High Precision Dosing

Biocorp's experience

PDA Pre Conference Workshop

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BIOCORP

A new need from High Precision Dosing

- Research on pediatric population and enrollment of children in clinical trials received a boost from 2012:
  - The Pediatric Research Equity Act (PREA) : each new drug should carry a pediatric study plan
  - Best Pharmaceutical for Children Act (BPCA) : 6 months of marketing pediatric exclusivity
- Children have to deal themselves with self injection, some of them quite early in their life (GH …)
- Would it be possible for pharma to consider the same concentration of a drug and have a delivery device able to inject very small volumes?

A new need from High Precision Dosing

- Move towards highly concentrated drugs
  - Viscous drugs
  - Large Volume
  - And/or high precision
- Situation can be found in the Insulin business, biologics in general

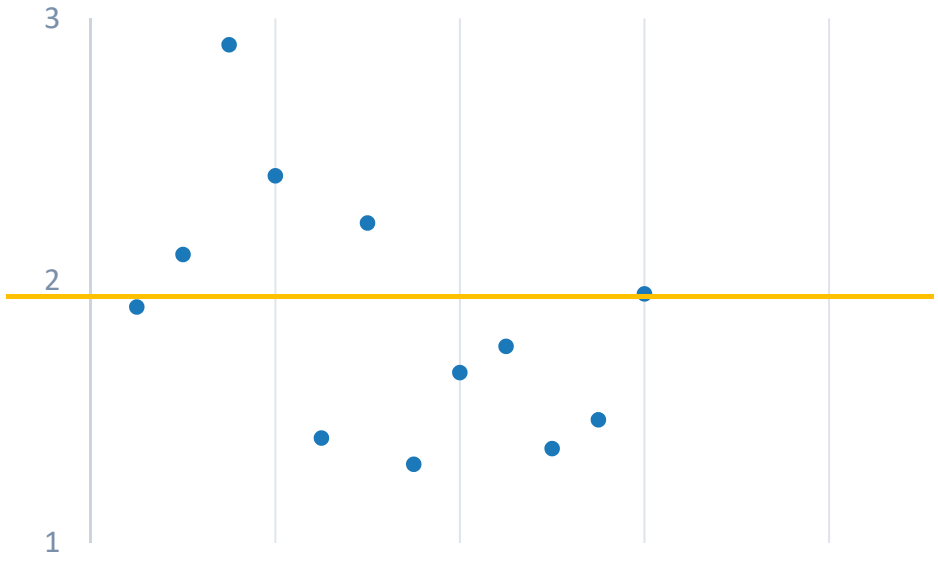
A new need from High Precision Dosing

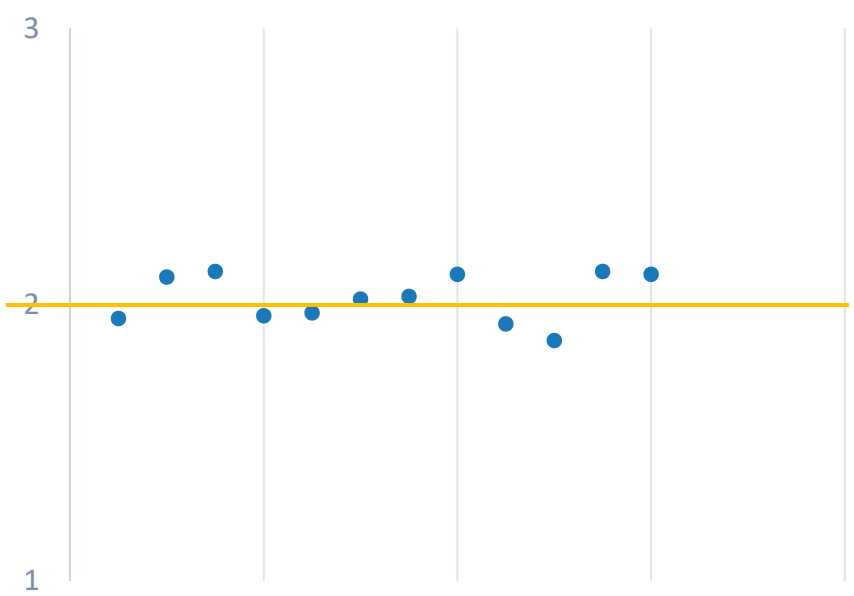
"The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection" July 2nd 2015

