



Breaking the Traditional CMC Development Pathway

2nd Cell & Gene Therapy
Products Symposium
Bethesda, MD

Alexandra Beumer Sassi, PhD, RAC

www.voisinconsulting.com

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Outline

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- Accelerated development - Regulatory pathways
- CMC development roadmaps traditional versus accelerated
- Specific CMC Challenges
- Possible strategies/mitigation plans to consider
- Take Home messages

Expedited access: Designations and Regulatory



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Fast Track (1997)	Break Through Designation (2012)	RMAT Designation (2018)	Priority Review	Accelerated Approval
<ul style="list-style-type: none">• Serious Condition• Preliminary non clinical and clinical show potential to address unmet medical need• FDA interactions• Rolling Submission and Review• Eligibility for Priority Review	<ul style="list-style-type: none">• Serious Condition• Preliminary clinical evidence• Substantial improvement on clinically significant endpoints over available therapies• All Fast Track advantages + timely and interactive communication with FDA during development• 282 BTP granted as of Nov 2018 (757 requests)	<ul style="list-style-type: none">• Regenerative Medicine• Preliminary clinical evidence show potential to address unmet medical need• Treat, modify, reverse or cure Serious Condition• All advantages from Fast Track and BTD, inc early interactions (surrogates discussed)• 26 products granted as of Nov 2018 (79 requests)	<ul style="list-style-type: none">• Serious condition• Significant improvement: <i>(evidence of increased effectiveness, elimination or reduction of a treatment-limiting drug reaction, evidence of safety + effectiveness in a new subpopulation)</i>• Reduced NDA/BLA review time from 10 month to 6 month	<ul style="list-style-type: none">• Serious condition• Approval possible on surrogate endpoint

Expedited access: Designations and Regulatory Procedures - EU



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PRIME Scheme

- Unmet medical need
- Major therapeutic advantage to patients
- Support **early** development
- Reinforced Agency support throughout development.
- Improve use of Regulatory and procedural tools
- **Multidisciplinary**
- **SA free of charges**
- **Enable accelerated assessment for MA**
- 46 granted, 150 denied (20 ATMP, 10 Biologics)

Accelerated Assessment

- Product is of major interest for public health and therapeutic innovation
- 150 evaluation days of MAA, rather than 210

Adaptive Pathways

- High Medical need
- Iterative development
- Approval in stages (from restricted patient population to wider pop)
- Approval based on early surrogates to be confirmed by real life data

Conditional MA

- Approval of a medicine that address **unmet medical needs** with **less comprehensive clinical data** than normally required
- Benefit of immediate availability >> risks of having less data
- Applicant should be able to provide the comprehensive clinical data in the future.

