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Applying modern technologies on well-established APIs

SEQENS Paracetamol reshoring project

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Paracetamol – A case study of mature molecule value chain

- Paracetamol global need **approximate 200 000 Tons per annum**, with slight growth of global consumptions (2-4%)
- Paracetamol based medications are essential worldwide and accessible for only few €uros in Europe
- Over the last decades, **the drug substance production massively shifted towards Asia driven by costs:**
  - Costs of production: labor, energy, safety, environmental and regulatory requirements
  - Costs of investment: equipment, labor and environmental and regulatory constraints & leadtime

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SEQENS engaged new paracetamol production project in France

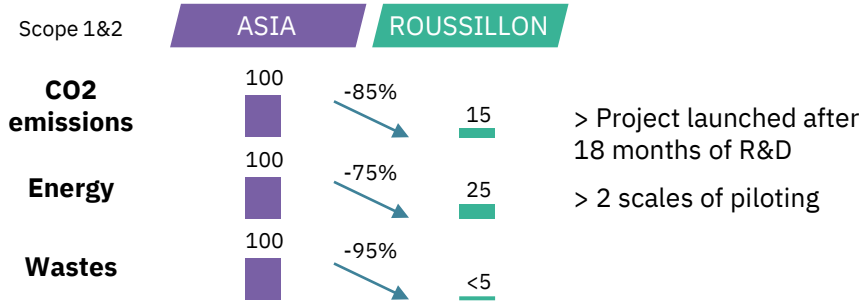
Project key figures:

- **15 000 Tons capacity**, equivalent to **half of European needs**
- Construction started beginning 2023, **commercial launch planned end 2026**
- **€120m investment** with c. 30% support of France 2030 program

Two enablers

INNOVATION

- To close competitive gap between EU & Asia
- To anticipate increasing environmental costs



> Project launched after 18 months of R&D

> 2 scales of piloting

CUSTOMERS

- Shared industrial risks supporting costs of investment and commitments on volumes over the long-term

Opella. UPSA

Improvements must be cumulated on all technical aspects to deliver required competitiveness

Industrial challenges are multiple, even for a well-known simple molecule

CHEMICAL ENGINEERING

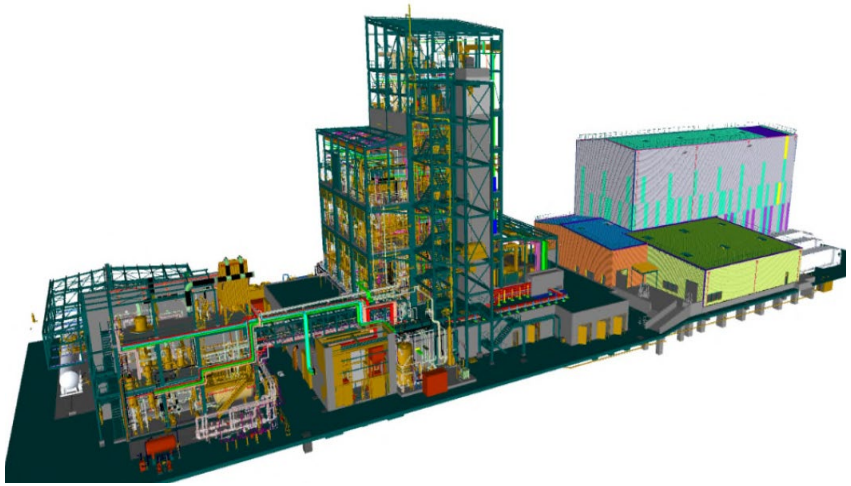
Switch from batch to continuous process:

- Wastes & impurities avoidance
- Energy savings
- Solvent recovery

AUTOMATION

- Numerically controlled process
- Automated packing & finished goods handling
- High bay storage

