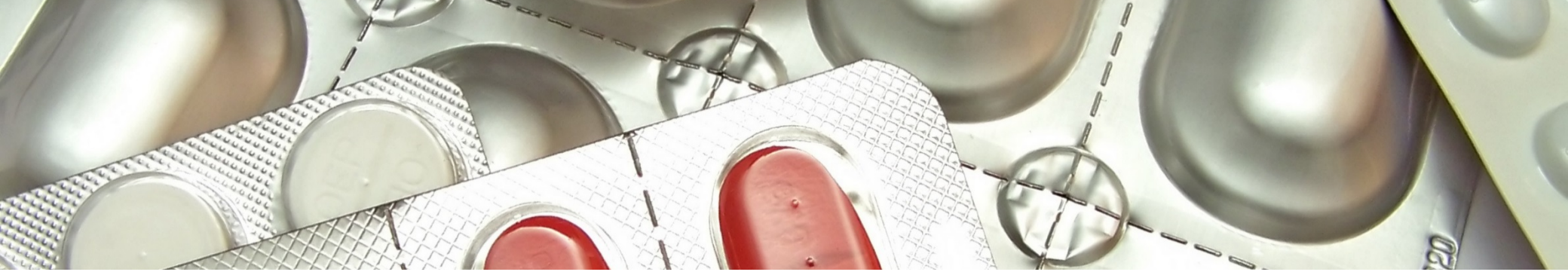


EXTRACTABLES & LEACHABLES ANALYSIS

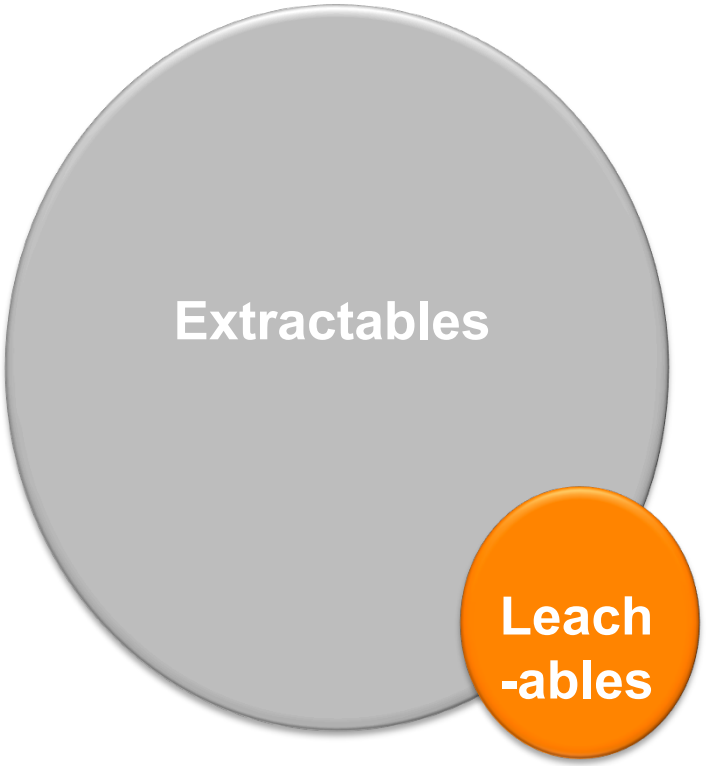
Chris Harbach, Validation Manager, SGS Wokingham, UK

WHEN YOU NEED TO BE SURE

SGS

WHAT ARE EXTRACTABLES & LEACHABLES ?

- Extractables
  - Compounds extracted from container closure systems by appropriate solvents
- Leachables
  - Compounds leaching into products from container closure systems during storage



WHY ARE WE CONCERNED?

Patient Safety

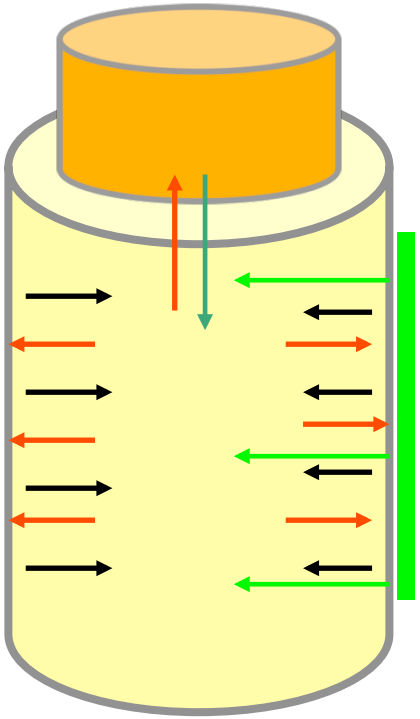
- Toxicity – carcinogenic and non-carcinogenic
- Leachables may cause changes in proteins:
  - Conformation
  - Aggregation
  - Degradation
- Adjuvant and/or immunomodulatory effects

PACKAGING CONCERNS – DRUG PRODUCT CLASSES

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component – Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	•Inhalation Aerosols & Solutions •Injections & Injectable Suspensions	•Sterile Powders & Powders For Injection •Inhalation Powders	
High	•Ophthalmic Solutions & Suspensions ▪ Transdermal Ointments & Patches •Nasal Aerosols & Sprays		
Low	▪ Topical Solutions & Suspensions ▪ Topical & Lingual Aerosols ▪ Oral Solutions & Suspensions	▪ Topical Powders ▪ Oral Powders	▪ Oral Tablets & Oral (Hard & Soft Gelatin) Capsules

Table adapted from “Guidance for Industry. Container Closure Systems for Packaging Human Drugs and Biologics.”, US FDA, Rockville, MD, May 1999.