Accelerated approval in emerging markets

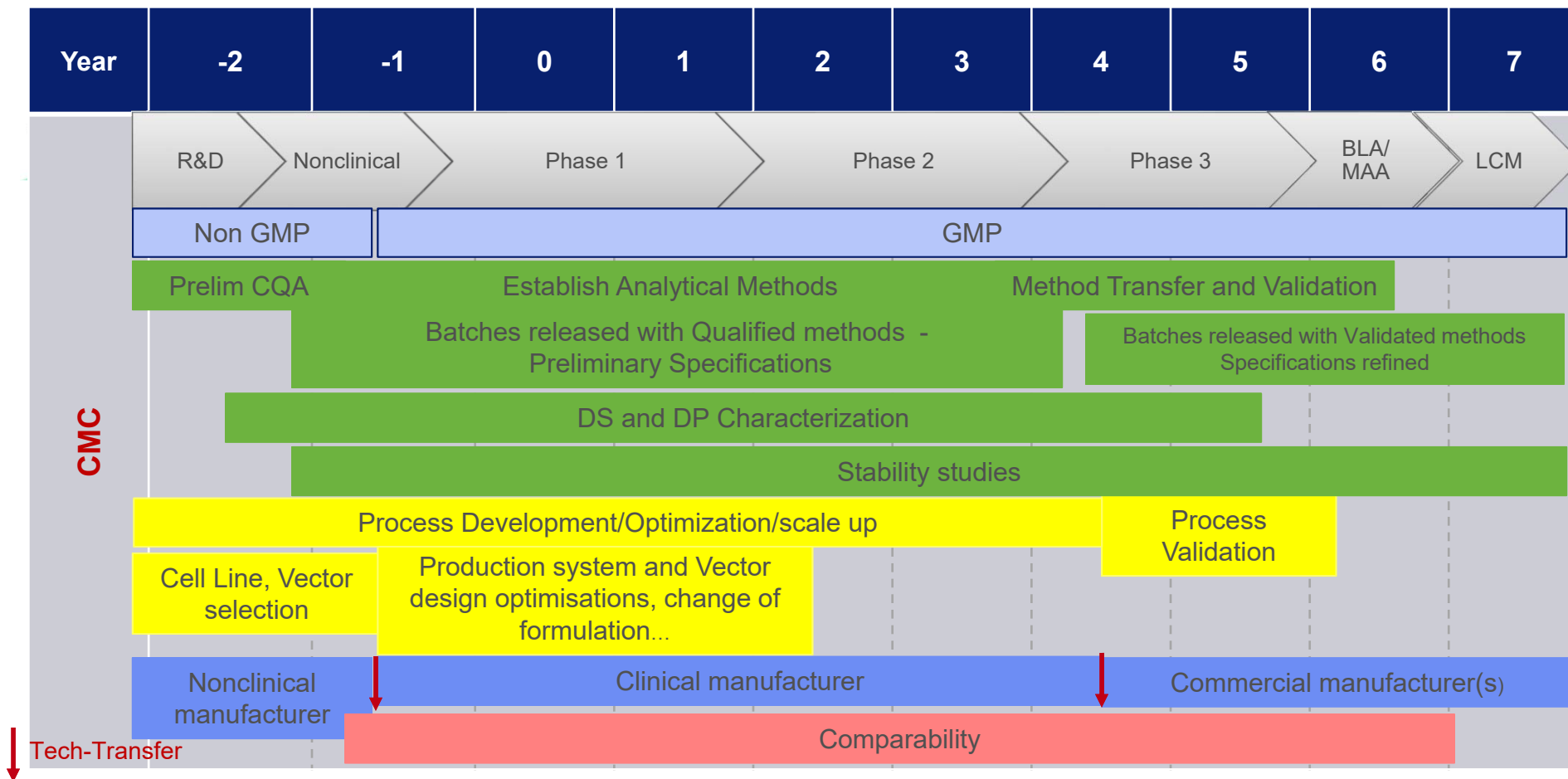
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- **Expedited review:**
 - Regulatory authorities speed up the review of certain products to enable faster approval: *Brazil, China, Egypt, Saudi Arabia, Singapore, Indonesia, South Korea, and Israel.*
- **Expedited submission (rolling submissions):**
 - Information and data-packages can be submitted and reviewed as they become available: *South Korea.*
- **Expedited development:**
 - Earlier submission and approval with a data set which may be less complete than from a standard development program (e.g., surrogate endpoints, phase 2 data only): *Brazil, South Korea, and Taiwan.*

CMC Traditional Development Roadmap/ Timelines


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Accelerated Development – Impact on CMC

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- Full regulatory compliance required
 - No specific CMC guidances available
 - Still addressed on a case by case basis
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- EMA Workshop on quality support to early access approaches (PRIME & Breakthrough) - November 26th 2018:
 - FDA/EMA/Industry discussion on CMC challenges
 - Possible solutions proposed – More flexibility
 - Presentations available on [EMA website](#)
 - May lead to new CMC dedicated Guidelines in support to accelerated development

Accelerated Development – CMC challenges

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- Overall, accelerated pathways **condenses CMC development occurring usually during Phase III**
- Limited Manufacturing experience → **Often still in a Clinical set-up at the time of BLA/MAA**
- Limited room for optimizations of Product and Process over development → **Suboptimal process at time of BLA/MAA**
- Reduced time for characterization → **difficulties to establish meaningful specifications**
- Reduced availability of data** → Method and Process Validation, long term stability not as complete by time of BLA/ MAA

How to keep the pace?