> Increasing process control and saving costs

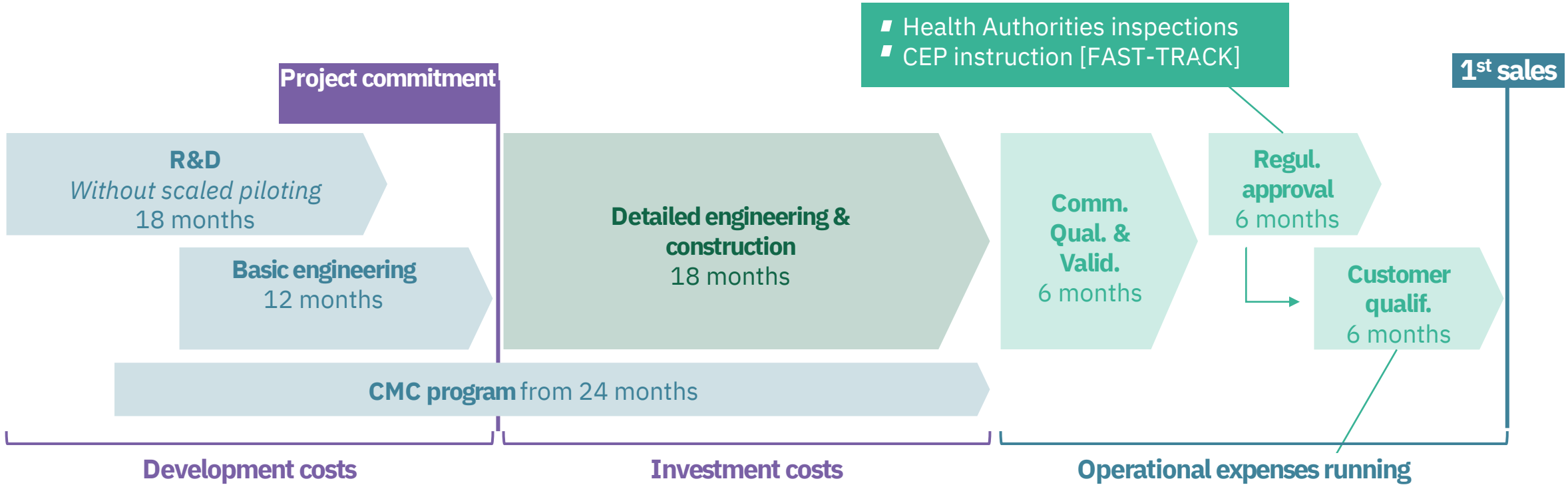


PROCESS & ANALYTICAL DEVELOPMENT

- Quality by design, leveraging data from early dev. & piloting to fasten industrial startup
- Improved analytical methods taking legacy into account

Necessary planning for an innovative new unit project: from 36 to 15 months

Assuming regulatory fast track & high customers expectations > **~15 months** from project execution success



Stakes:

- **Shorten the non-productive time**
- **Support ramp-up worldwide**

- Resources engaged before CEP issuance & stability results [FAST TRACK]
- Production site audit

Regulation discrepancies have an operational impact

Example 1: Monographs

Ph. Eur. Monograph Assay Method
Titrimetry, based on visual identification of the equivalent point
Ph. Eur. specification: **99.0 – 101.0 %**

QA/QC impact

- **Two analysis instead of one**
- **Time consuming:** heating reflux step (1h) + cooling
- **Manual method:** needs continuous presence of technician
- **No automation possible:** visual detection of titration end point
- **Not appropriate to our 24/7 production plan**
- **Additional manpower**
- **Cost of consumables, reagents and destruction**

USP Monograph Assay Method
HPLC with UV detector based on USP method
USP specification: **98.0 – 102.0 %**

Inventory impact

- **Analyze all stock according to all pharmacopeia:** increases lab workload
- **Create different article codes per pharmacopeia:** increases stock level and cost and creates supply chain complexity
- **Harmonize pharmacopeia:** very lengthy process (in progress)
- **Register equivalent method in regulatory dossier:** customers ww who have a spec of 99,0-101,0 with their current supplier are reluctant to file a variation with enlarged spec

