Special aspects of nanomedicines: Development, manufacturing and Characterisation

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Special aspects of nanomedicines

a) Why make nanomedicines?

b) Challenges for reproducible manufacturing, scale-up and stability

c) Established validated techniques for characterization

d) Key factors for ensuring quality by design

e) Challenges for formulation and development in respect of specific routes of administration

(a) Why make nanomedicines?

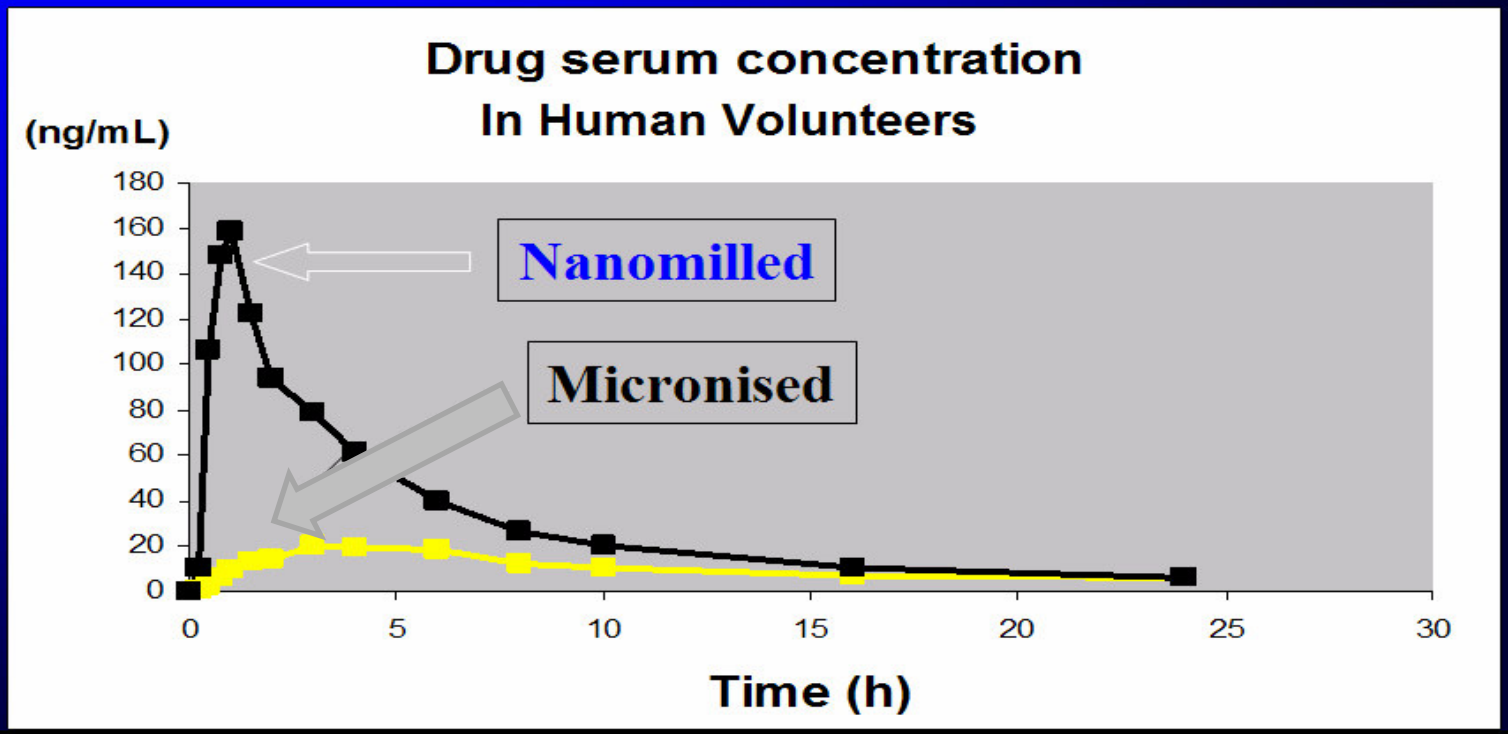
Drivers for nano medicines (oral route)

- For permeable molecules reduction in particle size can increase rate and extent of oral absorption.
- Lower particle size limit for conventional dry attrition methods such as air jet and pin milling is 1 to 5 microns
- If insufficient improvement in absorption is achieved using dry attrition, sub micron or 'nano' particles of the drug substance can be formed via a range of manufacturing technologies:[1]
  - Media milling e.g. NanoCrystal ® (Elan)
  - High pressure homogenisation e.g. NanoEdge (Baxter)
  - Precipitation e.g. HGCP (NanoMaterials Technology Pte)
  - Super Critical Fluids e.g. Dupont Micro / Nano Mill
  - Cryomilling e.g. NanoQUAD ™ (Nanotherapeutics Inc.)
  - Emulsions e.g. Bioaqueous SM (Dow Pharma)