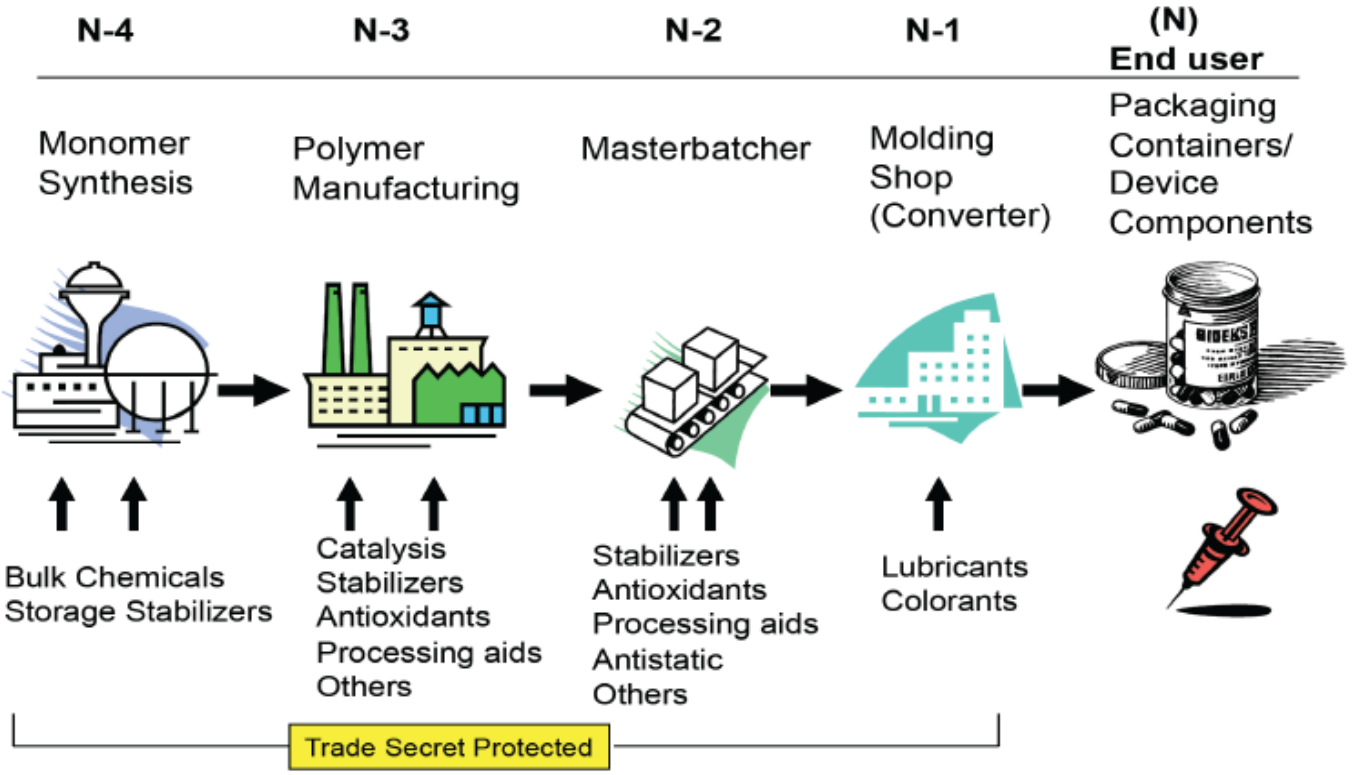
SOURCES



- Pack / product interaction
- Label adhesive / ink migration
- Secondary packaging
- In-process leachables?

POLYMER CHEMISTRY – SOURCES OF CONTAMINATION

Potential for Extractables and Leachables



Cindy Zweiben, Characterization of Extractables and Leachables in Parenteral Drug Products, Sept 2010