Regulation discrepancies have an operational impact

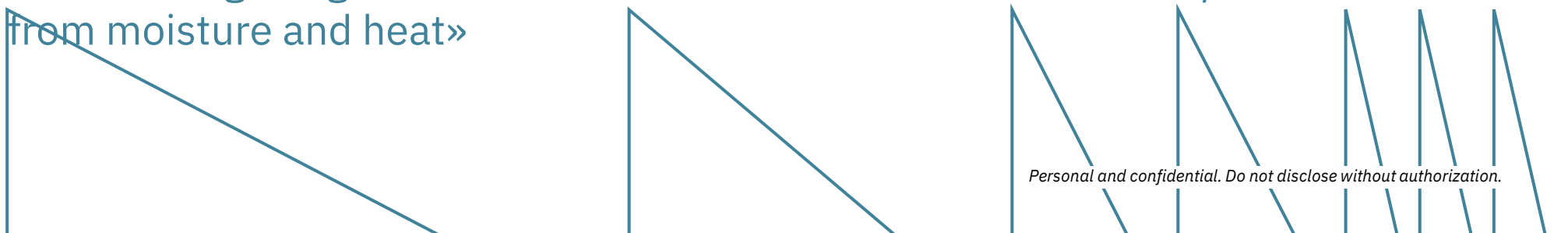
Example 2: REACH/CLP/labels

- Manufacture of PAP in Europe triggers the need to register higher tonnage band for **REACH registration of PAP** > cost impact for EU production only
- **Safety labels and safety data sheets** of the product are different in each country (language/pictograms/safety sentences) subject to EU inspections

  > Not authorized by law to have contradictory information on the label
  > Local language should be used but not known upon packaging operation
  > Having multiple language on the same label would trigger creation of a « leaflet label »

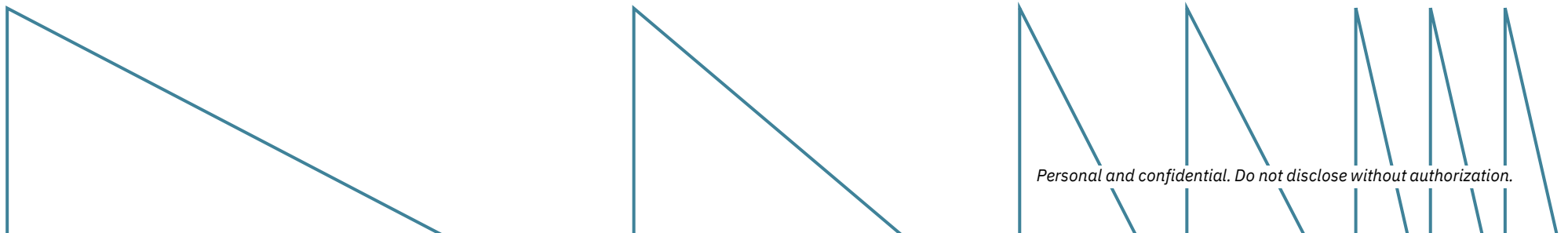
- **Pharma labeling requirements** are not harmonized

  > **Ph. Eur.** « *protected from light* »
  > **EMA** Stable in long term and accelerated : « *labelling requirement : none* »
  > **WHO** Stable in long term and accelerated : « *Do not store above 25 °C* »
  > **USP** « Preserve in tight, light-resistant containers, and store at *room temperature*. Protect from moisture and heat»



Old registration versus 2025 registration

OLD DOSSIER	NEW DOSSIER	CONSEQUENCES
1 synthesis step	2 synthesis step	Higher RSM production costs
N/A	ICH Q3D	Regular analysis and costs
Not existing	Nitrosamines	
N/A	ICH M7	Expected flexibility in the lifecycle
Not existing	QBD	
Not existing	Q13	



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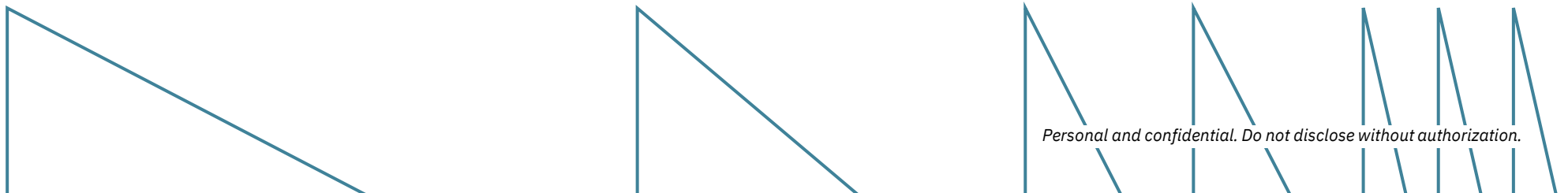
Support of authorities is key to accelerate time to market

- Regular meetings with **EDQM to tackle questions** on content of the dossier and discuss **fast track approval**
- Proactive discussion with **ANSM** to anticipate inspection
- **Customer ww requests** are very different to support a variation

> GMP certificate with legalization
> All regulatory statements (TSE/BSE, GMP, Q3C, Q3D, nitrosamines, latex, melamine…)
> Other certificates: Kosher, Halal
> Samples from consecutive or non consecutive batches
> COA
> One DMF per region
> Customer audit
> Batch records
> Examples of labels
> GMP equivalence or inspection triggered – hard to leverage non EU inspections



Continuous process drives innovative thinking

- **ICH Q13 is a helpful guideline** but deserves detailed workshops for practical implementation
- **Definition of a batch in continuous process and** define management of non-conforming product at several steps without compromising the continuity of operations or the traceability.