1 P Shah, Use of nanotechnologies for drug delivery, MRS Bulletin, 31 (2006) 894-899

Improved Pharmacokinetics from oral dosing of drug product containing 'Nano' API

(error bars not shown, the 2 profiles are statistically different)



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Current portfolio of Nanomedicines

- Media milled drug products:
  - Rapamune® (sirolimus), immunosuppressant, 1mg and 2 mg strength tablets. Wyeth, August 2000
  - Emend® (aprepitant), anti emetic, 80 and 125 mg capsule. Merck, April 2003
  - Megace® ES (megestrol), anti neoplastic, 125 mg / mL oral suspension. Par, July 2004
  - Tricor® (fenofibrate), lipid regulation, 48mg tablet. Abbot, December 2004
  - *Plus,* undergoing regulatory review: paliperidone palmitate plus NanoCrystal® tech, schizophrenia. once-monthly injection. Filed in USA December 2009

Current portfolio of Nanomedicines (cont.)

- Other 'nano sized' medicinal products:
  - Imaging agents: Feridex ® (ferumoxides injectable solution), 11.2 mg / mL iron. Bayer; withdrawn Nov2008
  - Liposomes: Doxil ® (doxorubicin HCl liposome injection), ovarian cancer *et al*, 2 and 1.67 mg / mL injection. Ortho Biotech, September1995
  - Albumin-bound nanoparticles: Abraxane™ (paclitaxel protein-bound particles for injectable suspension), breast cancer, 5 mg / mL injectable suspension. Abraxis BioScience (American Pharmaceutical Partners) February 2005
  - Triglide™ (fenofibrate), lipid regulation, 50 and 160 mg tablets, SkyePharma IDD® P technology, July 2005
- Overall: relatively few products available, usually systemic rather than targeted delivery

(b) Challenges for reproducible manufacturing, scale-up and stability

Challenges

1. Optimising the manufacturing process to produce the selected drug substance particle size distribution within the drug product
   – Apply Quality by Design tools ….. *more later*

2. Scale up – derive process models from manufacturing parameters

Challenges

3. Stability
   a) Establish acceptable chemical & physical data to support shelf life – consider shipping trials!
   b) Predicting product performance *in vivo* – are 'nanoparticles' delivered to target site?
4. Establishing limits for process impurities
   – Control through specifications e.g. zirconium and yttrium, for media milling

- 1, 2, 3a and 4 – apply to conventional medicines. 3b is a special consideration for nanomedicines – see next section

(c) Established validated techniques for characterisation

Characterisation

- Need to develop analytical methods to fully characterise 1 nm to 1000 nm sized materials
- Regulatory agencies now placing more focus on nanotechnology platforms and are requesting validated predictive characterisation techniques i.e. meaningful *in vitro / in vivo* analytical methodologies
- Definition of measurement standards still undergoing active discussion e.g. BSI NTI/1 nanotechnologies standardisation committee

Characterisation techniques

i. Laser diffraction – widely used, need to consider algorithms and presence of insoluble formulation components
ii. Photon Correlation Spectroscopy – also widely used, need to consider sample preparation (filtration), different calculation basis to laser diffraction
iii. Light scattering e.g. nanosight
iv. Plus others e.g. SEM, X ray diffraction to check on particle morphology