TYPICAL COMPONENTS

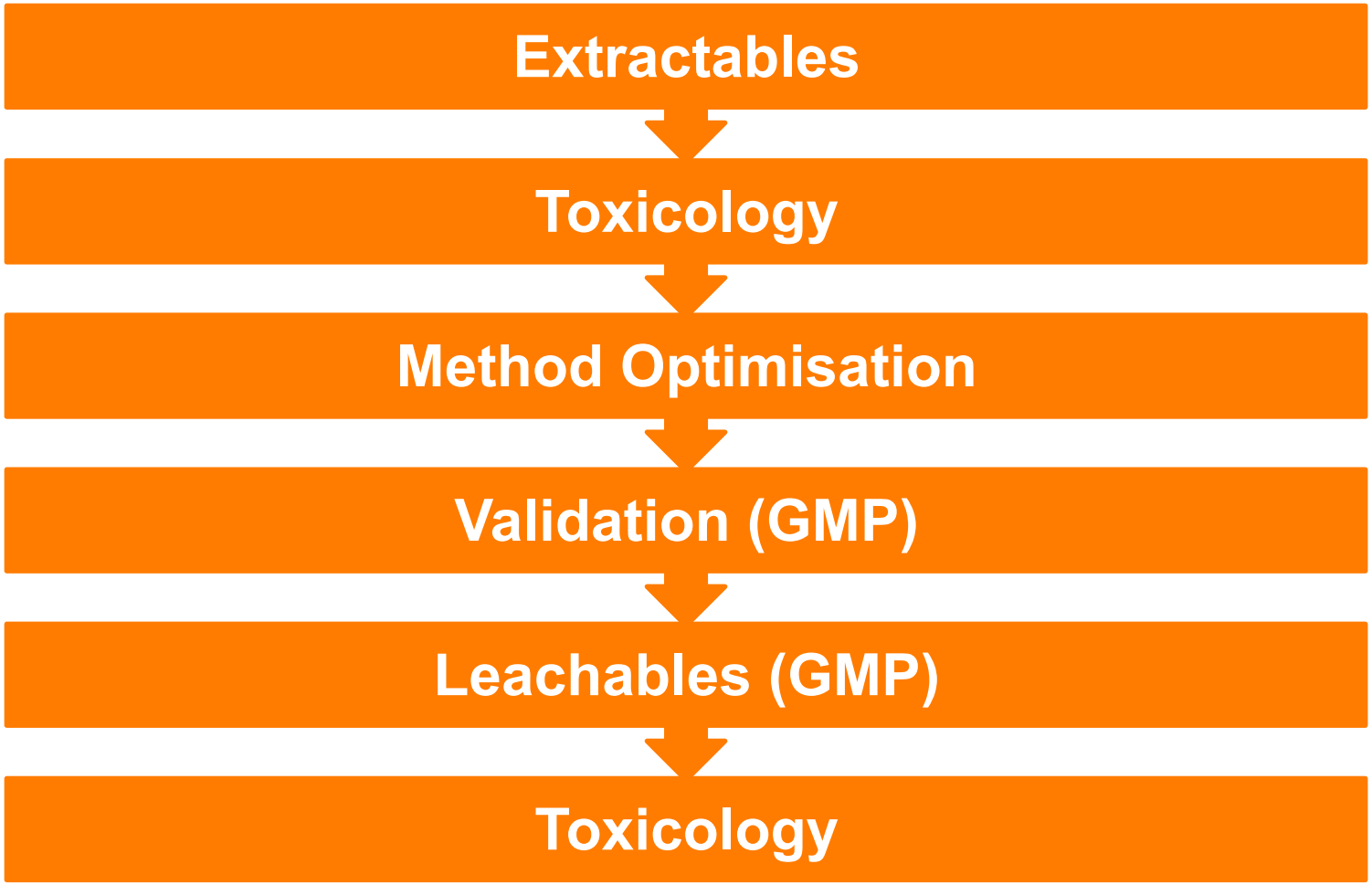
TYPICAL EXTRACTABLES

- Plasticisers – e.g. dialkylphthalates
- Antioxidants – e.g. phenolics and amines
- Polycyclic aromatic hydrocarbons from carbon black
- Silicones
- Oligomeric compounds
- Trace metals
- Vulcanisation agents and accelerators (e.g. MBT)
- Nitrosamines in sulphur cured rubbers
- Ink and adhesive from secondary packaging

