International Pathways for Accelerated Development: Lessons Learned

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Global Regulatory CMC

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Outline

- Accelerated Development Pathways
- Recent Biogen Global Experiences – Spinraza (nusinersen) injection and Aducanumab
- Conclusions
- Useful References

Accelerated Development Pathways

- US: Fast Track, Breakthrough, Priority Review, Accelerated Approval (Emerging Technology Program)
- EU: PRIority MEdicines(PRIME) Initiative, Adaptive Pathways, Accelerated Assessment, Conditional Marketing Authorisations
- Japan: SAKIGAKE Strategy
- Others: Priority and Accelerated mechanisms exist or are in development in many countries and regions globally (e.g. Kingdom of Saudi Arabia Verification/Abridged Route)

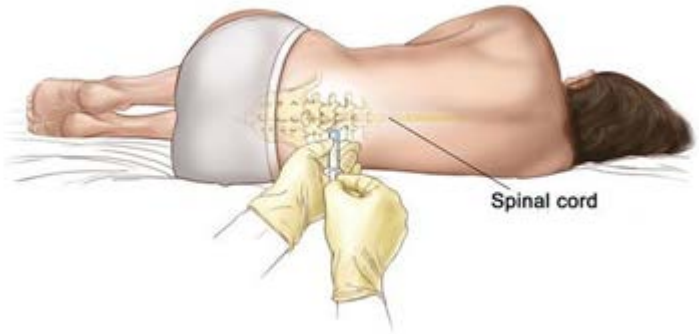
Recent Biogen Global Experience: Spinraza (nusinersen) Injection

- 18-mer, full 2'-MOE, full phosphorothioate anti-sense oligonucleotide

5' ^{Me}U ^{Me}C A ^{Me}C ^{Me}U ^{Me}U ^{Me}U ^{Me}C A ^{Me}U A A ^{Me}U G ^{Me}C ^{Me}U G G 3'

4 nucleotides: MOE ^{Me}U, MOE ^{Me}C, MOE A and MOE G

- Drug Product: 2.4 mg/mL in artificial CSF: 12 mg in 5 mL, aseptically filled in 6R vial, for intrathecal (IT) delivery
- Indicated for 5q-Spinal Muscular Atrophy (SMA)
  - (Exact approved indication varies with country)



Approved in 8 Regions So Far!