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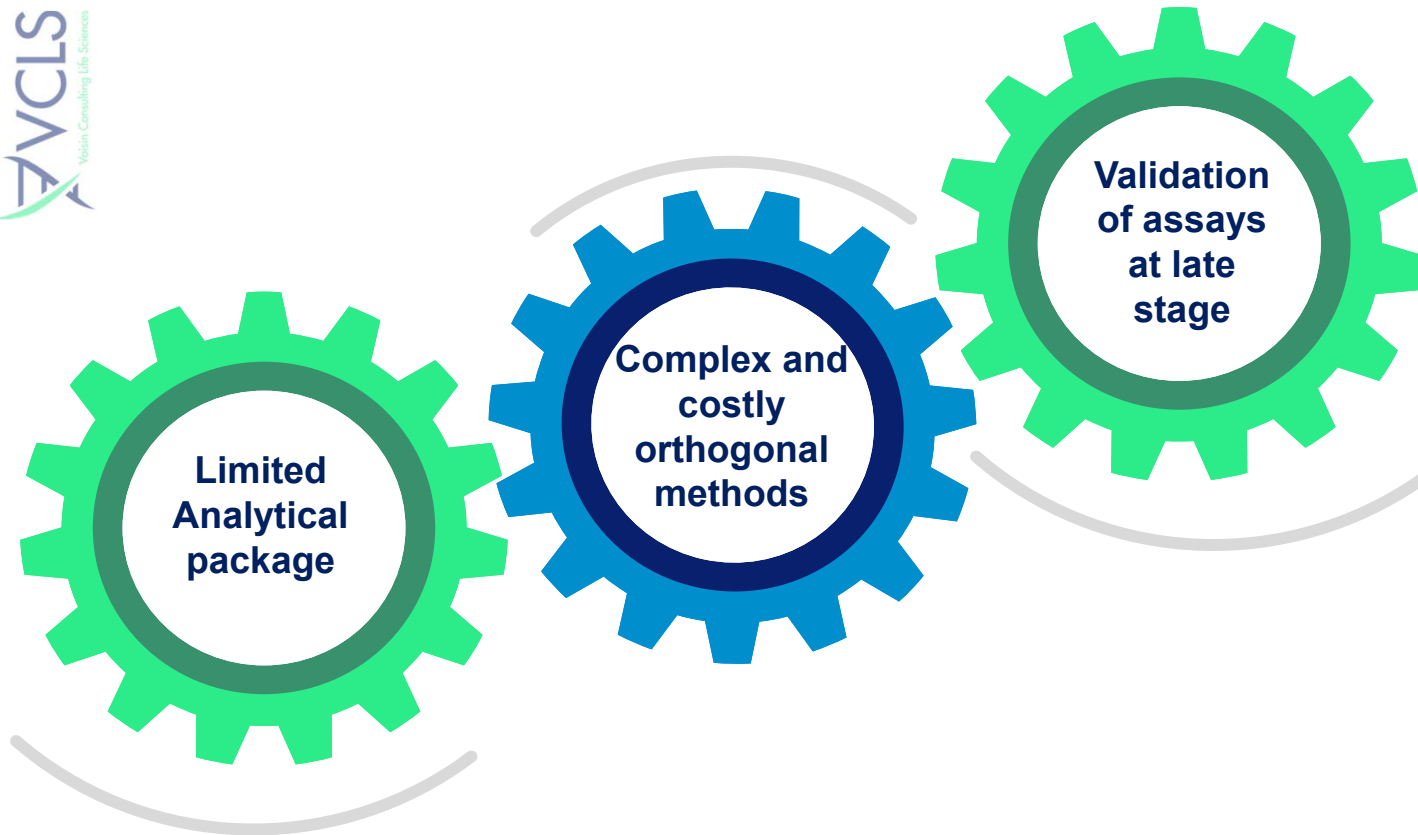
*“Flexibility can be considered in terms of WHEN
the quality data comes in and not IF”*

- Capitalize on **existing strategies** established for small molecule and translate to biologics (validation data)
- Use **prior knowledge**. Capitalize on **development** and **pilot scale**
 - Make use of the Risk-Based Approach (**RBA**) to identify risks,
 - Adjust CMC development plan accordingly
 - Define priorities and include articulated mitigation plan
 - Justify lack of data at time of filing
 - Product Life Cycle Management Planning