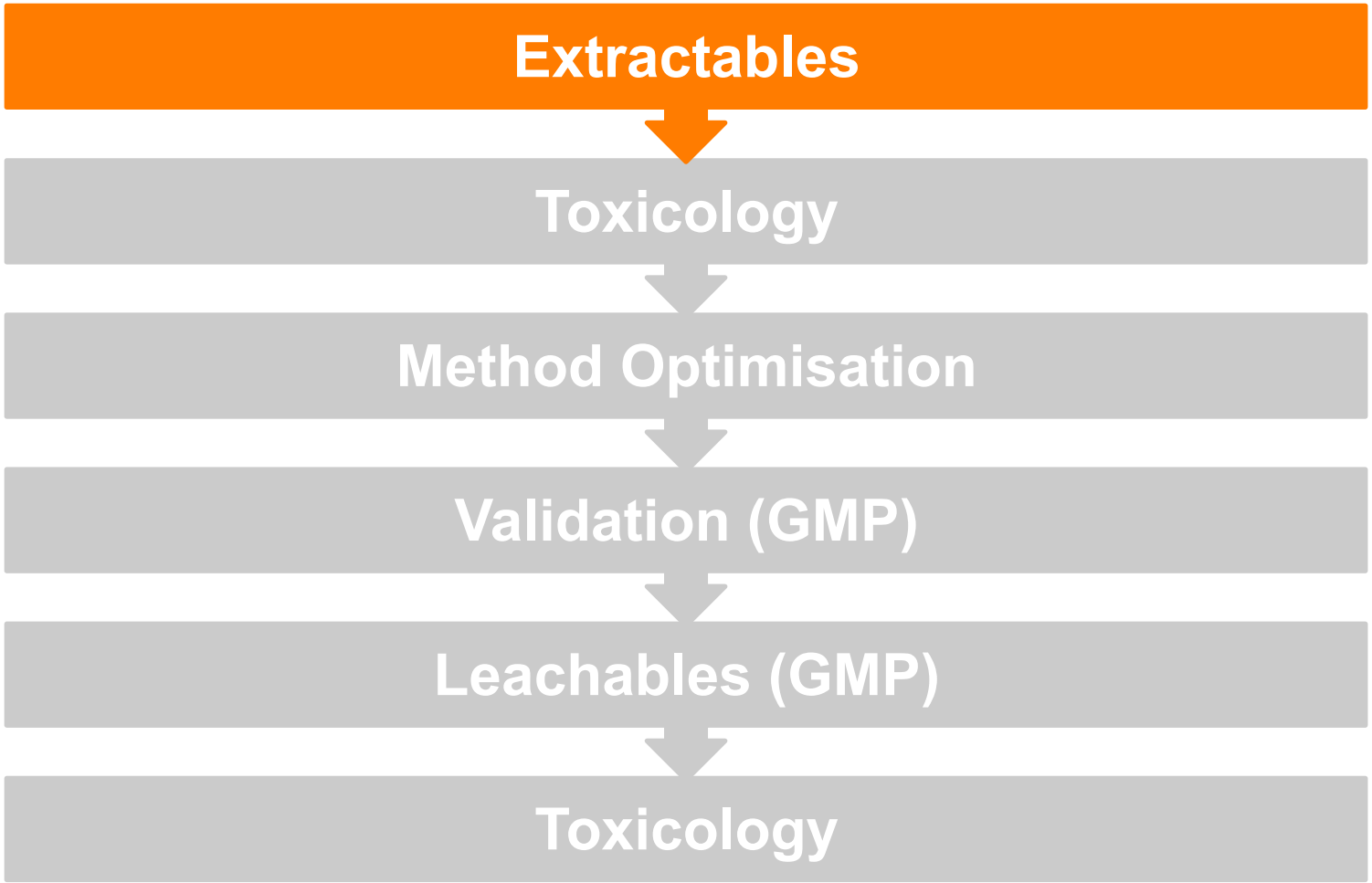
GUIDANCE

- FDA: Container Closure Systems –1999
- FDA: Nasal Spray & Inhalation Solutions – 2002
- EMA: Plastic Immediate Packaging – 2005
- EMA: Quality of Inhalation & Nasal Products – 2006
- PQRI: Extractables & Leachables in OINDP – 2006
- USP – 2015
  - <1663> Assessment of Extractables …
  - <1664> Assessment of Drug Product Leachables…
- Other industry bodies

OVERVIEW OF THE E&L PROCESS



OVERVIEW OF THE E&L PROCESS



ANALYTICAL CHALLENGES OF EXTRACTABLES PROFILING

The Challenges

- Depend on chemistry of CCS
- Concentrations depend on extraction conditions
- Are complex chemical mixtures
- Can be at trace levels