SPINAL MUSCULAR ATROPHY IS A SEVERE AND OFTEN FATAL GENETIC NEUROMUSCULAR DISEASE

Number one genetic cause of death in infants

Caused by deletion of the SMN1 gene

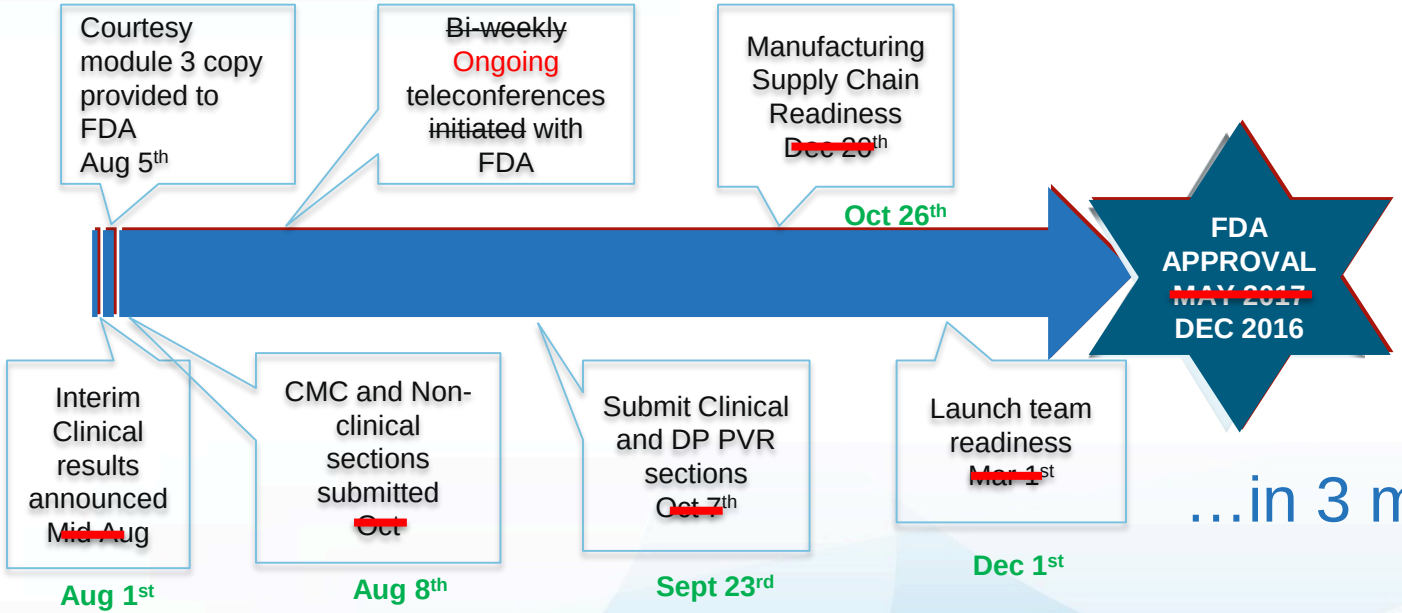
- **Leads to lack of survival motor neuron protein, which is necessary for the function of motor neurons**

People with SMA experience various levels of progressive muscular atrophy and weakness as motor neurons degenerate

Affects 30,000 - 35,000 patients in the U.S., Europe and Japan

Road to FDA Approval…

- Anticipated interim clinical results Aug ’16, and completed CMC section early to submit as rolling submission.
- Priority review granted
- FDA engagement and collaboration were established due to SMA unmet medical need; this resulted in accelerated review timelines: ***11 info requests*** ~~& 42 CMC queries~~