CMC Challenge: Analytical Development

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- **Issues on data interpretation**
- **Setting specifications**
- **Establishing comparability**

CMC Challenge: Analytical Development

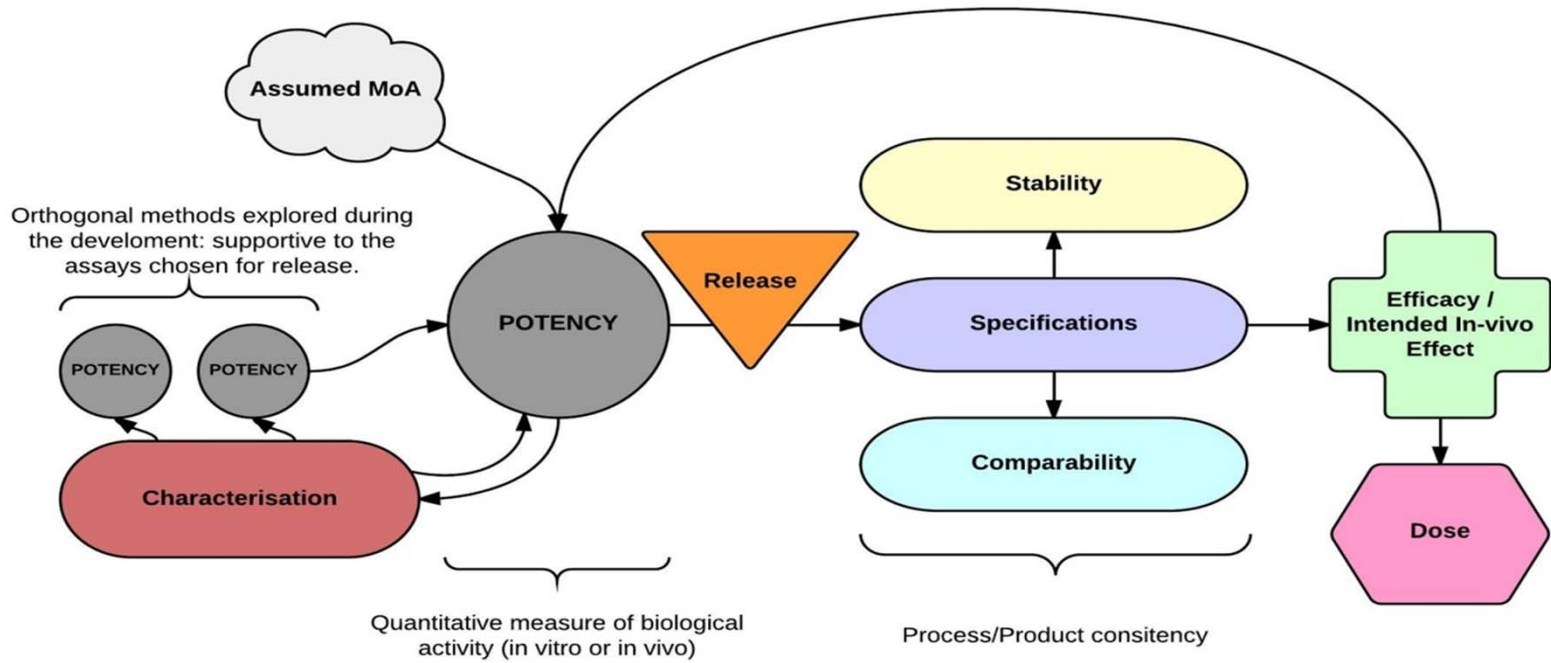
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- ➔ Consider development of relevant assays earlier.
- ➔ Avoid major changes in analytics in order to build a solid analytical history file from early stage forward.
- ➔ Consider moving assay qualification/validation sooner in development to strengthen analytical package