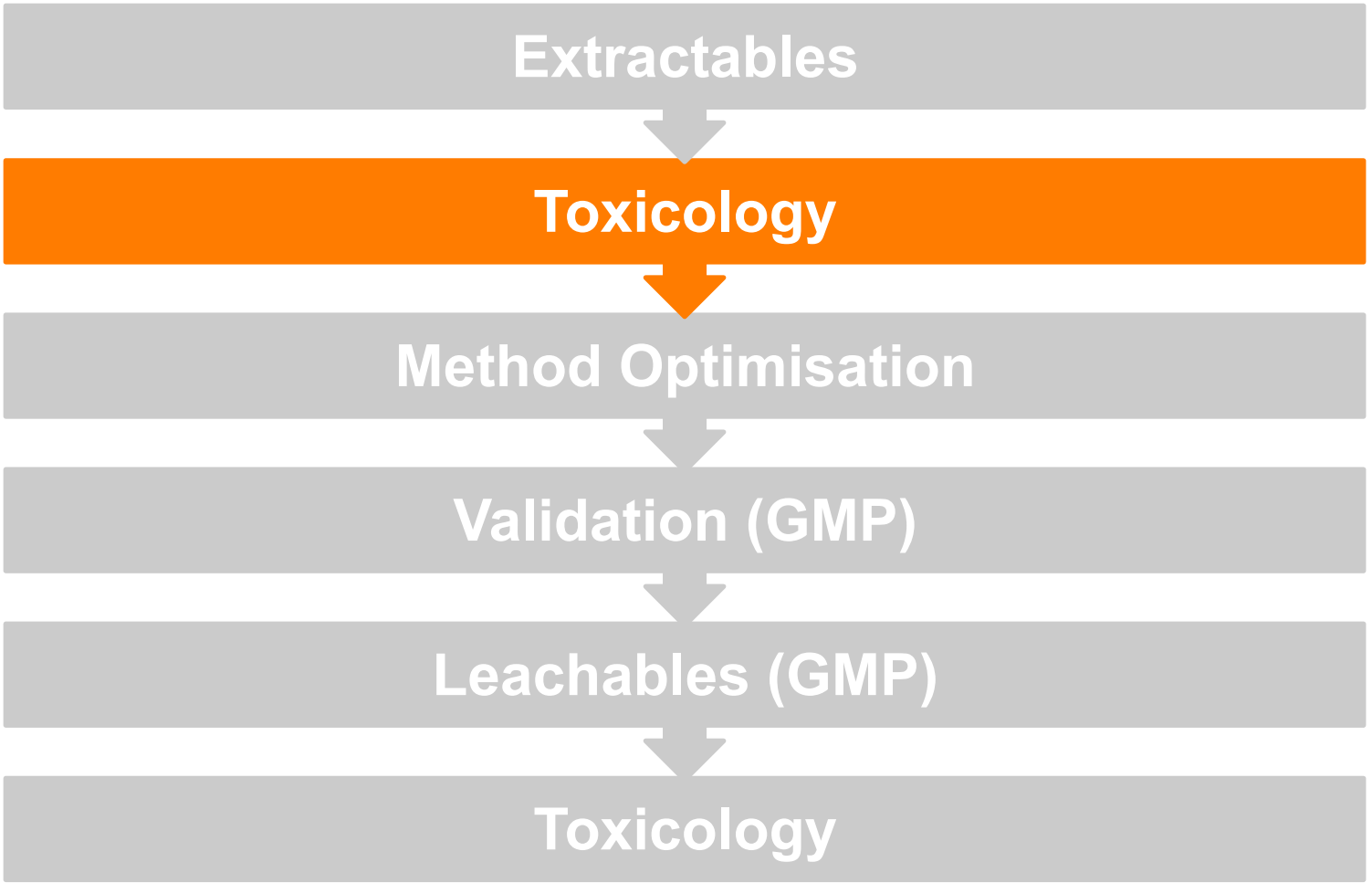
The Solutions

- Understand polymer chemistry
- Choose appropriate extraction conditions; concentrate extracts
- Analytical methods for separation and detection
- Sensitive detection techniques

CONTROLLED EXTRACTION STUDIES

- Multiple solvents – range of polarities; chosen based on drug formulation
- Multiple vigorous extraction techniques
- More aggressive conditions than normal – “worst case”
- Multiple analytical techniques
- Identification and quantitation of individual extractables above defined toxicological thresholds