Medications	Priority	Main reasons
Trastuzumab	SC > IV	Higher patient preference in addition to comparable efficacy and safety profile[10–12]
Rituximab	SC > IV	Reduced active health care professional time, declined total mean staff costs, as well as reduced patient time in the treatment room[15]
Anti-TNF medications	SC > IV	Higher patient preference (SC anti-TNF agents versus IV anti-TNF agents) and superior efficacy (SC golimumab versus IV golimumab)[17–19]
Bortezomib	SC > IV	Lower incidence of neuropathy in the treatment of multiple myeloma, more time efficient for the patient and institution, and higher patient preference[20,22]
Amifostine	SC > IV	Significantly lower acute toxicity (hypotension, skin rash, and local pain)[27–29]
rhGM-CSF	SC > IV	IV dose of rhGM-CSF was less potent at inducing a leukocytosis than equivalent SC doses and was associated with a higher incidence of generalized rash and first-dose reactions[30,31]
G-CSF	SC > IV	Shorter time to neutropenia resolution and lower dose in alleviating neutropenia with SC G-CSF compared with IV G-CSF[32,33]
Recombinant human interleukin-2	SC > IV	More patients with metastatic renal cell carcinoma experience stable disease, and fewer patients undergo disease progression and lower clinical and hematologic toxicity[35,36]
Immunoglobulin	SC > IV	Pharmacoeconomic advantages[37–40]
Epoetin alfa	SC > IV	Substantially reduced costs of epoetin due to dose saving in hemodialysis patients[48,50–54]
Heparin	SC > IV	Significantly less discomfort at the injection site, better mobility and patients' overall preference, and more cost-effectiveness compared with IV heparin therapy[55,56]
Opioids	SC > IV	Regarding major adverse events, adjusted odds ratio (95% confidence intervals) in IV and SC group relative to the oral group was 6.10 (4.43–8.39) and 2.07 (1.48–2.89), respectively

- SC > IV as a preferred route of drug delivery in a vast majority of cases
- Injections or conversion from IV drugs often administered on a volume per kg basis can be a challenge

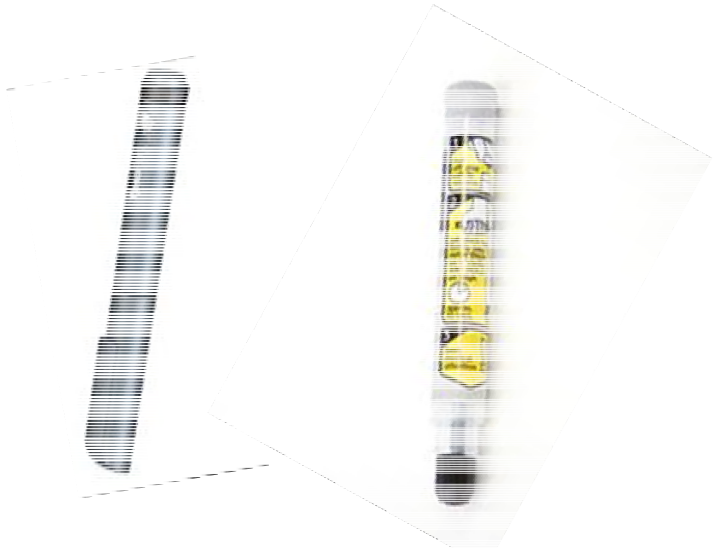
Repeatability in small dose delivery is the challenge