Analytical Development Challenges - Potency

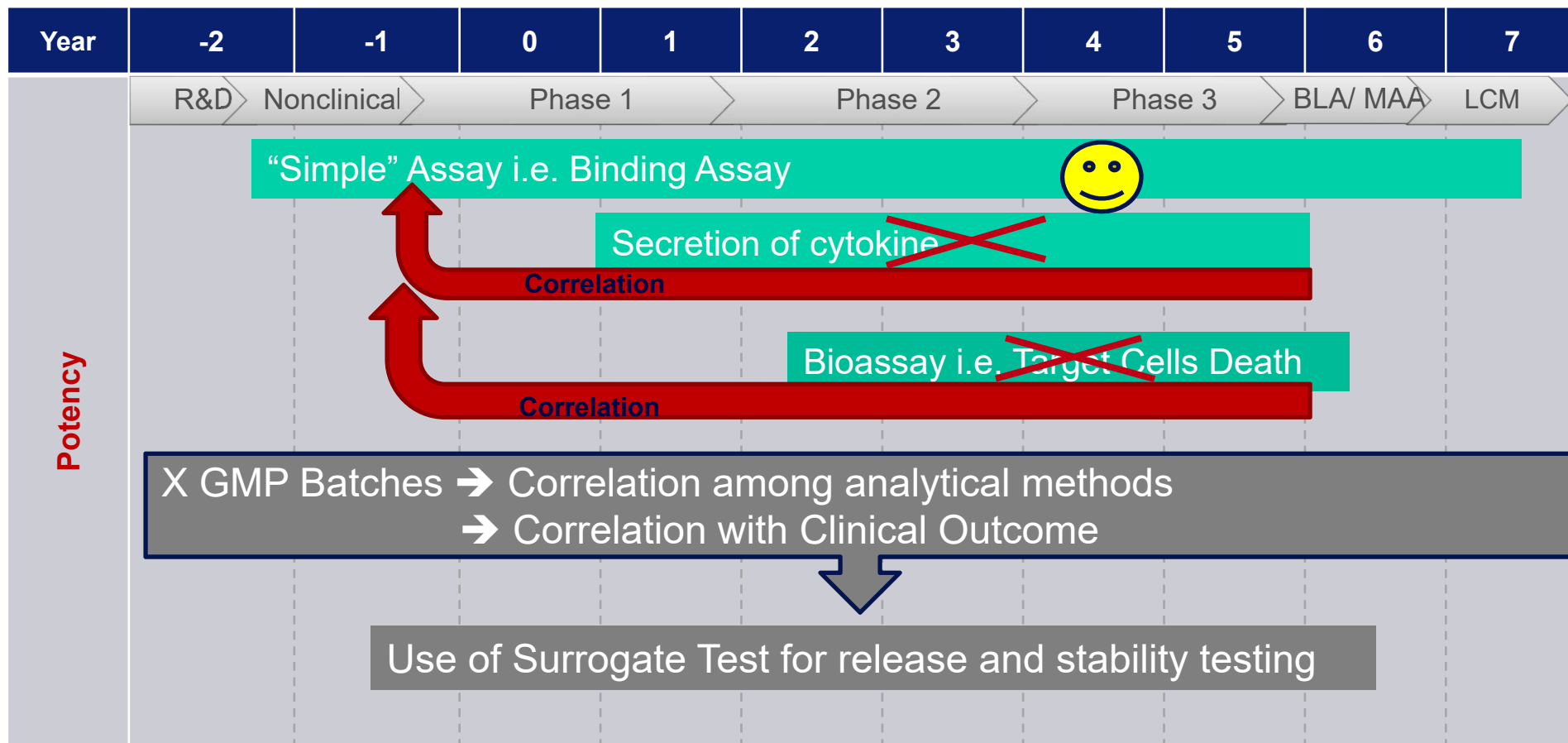
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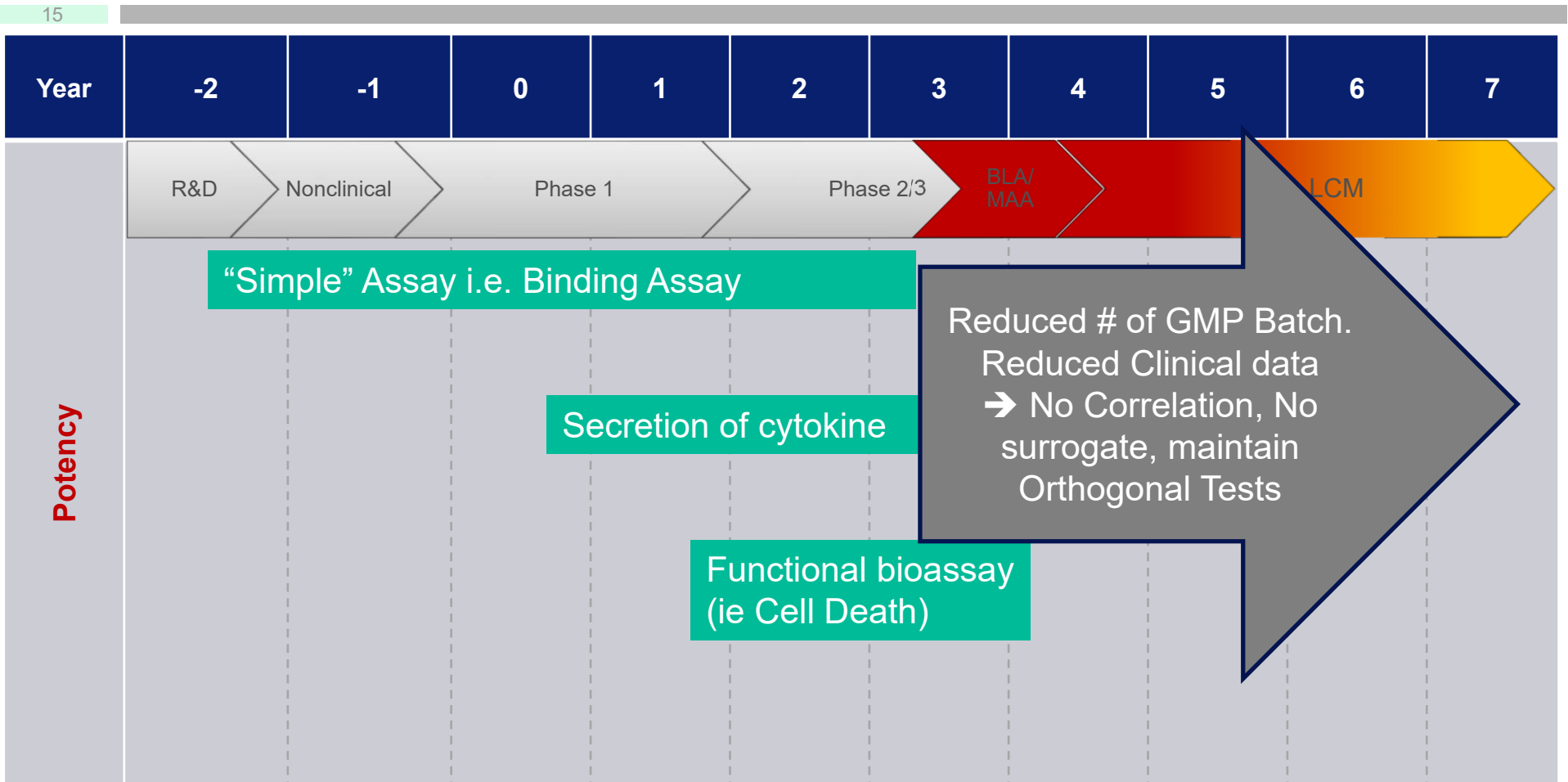
The Challenges of Potency Assay Development for Cell-based Medicinal Products in Europe – Regulatory Rapporteur
Pimpaneau, Gianelli, Dupraz, Trouvin – May 2015