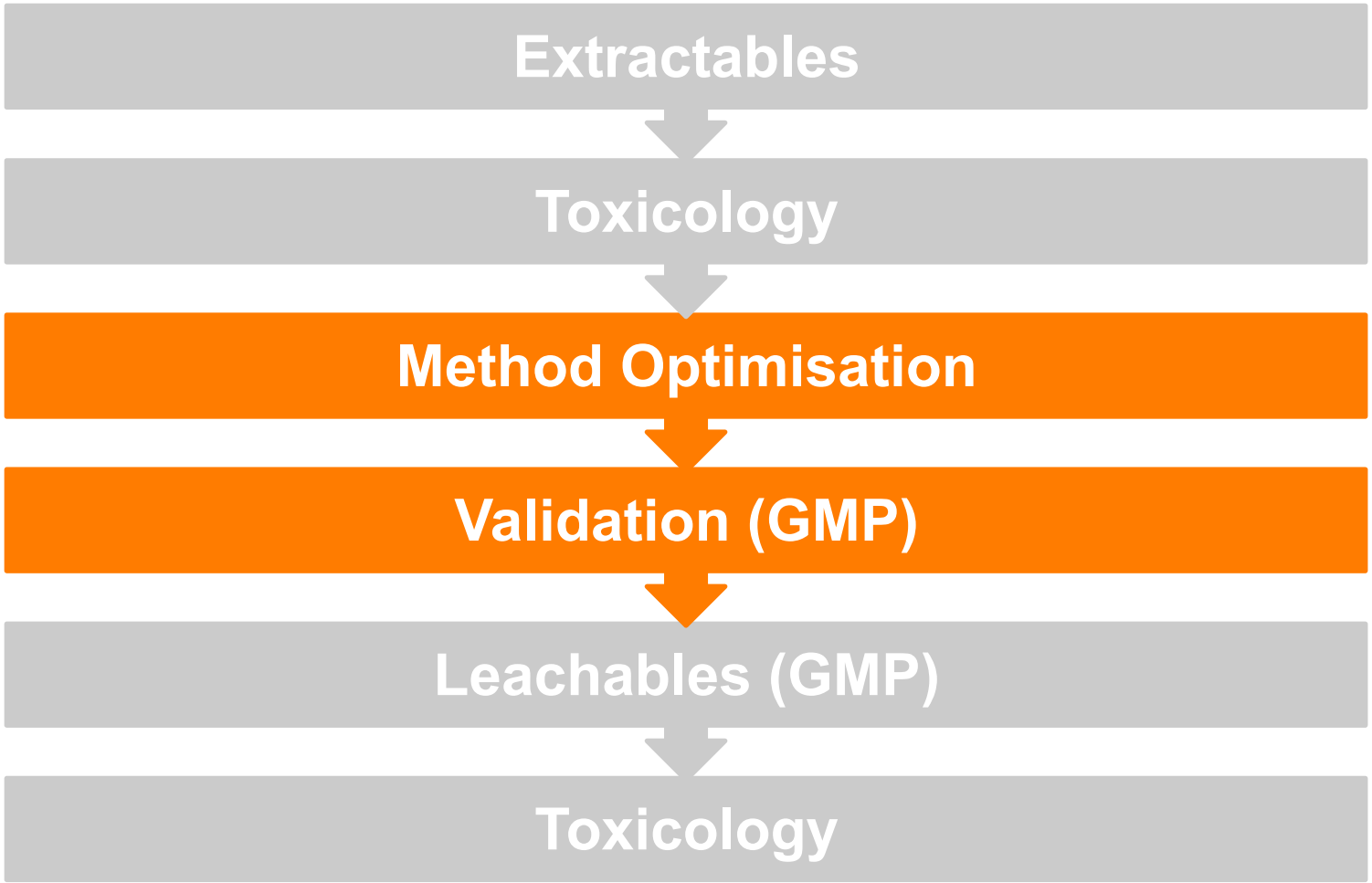
OVERVIEW OF THE E&L PROCESS



TOXICOLOGY

- Extractables report submitted to expert toxicologist
- Detailed toxicological report
- Recommends which extractables to:
  - Validate methods
  - Analyse as potential leachables

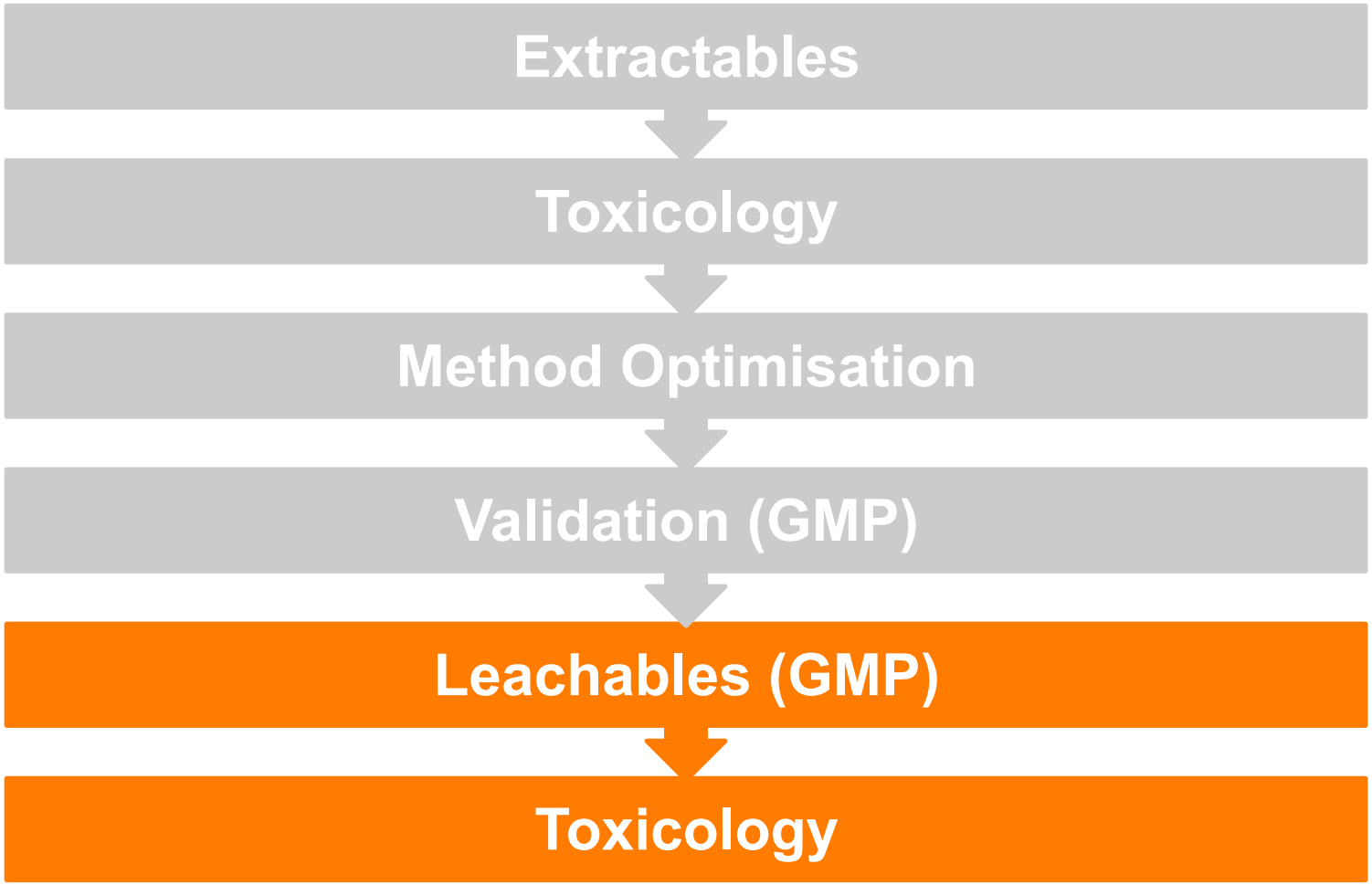
OVERVIEW OF THE E&L PROCESS



METHOD OPTIMISATION & VALIDATION

- Method optimisation
  - Extractables in relatively pure solvents; do API and/or excipients interfere?
  - Conduct method optimisation before validation
- Validation in-line with ICH Q2(R1) under cGMP
  - System suitability and specificity
  - Accuracy
  - Precision (repeatability, intermediate precision)
  - Linearity
  - Quantitation limit, range
  - Robustness / ruggedness