- Repeatability is the biggest challenge to meet with small dose delivery
- Accuracy level expected is most often overpassing ISO standards (ISO 11608 for pen injectors for instance)

A wide range of containers exist for SC injections



- Dealing with several type of primary containers
  - Cartridges – 2mL, 3mL, Dual Chamber …
  - Syringes – 1mL long, 2,25mL
  - Specific drug container

- High precision dosing is highy related to the choice of this primary container
  - Tolerances of the container
  - Filling process
  - Standardisation of the process – on demand filling process or high volume/standard processes

Focus on pen injectors

Three parameters need to be under control

Primary Container

- Glass containers have – by manufacturing nature large tolerances
- Plastic containers offer a better repeteability over different batches and time
- Plungers are impacting breaking forces and gliding forces = need to characterize potential dispersions

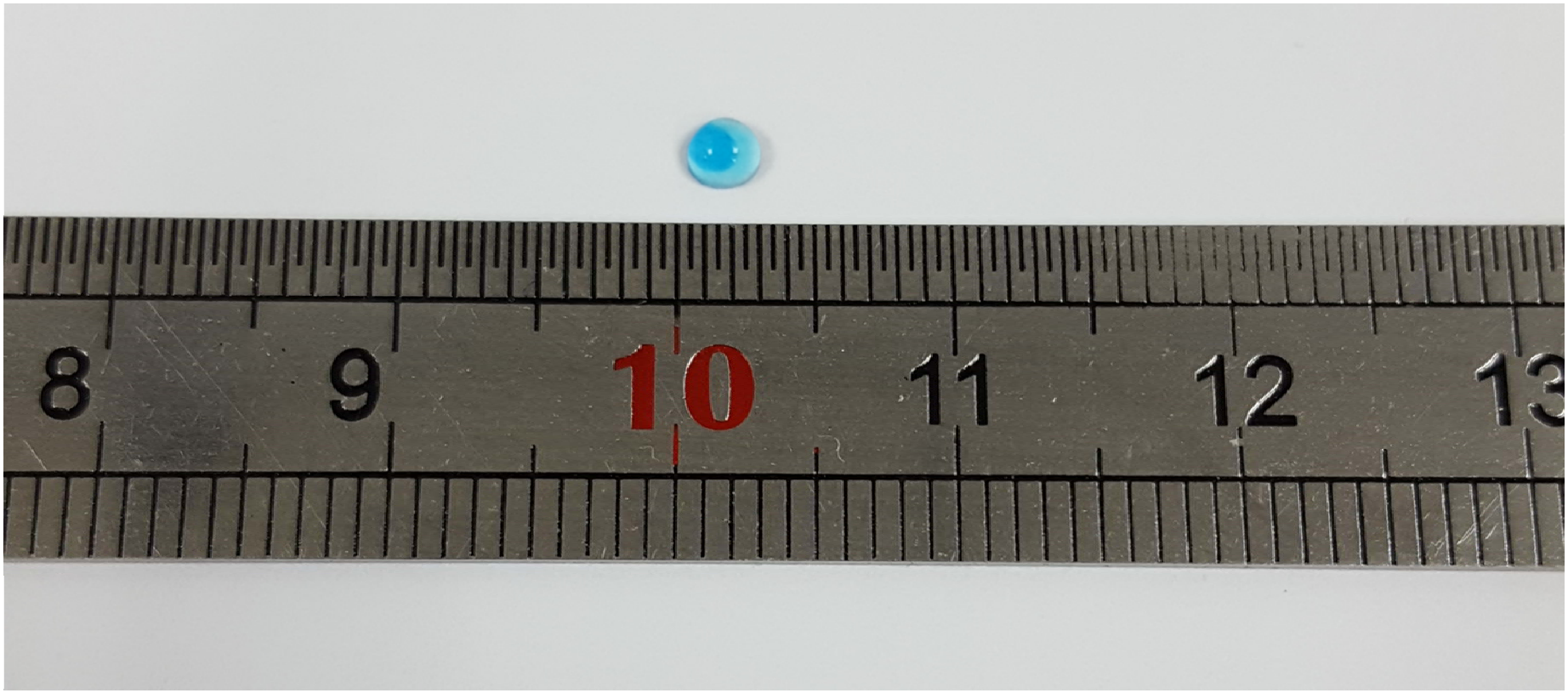
Design Robustness

- Accuracy is highly linked with the design of the device
- Optimization of friction level
- Robusteness on large scale production – variability of the pieces