Characterisation – a cautionary tale

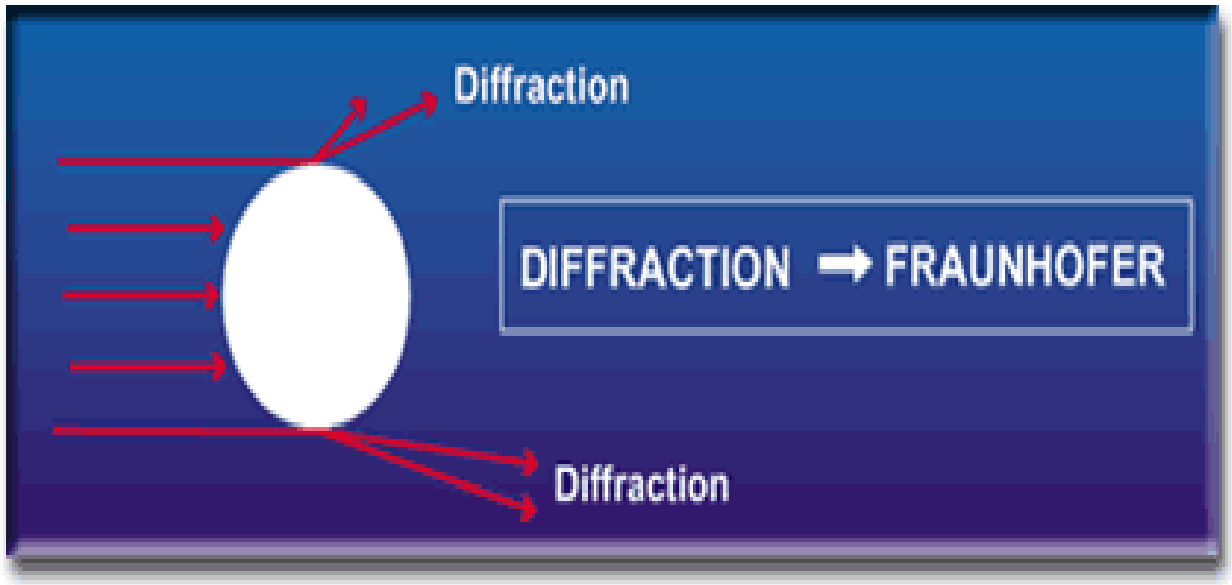
- Application of laser diffraction to analyse sub micron particles of drug substance in an aqueous suspension

- Data calculation: two theories employed
    i. Fraunhöfer
    ii. Mie

Calculation of the data

– (i) Fraunhöfer approximation

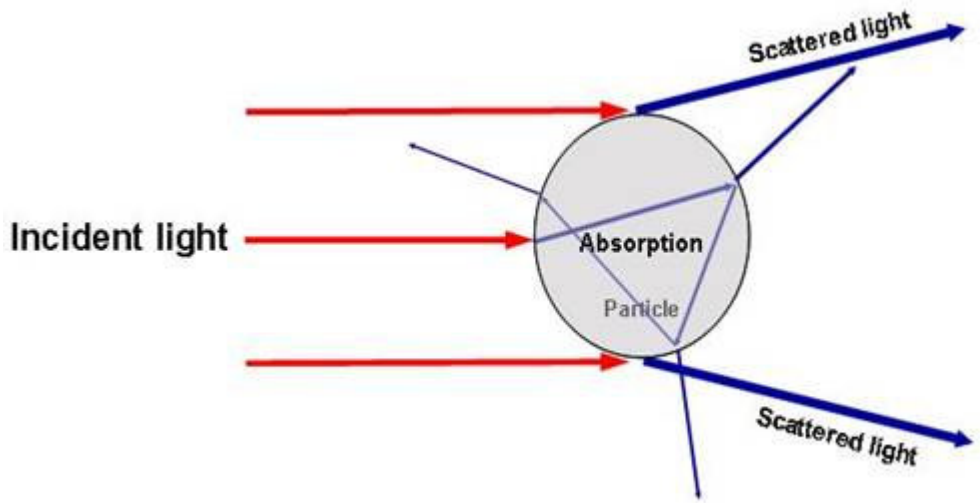
- Simple diffraction theory, scattering pattern derived for large particles without reference to the optical properties of the material. Assumes particles are opaque, default technique at micron scale



Calculation of the data

– (ii) Mie theory

- As size approaches the wave length of light i.e. 400 to 700 nm, the scattering pattern becomes more complex
- Mie theory predicts the angular scattering of light from a particle
- For this, the Refractive Index (RI) of the particle and dispersant is required, along with the absorption part.