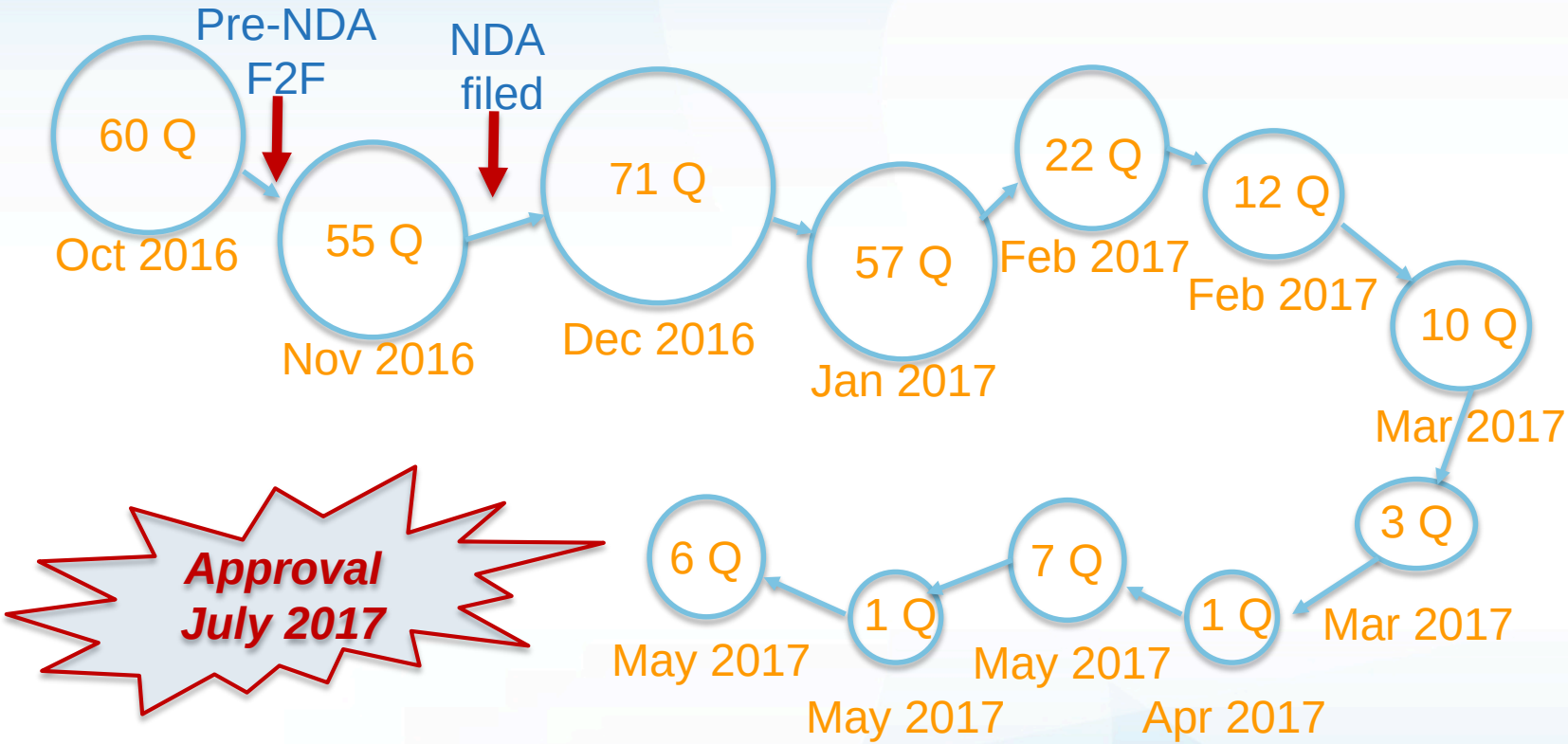
…in 3 months!