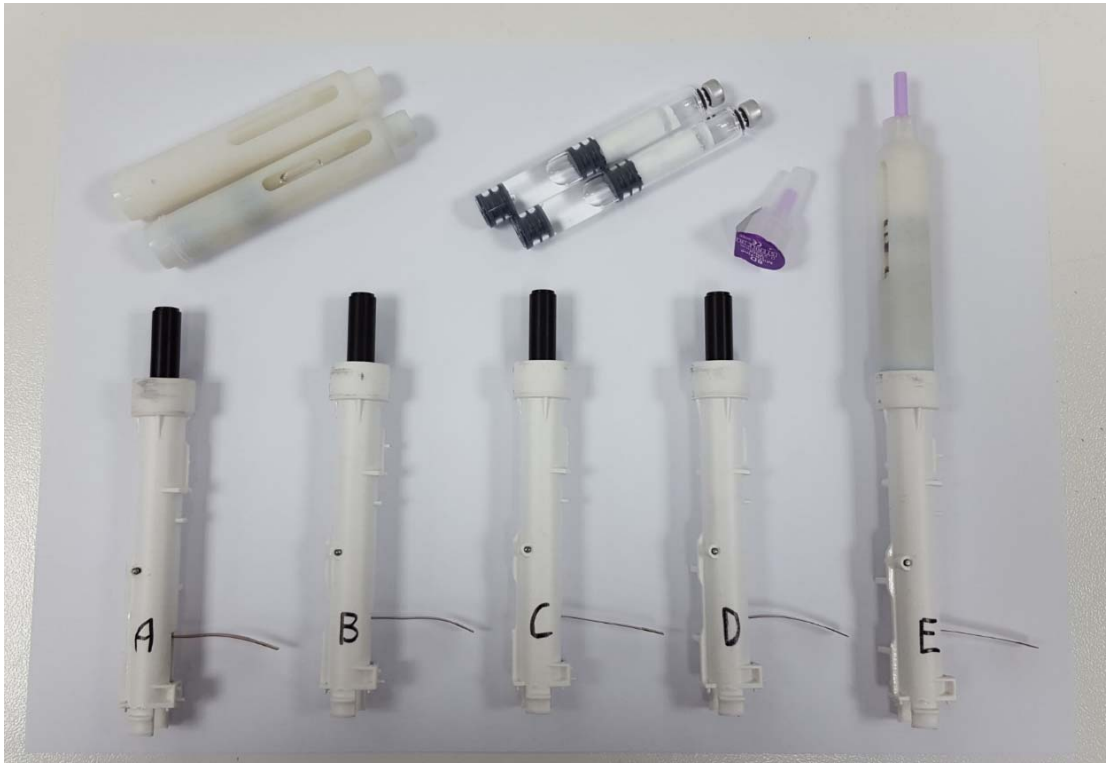
Patient Use

- If small dose accuracy is the objective, patients can directly impact the overall accuracy of the device with :
  - Force required to inject – and applied to a piston
  - Priming and impact of a needle empty or not
  - Time after injection and release of the plunger