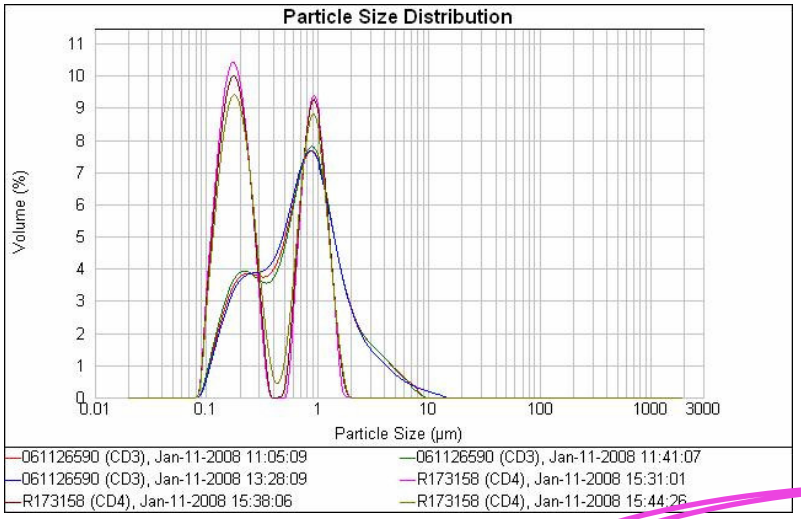


Early development project

- Driver: increase in oral exposure
- Objective: to reduce API particle size to an X90 particle size of < 1 micron *i.e. small but not excessively so.*
- Media milling employed, Fraunhöfer theory for laser diffraction analysis
- ! Barrier: appeared to reach a lower particle size limit above target for two batches
- ! Issue: instability of colloid observed

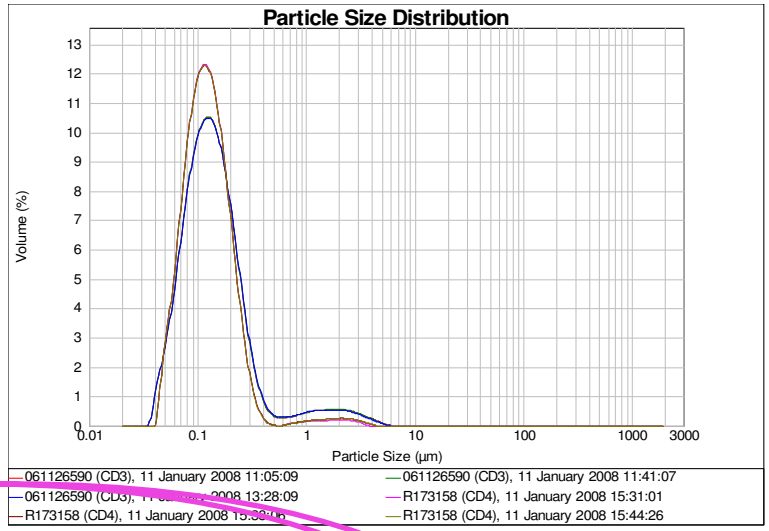
Comparison of Fraunhöfer and Mie data

Fraunhofer



Batch	X_{10} (um)	X_{50} (um)	X_{90} (um)
061126590 (CD3)	0.19	0.74	2.2
R173158 (CD4)	0.13	0.26	1.2

Mie



Batch	X_{10} (um)	X_{50} (um)	X_{90} (um)
061126590 (CD3)	0.07	0.13	0.30
R173158 (CD4)	0.07	0.12	0.23

Particle size much smaller than initial analysis showed, stabiliser levels altered to overcome depletion issue

When should Mie theory may be applied?

- Within the various pharmacopoeias, the answer to this question is not clear i.e.
  - EP: < 2um
  - USP: < 25um
  - JP: < 1um

- Internal (GSK) guidance is:
  - The Fraunhöfer optical model is recommended
  - If Fraunhöfer data is inconsistent other techniques e.g. scanning electron microscopy, PCS, then the refractive index values will be measured and Mie Theory applied.

Validation of sizing methods

- Use established Industry standards – once again there is nothing ‘new’ or ‘unusual’
  - Demonstrate precision, robustness etc.

- Consider *in vivo* conditions e.g. simulate pH of target area

- Develop *in vitro* methods to test drug product intermediates and drug product i.e. not simply for particle formation step

(d) Key factors for ensuring Quality by Design

(d) key factors for ensuring quality by design

- Apply QbD tools
  - Design Of Experiments
  - Use of Process Measurement Technology tools
  - Multivariate analysis to derive a process signature
  - Application of statistical process charts to monitor and control manufacturing process

- For example: GSK “nanomilling” process at the Cork site

QbD worked example: media milling

- Critical Process parameters
  - Bead diameter
  - Bead loading
  - Motor speed
  - Motor current
  - Mill pressure
  - Product temperature
  - Product flow rate
- Main output: API particle size

The campaign: 12 x 200 kg batches

- Water based drug product
- Solids loading ~ 60% w/w

- Seven bead mills employed in series
- One pass process

- Milling duration 150 minutes

- Input particle size: X90 (by volume) > 10 microns
- Output particle size X90 (by volume) ~ 450 nm