EU Accelerated Assessment

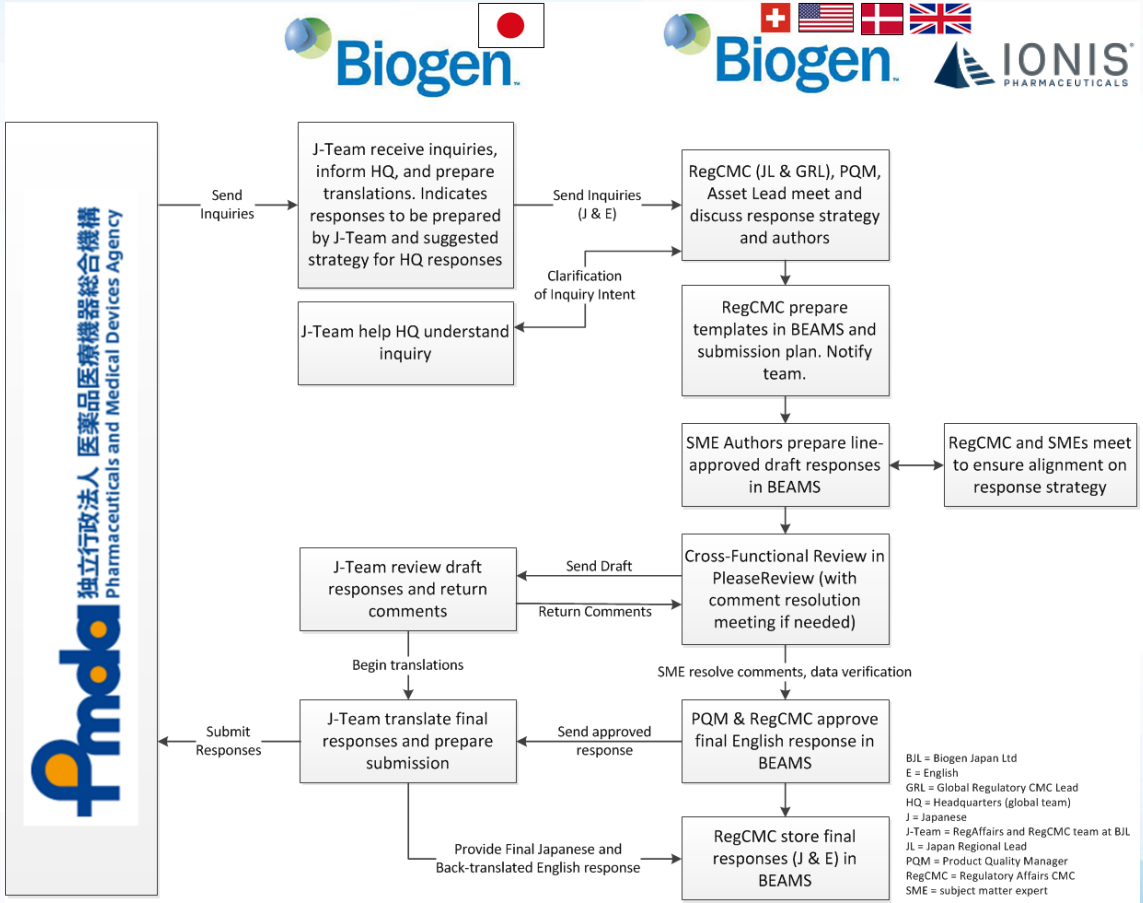
Milestone	Date	Comments
MAA Submission	10 Oct 2016	Validation to Start Date
MAA Procedure Start	27 Oct 2016	Day 0
(Co) Rapporteurs AR	23 Dec 2016	Day 60 (~Day 80)
List Of Questions	**24 Jan 2017**	**Day 90 (~Day 120)**
Response Deadline	**17 Feb 2017**	***78 CMC Questions***
Preliminary AR	9 Mar 2017	(~Day 150)
List of Outstanding Issues	14Mar17	
Response Deadline*	14Mar17	
*Preliminary AR**	16Mar17	
CHMP Opinion*	21Mar17	
Commission Decision	***30 May17***	*Day 215*

Biogen

Japan: 12 Rounds; > *300 CMC Queries*



Japan: Inquiry Response Process



Days, not Weeks!

Japan Specific m1.2 & m1.13 Sections

- Process description must be (re)written for legally binding section of application (Application Form m1.2)
  - Process summary; describing items that have impact on the process/ quality
- Process parameters must be defined as
  - PCA (partial change application), << 15 L>> Requires approval to change
  - MCN (minor change notification), 『–20ºC』 Must notify of change
- Module m1.13, provides a detailed description. Though not legally binding, it forms the basis of understanding for m1.2 and gives information on every parameter & range, and justifies why it is PCA, MCN or neither.
- PMDA can request changes to parameter designations in m1.2 based on their understanding of m1.13

Recent Biogen Global Summary: Spinraza (nusinersen) Injection

- Regular communications between the developer and FDA through development and licensing process are key to rapid approval in all markets (e.g. FDA[1])
- To meet significant parallel MoH timeline expectations during MAA review for accelerated programs internal company resources are required which need to be:
  - decisive
  - nimble/flexible & innovative
  - empowered
  - prepared to agree post-approval commitments
- Be prepared for MoHs to contact the company seeking early regulatory engagement
- Accelerated opportunities may exist in markets where there are no formal published procedures

[1] Development of gene therapies—lessons from nusinersen: Xu L., Irony I., Bryan W.W. & Dunn B: Gene Therapy (2017) 24, 527–528 (2017)