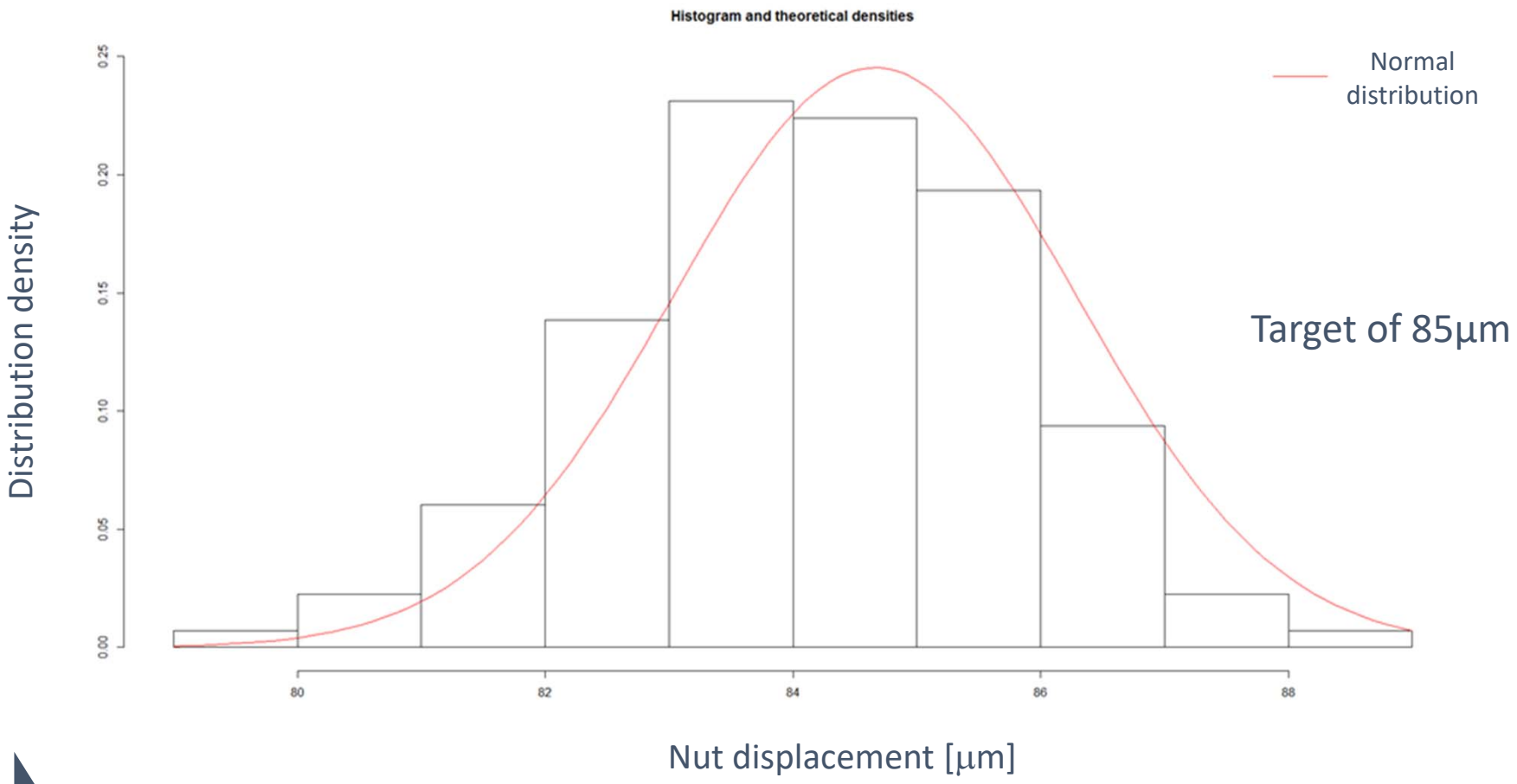
Case – Injection of 5µL



Material – Motor Driven Pen Injector