Conventional campaign analysis: control of product particle size

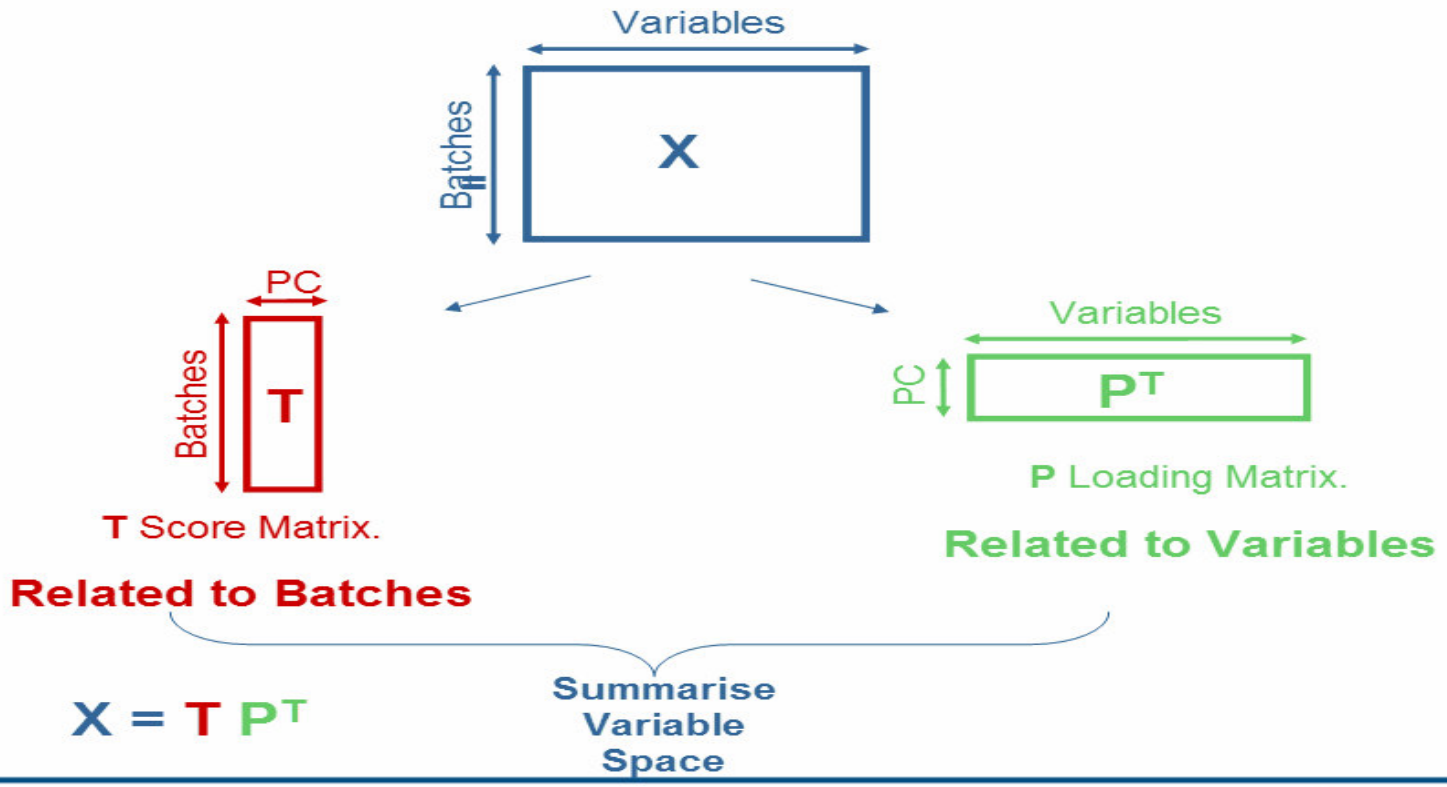
- 12 batches
- X 90 range: 0.43 to 0.48 um
- Average = 0.45 um
- Standard deviation = 0.014
- 3 sigma = 0.041
- Good control?