Potency Assay Development Roadmap – Traditional

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CMC Assay Development Roadmap – Accelerated

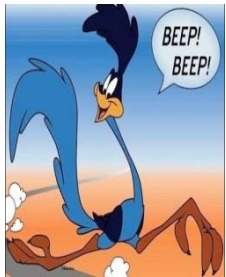


CMC Challenge: Process Validation

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- Complete PV data to be submitted in BLA/MAA (requirement for Biologics)
 - ➔ Challenge with accelerated development
- Move toward NCE approach for which no PV data from commercial scale needed at time of filing (PV protocol submitted + data available at time of PAI)



- ➔ *Risk assessment of each process steps to adjust Validation Strategy accordingly*
- ➔ *Reinforce with Prior Knowledge, Process Development/Characterization Data*
- ➔ *Propose a hybrid approach with 1 or 2 PV run completed prior approval and complete post approval or concurrent to review*

CMC Challenge: Stability

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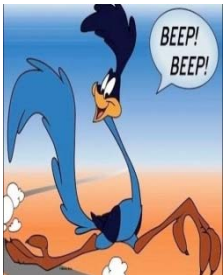


- Only limited number of batches → limited Real Time Data
- For CGTs, calculation of Shelf Life extrapolation is not always welcome

→ *Collect as much supportive data as possible → Stability data obtained from early development batches*

→ *Discuss stability protocol for commercial batches during agency consultations*

→ *Commitments during review and post-approval*



CMC Challenge: Comparability

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- Process changes are inevitable
- Comparability is more frequently required
- The impact of change must be assessed



- ➔ *Reduced comparability ➔ More focused comparability (RBA, tailored to changes)*
- ➔ *Anticipate changes early to build in comparability in tiered approach*
- ➔ *Consider filing with clinical manufacturing site. Introduce the commercial site Post Approval*

CMC Challenges – LCM and Post Approval activities

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- First 2 years post MA are usually extremely busy for Complex Biologics
 - Life Cycle Management planning can reinforce overall strategy
- *Plan in advance any post approval change required to meet BLA/MAA commitments*
- *Start considering parallel complementary process development supporting LCM*
- *Finalize transfer to full commercial manufacture*
- *Consider Post Approval Change Management Protocol (PACMP) in EU and Comparability Protocols in the US*

Zolgensma (onasemnogene abeparvovec-xioi), AveXis, Inc. (Novartis)

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- **BLA Approval:** May 24th, 2019 (8 months review)
- **Indication:** treatment of pediatric patients < 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene.

Post-marketing commitments:

1. AveXis agrees to develop and qualify a suitable method for quantifying (b) (4), providing the method qualification report and providing an additional process validation report for (b) (4).
2. AveXis agrees to validate the robustness of the (b) (4) assay per protocol REC-2566 and will provide the validation report.
3. AveXis agrees to update the (b) (4) assay to include the assay validity criterion for the reference standard and provide the supplemental validation report for robustness.
4. AveXis agrees to revise the Bioburden Determination operating procedure (SOP-085) to be compliant with (b) (4), including (b) (4) on (b) (4). AveXis agrees to implement the revised SOP-085 for all bioburden tests and to provide the revised SOP-085.



Zolgensma clinical impact

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*“A diagnosis of SMA is devastating, leaving untreated babies who have the most severe form with **painfully short, highly medicalized lives**, during which they are unable to lift their heads, sit or roll, have difficulty swallowing and breathing and need 24-hour care”*

*“In the START clinical trial we conducted with Zolgensma, **all children were alive at the conclusion of the study and many were able to sit, roll, crawl, play and some could walk**. This level of efficacy, delivered as a single, one-time therapy, is truly remarkable and provides a level of unprecedented hope for families battling SMA Type 1. We now have data four years out from the trial, and we see the durability of this gene therapy.”*

Jerry Mendell, M.D., PI at the Center for Gene Therapy at The Abigail Wexner Research, Institute of Nationwide Children’s Hospital in Columbus, OH

Take Home Messages

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- Accelerated developments, imply shorter timelines for eligible products, hence the need for innovative and pragmatic approaches to ensure:
 - Adequate Product and Process Development
 - Sufficient CMC for initial commercial readiness
 - Relevant proof of quality and safety
- Moving Faster does not mean agencies will accept less in terms of CMC:
 - CMC cannot compromise Product Supply and Patient safety
 - Anticipate characterization effort earlier in development
 - Focus on core Process and Product data needed to ensure reproducible and hi-quality Product manufacturing, even if formal validation is postponed
 - Plan for completion of the CMC exercise over Post approval activities (Commitment to meet conditional approval, LCM, PACMP...)