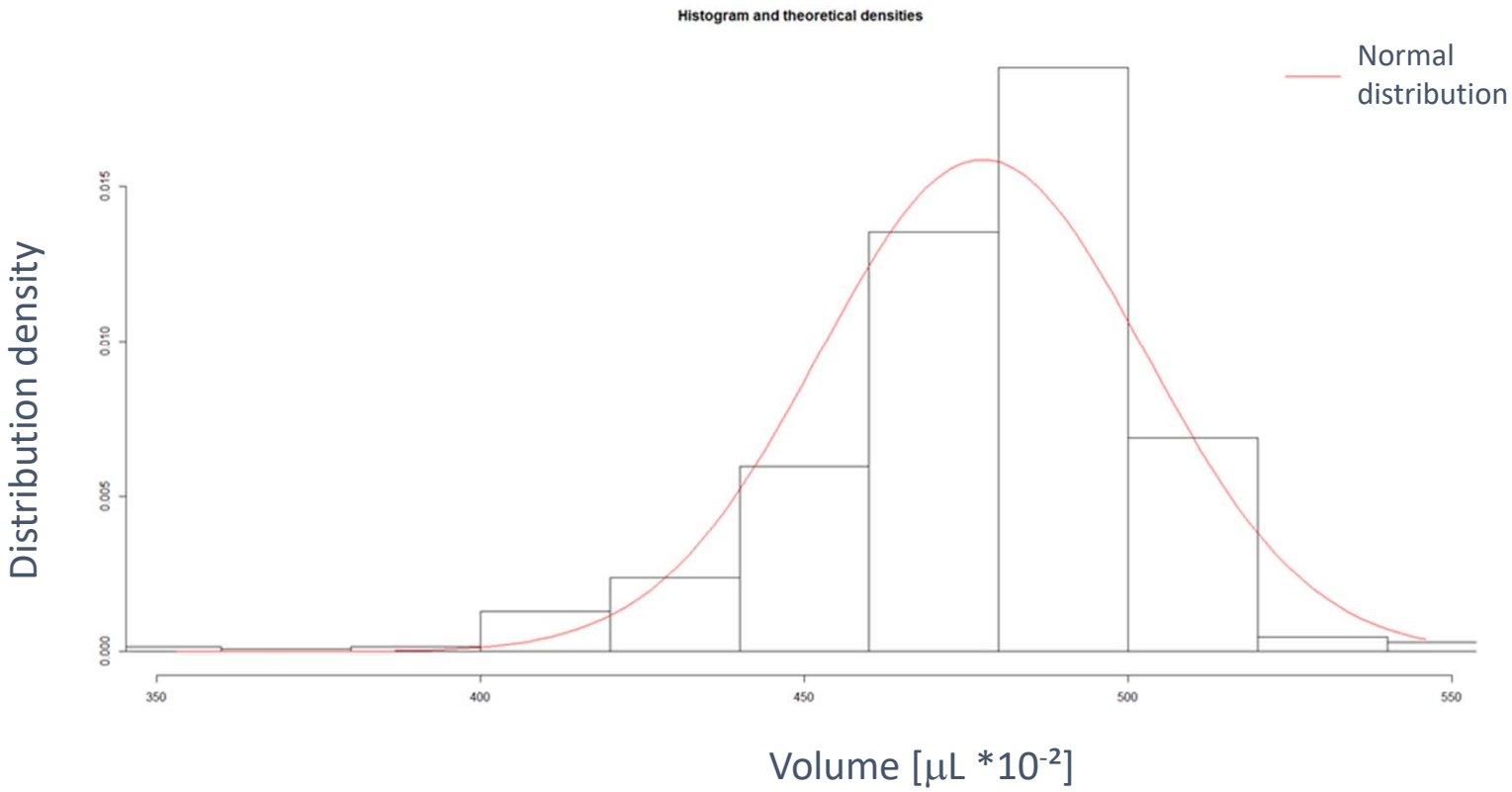
First test : Measurement of a nut displacement