Alternative campaign analysis

- Critical Process parameters
  - Bead diameter (fixed)
  - Bead loading (fixed)
  - Motor speed – monitored by Aspen Tech IP21
  - Motor current – monitored by IP21
  - Mill pressure – monitored by IP21
  - Product temperature – monitored by IP21
  - Product flow rate – monitored by IP21
- Method of analysis
  - Applied chemometric method of partial least squares to multivariate control charts

Alternative campaign analysis

Principal Components Analysis (PCA)
Dimension Reduction (of Design Space)



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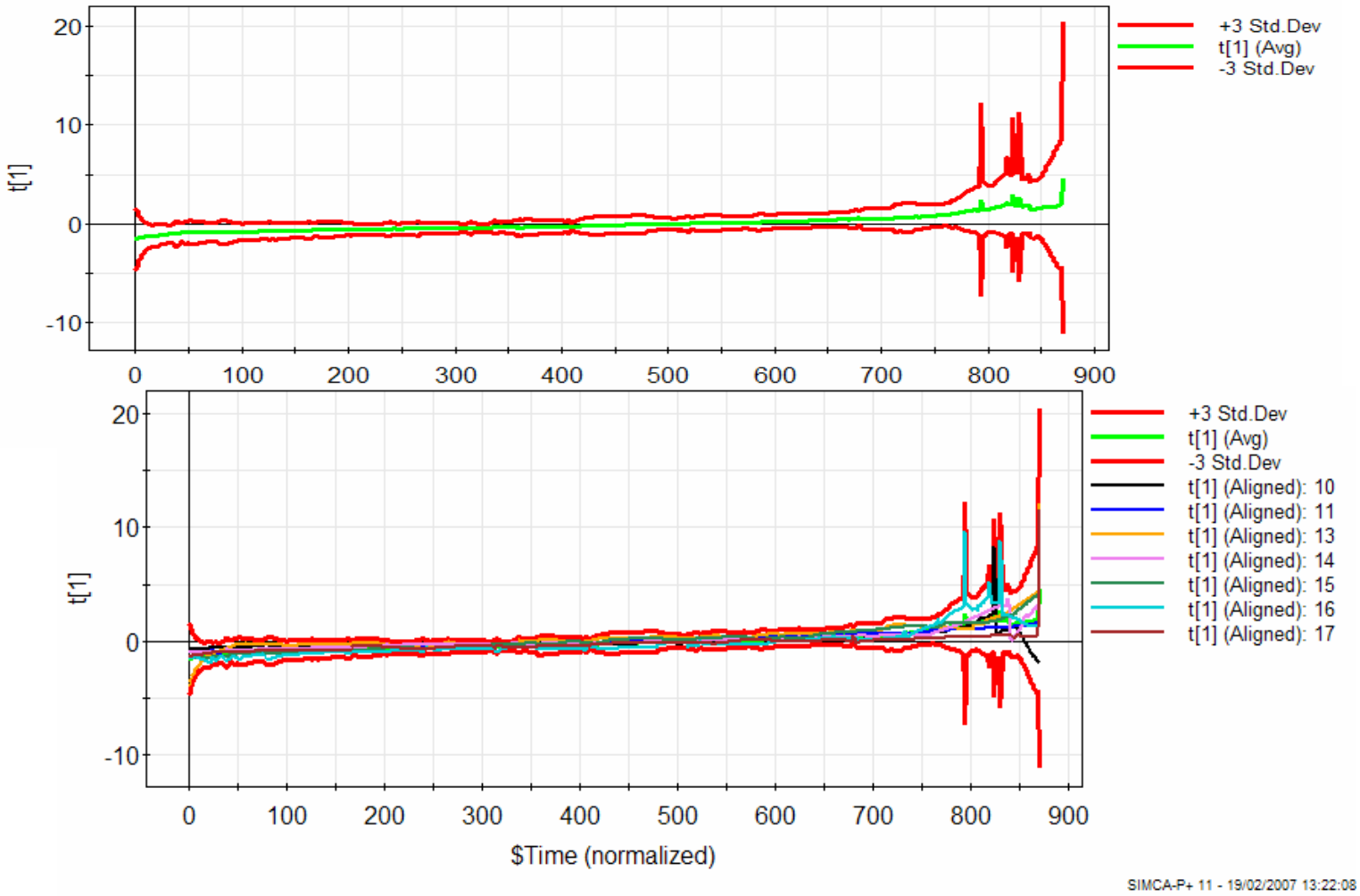
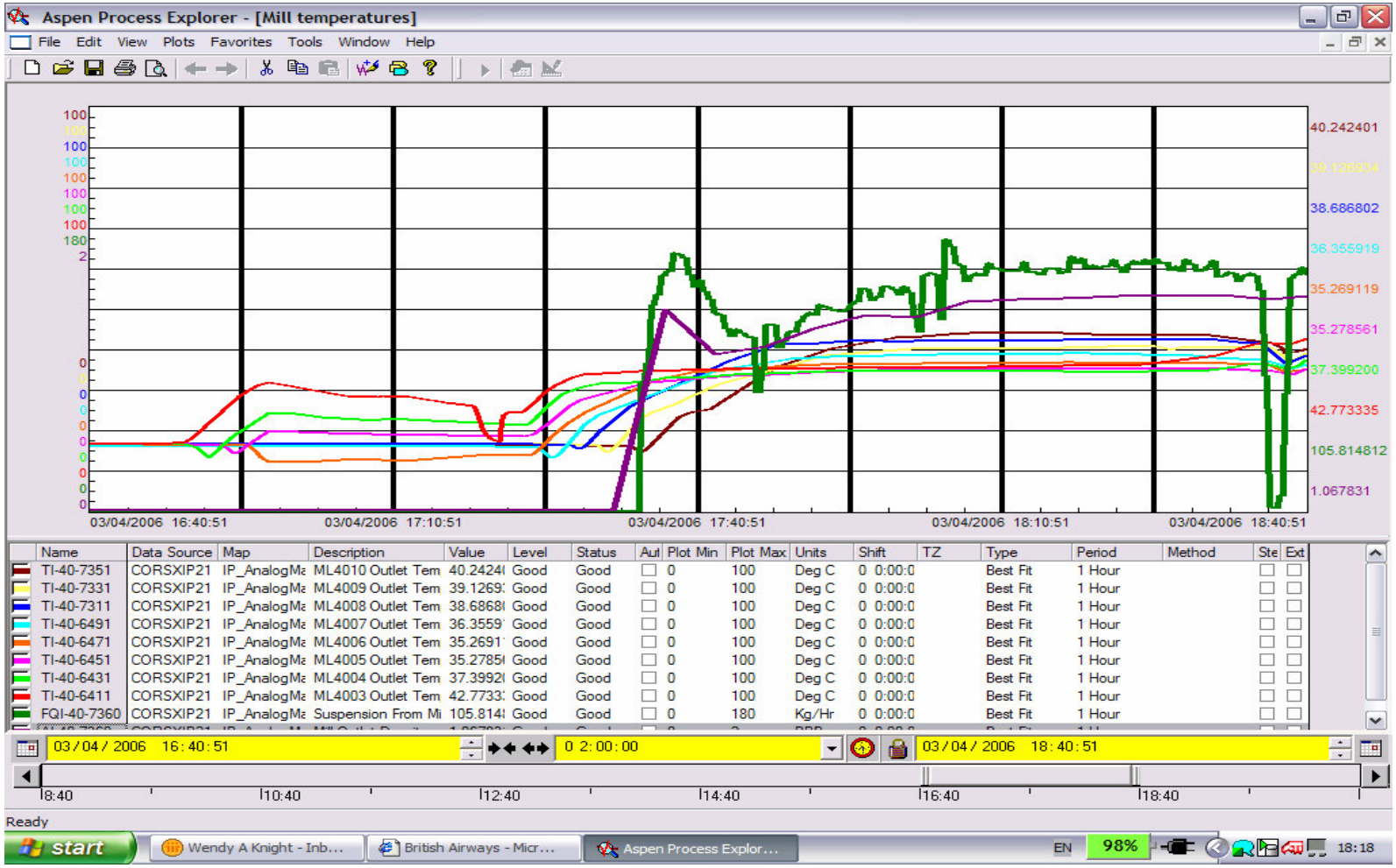
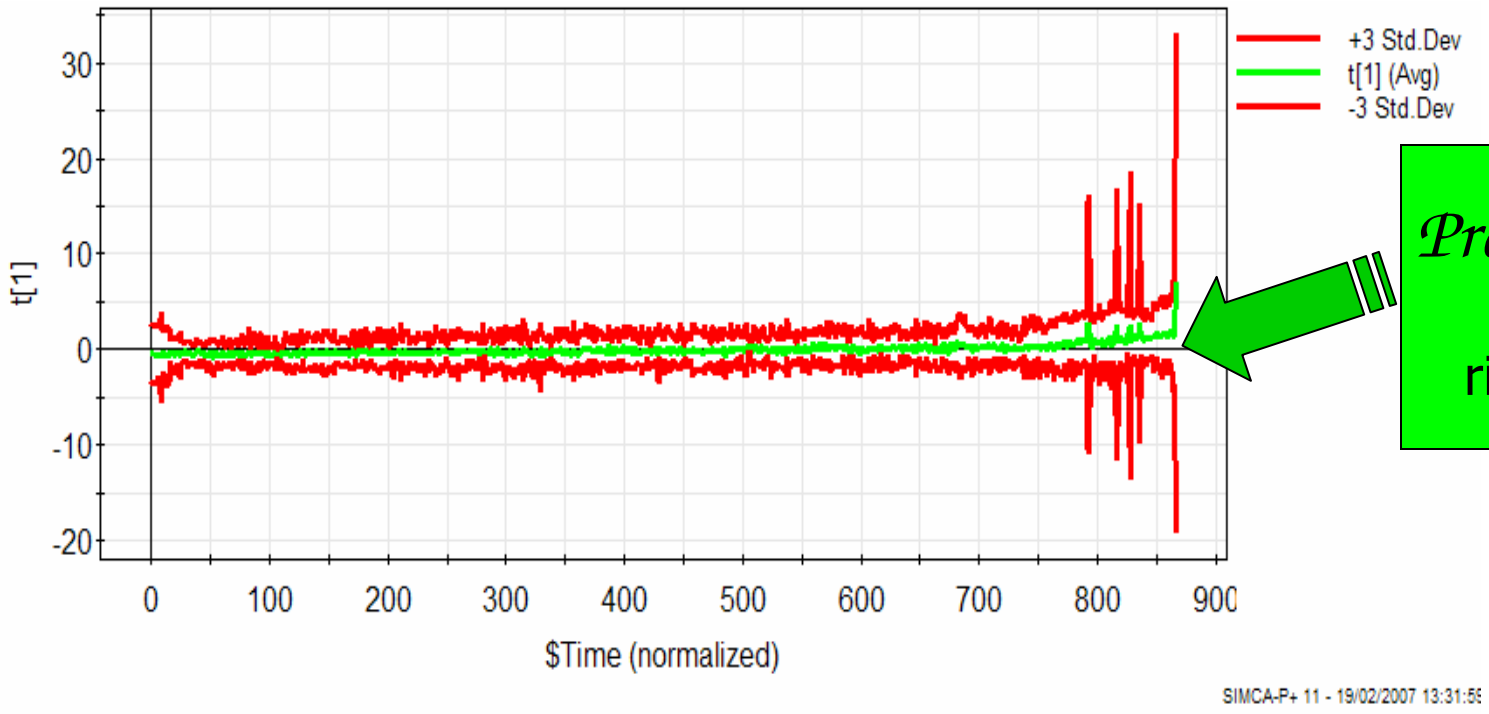
Multivariate control chart for mill 1