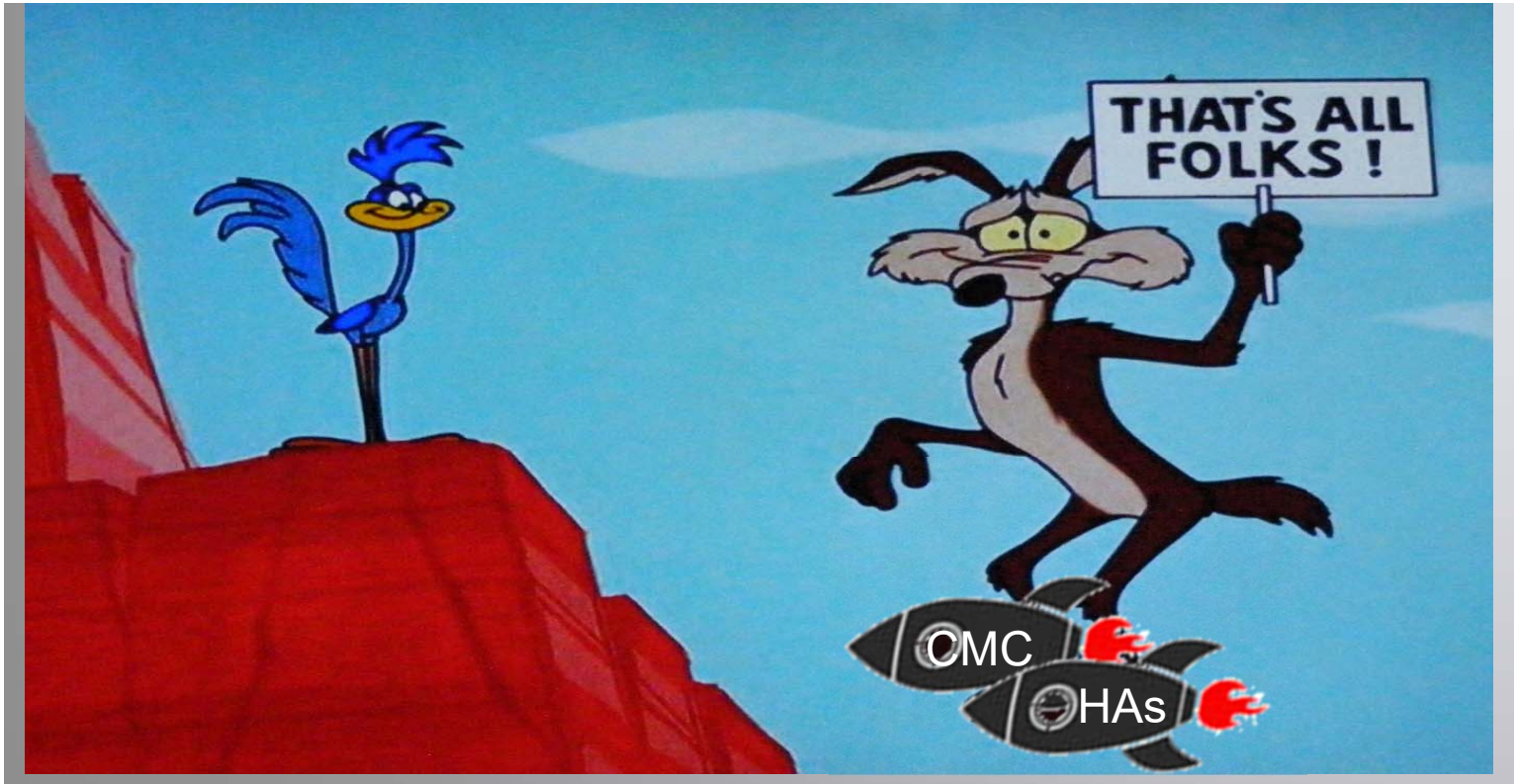
Take Home Messages

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When Less CMC information is available, apply Risk Based Approach :

- Use prior knowledge when applicable
- Define priorities
- Classify the potential impact and propose relevant mitigation measures
- Assess suitability in the light of patient benefit from earlier access to the treatment



Thank You



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