Target of 85µm

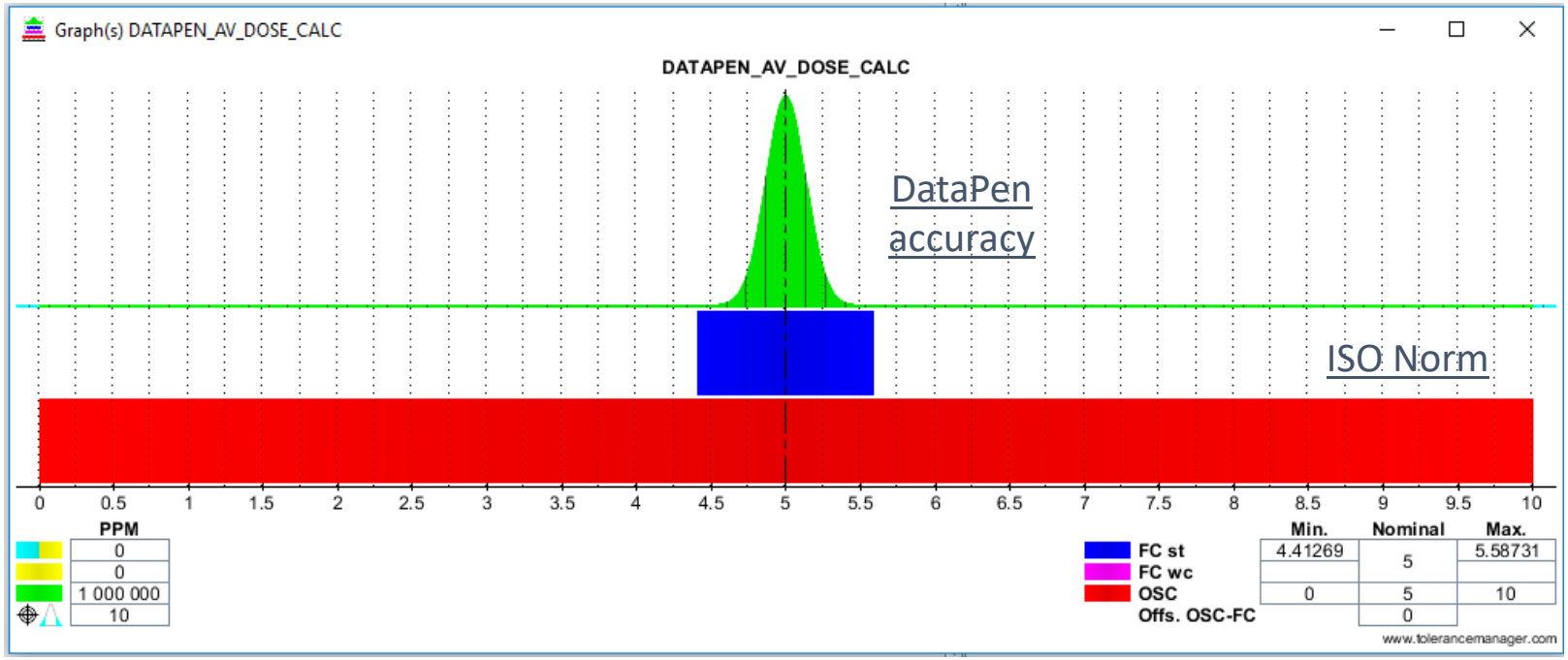
Repeatable and Accurate nut displacements : σ = 1,63 µm [Target : 85 µm]

Second test : Volume measurement



The dose injected would have an IT tolerance of [4,40µL – 5,59µL] – a= 95% P = 97,5%
[Target : 5 µL]

Accuracy vs ISO 11608



Conclusion

- Small volumes injections remain a very complex challenge
- Demand driven by peadiatric indications or highly concentrated biologics drugs with volume to weight related dose
- The patients, its injection device and environnement can impact the delivered dose
- Motor Driven pen injectors in this context reveal to be a very suitable solution
  - Accuracy and Repeatability are met
  - Reduction of patient impact during selection and injection of doses
  - Can go over the ISO 11608 requirements