OVERVIEW OF THE E&L PROCESS



LEACHABLES ANALYSIS & TOXICOLOGY

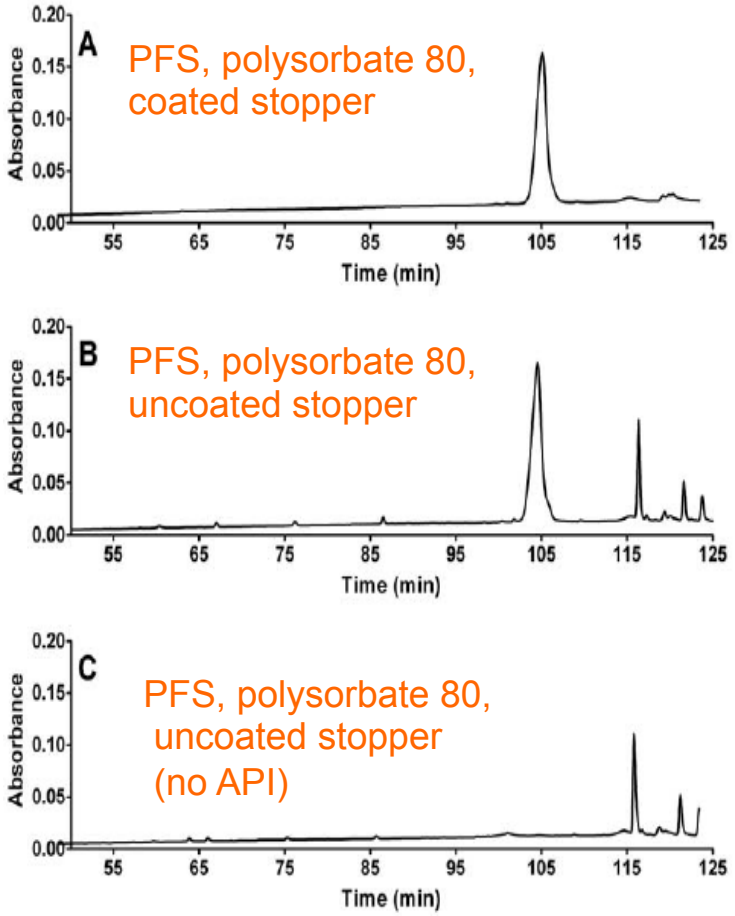
- Leachables (validated methods to cGMP)
  - Specific to each finished product
  - Multiple points over shelf-life; including end
  - Use stability trial samples
  - Appropriate detection limits
- After leachables analysis
  - Compare extractables and leachables
  - Which leachables are of concern?
  - Toxicological assessment
  - Data inform routine extractables testing on component batches

CASE STUDIES IN BIOLOGICS

(1) STOPPER LEACHABLES

- Antibody-mediated pure red cell aplasia (PRCA) in patients increased sharply from 1998
- CCS: Pre-filled syringes; uncoated rubber stoppers
- In 1998, the HSA in EPREX® replaced with polysorbate 80
  - Sharma et. al., Eur J Hospital Pharma, 5:86-91
  - Casadevall et. al., N Engl J Med, 346:469-475

(1) STOPPER LEACHABLES



4-*tert*-amylphenol
2-chloro-4-*tert*-amylphenol
Vultac® 2 disulfide
2,2'-methylene-bis-4-*tert*-amylphenol
Vultac® 2 trisulfide
Vultac® 2 tetrasulfide
Vultac® 2 pentasulfide
Vultac® 2 hexasulfide