  Less flexibility for reprocessing of NCF intermediate
- Continuous process deserves **specific technologies non-traditional in batch production**
- **One batch is 15 tons,** which deserves careful management of release
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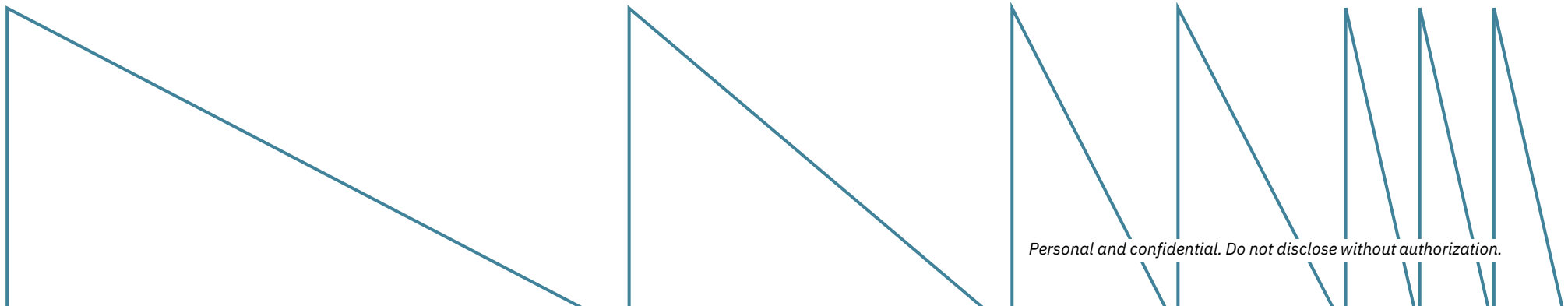
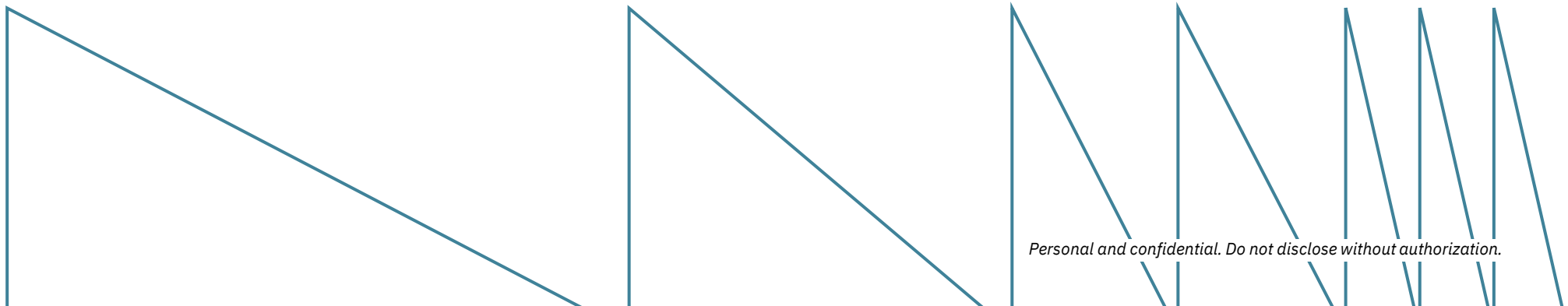


Key take-aways of such a project

- Certification process preparation to deliver **fast-track** = time & energy
- **Regional authorities' specificities** driving cost per unit and regulatory costs > harmonization is key
- **RSM requirements** limiting potential of new supply chain -> so far one source is officially available
- The **operating and environmental permitting process** is very similar to the Pharma/GMP/regulatory process > combined constraints entrepreneurship



Conclusions

- A **collaborative work** between customers, public authorities and the producer is **crucial** to make the project happen
- A reshoring project in EU in 2025 needs to be focused on **efficiency and sustainability** to remain cost competitive versus Asian competitors over the long-term
- Seqens is proud to be part of such a project to provide EU with local, sustainable and competitive production and **support EU health sovereignty**

THANK YOU

QUESTIONS ?