Recent Biogen Global Experience: Aducanumab

- Aducanumab is Biogen's investigational monoclonal antibody being developed for patients with Alzheimer's Disease
- EU:
  - Eligibility Criteria for PRIME includes "*medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. These medicines are considered priority medicines by EMA. To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data.*"[1]
  - Application for inclusion of Aducanumab in PRIME was prepared in advance of the formal launch of the scheme and accepted in May 2016, Rapporteur assigned at June CHMP meeting and kick-off meeting held in September 2016
  - Kick-off meeting with EMA, Rapporteur and CHMP/SAWP chairs was extremely constructive
    - Post-authorization strategy is key and needs to be agreed
    - Potential for acceleration of Centralised Scientific Advice procedure

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439

Recent Biogen Global Experience: Aducanumab

- US:
  - In September 2016 the U.S. Food and Drug Administration accepted aducanumab into its Fast Track program[1]
    - Intended to facilitate the development and expedite the review of drugs to treat serious and life-threatening conditions so that an approved product can reach the market expeditiously
    - Features of Fast Track Designation include opportunities for frequent interactions with the review team, potential eligibility for priority review and rolling review
    - Provides potential opportunities to discuss accelerated CMC development strategies

[1] http://media.biogen.com/press-release/neurodegenerative-diseases/biogens-investigational-alzheimers-disease-treatment-aduc-0

Recent Biogen Global Experience: Aducanumab

- Japan:
  - SAKIGAKE = Forerunner or Pioneer
  - Designation criteria for SAKIGAKE designation system:
    - Medical products for diseases in dire need of innovative therapy
    - Development & NDA in Japan being world's first or simultaneous with other countries
    - Prominent effectiveness expected on non-clinical and early phase clinical trials
  - Aducanumab selected in Round 2 (Oct 2016-Apr 2017)[1]
  - Two Pre-Consultation Quality Meetings held December 2016 and December 2017

[1] http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/170421-01.html

Conclusions

- Many of the accelerated development opportunities were developed with a focus on accelerated clinical development
- Acceptance into these programs will inevitably decrease the amount of time available for the development and understanding of the critical aspects of Chemistry, Manufacturing and Controls (CMC)
- CMC aspects must not be on the critical path for early access to these medicines
- The CMC strategy must always provide assurance of safety and quality within this context **but it must also** assure the flexibility to deliver consistent and reliable supplies of product to patients

Conclusions

- Regular communication with licensing authorities through development and registration is key to the approval of an acceptable CMC approach
- CMC specific considerations:
  - Product Development:
    - Importance of risk assessment and risk mitigation approaches
    - Consider timing of process scale-ups and site transfers
    - Tentative specifications based on limited numbers of batches
    - Use of prior knowledge to support development, process and product quality control strategies
  - Procedural:
    - Use of reference assessment reports
    - GMP & Inspections planning
    - Post-approval commitments
    - Close collaboration with Agency CMC review staff, partner companies, manufacturers etc

Useful References

- Trade Association:
  - EFPIA-EBE White Paper on Expedited CMC Development: Accelerated Access for Medicines of Unmet Medical Need – CMC Challenges and Opportunities (Final Version - December 2017) https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/regulatory-affairs/
- EU:
  - PRIME http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439 & First anniversary of PRIME: experience so far: Workshop: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/03/event_detail_001407.jsp&mid=WC0b01ac058004d5c3
  - Adaptive Pathways http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce
  - Accelerated Assessment http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000955.jsp&mid=WC0b01ac05809f843a
  - Joint Biologics Working Party / Quality Working Party workshop with stakeholders in relation to prior knowledge and its use in regulatory applications http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/07/event_detail_001500.jsp&mid=WC0b01ac058004d5c3
- US:
  - Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review https://www.fda.gov/ForPatients/Approvals/Fast/default.htm
  - Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf
  - Emerging Technology Program https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm523228.htm
  - Development of gene therapies—lessons from nusinersen: Xu L., Irony I., Bryan W.W. & Dunn B: Gene Therapy (2017) 24, 527–528 (2017) - http://www.nature.com/articles/gt201764
- Japan:
  - MHLW “Strategy of SAKIGAKE” http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html