Sharma et. al., *Eur J Hospital Pharma, 5:86-91*

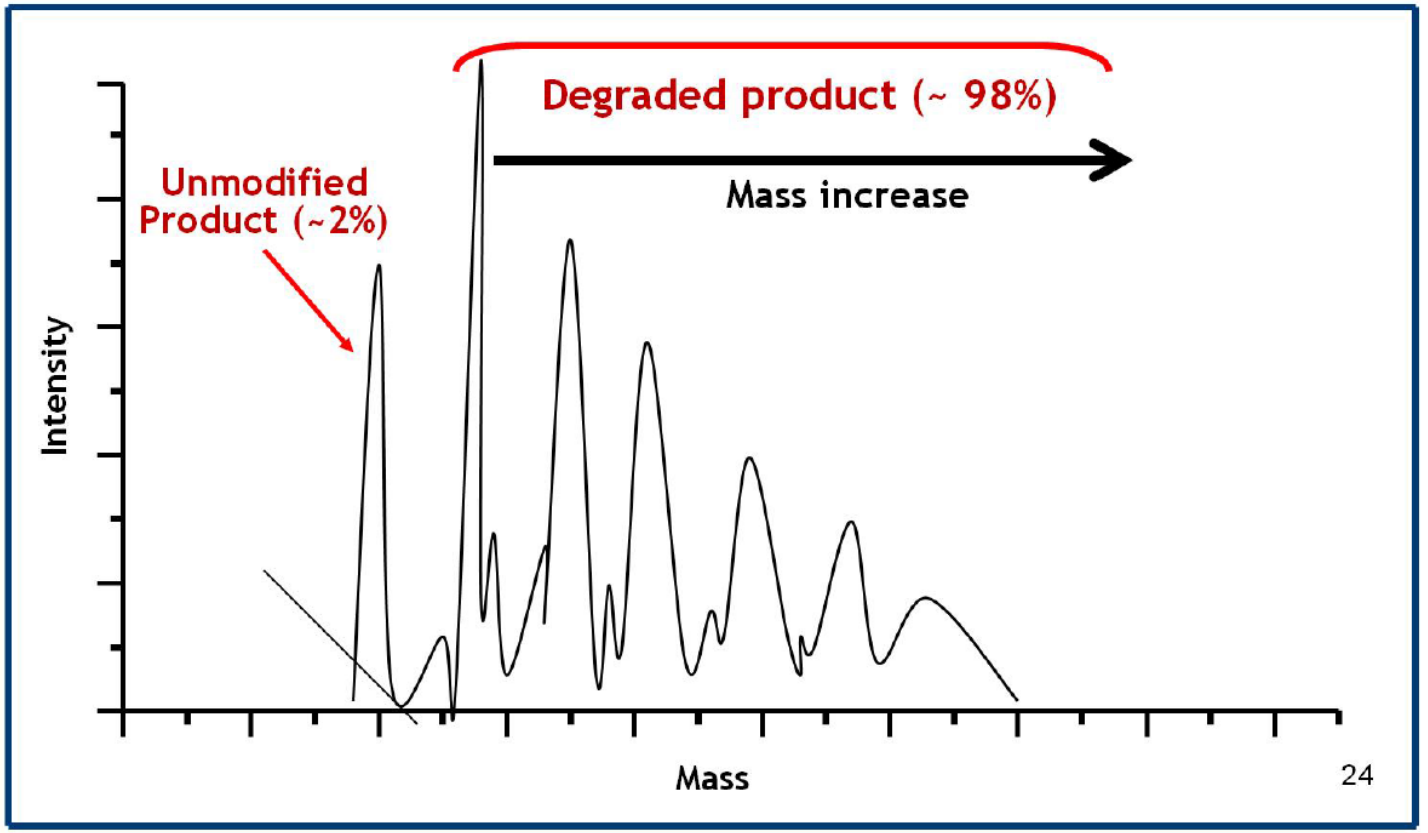
(2) IRON LEACHABLES

- Iron leachables caused adducts
- Shelf-life extended from 15 to 18 months
- Uncoated stoppers release iron (< 1ppm)
- Iron catalyses protein + preservative reaction
- OOS result (> 50% modification)
- Moderate potency decrease

Ingrid Markovic, E&L USA, Silver Spring, May 2014

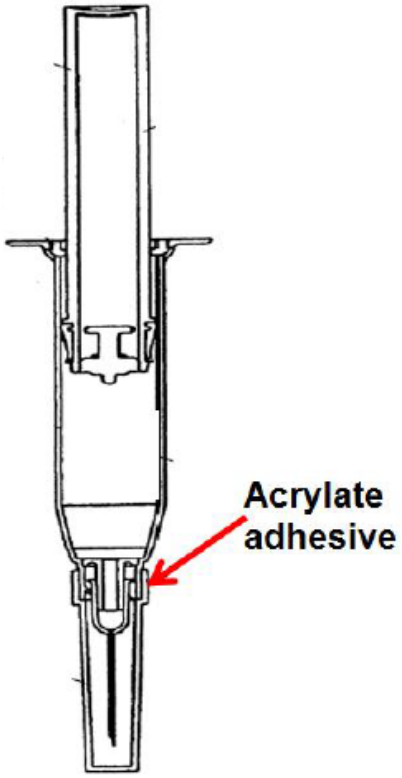
(2) IRON LEACHABLES

Simulated Chromatogram of Severely Degraded Lot



Ingrid Markovic, E&L USA, Silver Spring, May 2014

(3) ADHESIVE LEACHABLES



- Staked needle PFS
- Acrylic acid (~ 5ppm) from adhesive leached into drug
- Covalently modified protein at three sites
- Protein became negatively charged
- Change PFS type

Ingrid Markovic, E&L USA, Silver Spring, May 2014

CASE STUDY SUMMARY

- Minor, non-toxic leachables may cause issues with product quality and hence safety
- A more rigorous approach to leachables testing may be warranted for biologics

THANK YOU FOR YOUR ATTENTION

Agriculture, Food and Life

Dr Chris Harbach
Validation Manager

SGS M-Scan Ltd
2-3 Millars Business Centre,
Fishponds Close,
Wokingham
Berkshire, RG41 2TZ, UK

Phone: +44 (0) 118 912 1190
Fax: +44 (0) 118 912 1191
E-mail : chris.harbach@sgs.com

Web : www.sgs.com/biopharma

CONTACT US

LABORATORY SERVICES

lss.info@sgs.com

EUROPE : + 41 22 739 9548
AMERICAS : + 1 866 SGS 5003
ASIA : + 65 637 90 111

www.sgs.com/lifescience

CLINICAL RESEARCH

lss.info@sgs.com

EUROPE : + 33 1 53 78 18 79
AMERICAS : + 1 877 677 2667

WWW.SGS.CO.UK

WHEN YOU NEED TO BE SURE

SGS