Process control: move from univariant monitoring e.g. mill temperature



To … a risk based assessment utilising an established Multivariate *process signature*



Process signature
"in control,
risk dissipated"

(e) Challenges for formulation and development in respect of specific routes of administration

Challenges for formulation and development in respect of specific routes of administration

- ALL DOSAGE forms:
  - setting a particle size specification
  - mean, x10, x50 / x90 (volume distributions)?
  - a special aspect e.g. span or x70?
  - use the whole distribution?

Challenges for formulation and development in respect of specific routes of administration

- Oral
  - Restricted list of acceptable excipients
  - For aqueous based manufacturing processes: microbiological shelf life
  - Recovery of ‘nanoparticles’ from solid dose forms – drug product intermediates or drug products
  - Titration of drug substance particle size verses biological effect – “how small should we go to?”
    - ✓ Run biostudy prior to Phase III clinical studies
    - ✓ Ensure size distributions do not overlap
  - Consider fate of drug nanoparticles – will unusual absorption mechanisms occur?

Challenges for formulation and development in respect of specific routes of administration

- Parenteral
  - More restricted list of acceptable excipients
  - Selection of sterilisation method; validation of sterilisation method
  - Optimisation of manufacturing process to achieve sub 220 nm drug substance particle size

- Respiratory
  - Highly restricted list of acceptable excipients
  - Novel area of investigation, new platform of analytical methodology required to establish specifications

Finally ….

- Another areas to consider outside the scope of this session
  - **Ethics**

Ethical & public engagement considerations

- Several codes of ethics for nanotechnology
  - European commission code of conduct for responsible research http://www.cordis.europa.eu/search/index.cfm?fuseaction=news.document&N_RCN=29114
  - Responsible Nanocode http://www.nanotechia.org/content/activities2/responsible-nano-code/

- Depiction of nanotechnology: “high tech” or consumer friendly? Labelling of nano products?

✓ Need engagement with public as well as NGOs, governments and regulatory agencies

Try this: http://www.nanoandme.org/home/

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Any questions?