drug substance manufacturing processes involves generation of large and complex data sets. Manufacturing processes typically contain several process steps, with multiple stages and analytical equipment that may in turn generate many outputs. The transition to digital data management therefore requires close collaboration between service provider and customer in order to suit the customer's needs.
Methods: We describe the process from project initiation to initial data analysis as follows:
(1) design and generation of the Discoverant® platform,
(2) integration of instrumentation and automation of data retrieval, analysis and sharing,
(3) data visualization to allow identification of batch abnormalities and to highlight areas that are off target or out of normal ranges and limits,
(4) identification of correlations within a process for a given product but also between products,
(5) characterization of the manufacturing process to assist process understanding and support future product manufacture.

Results: Through implementation of a digital data management platform, the automation and standardization of data retrieval have been realized. Data analysis and sharing capabilities have been enhanced and will aid future development of toxins and streamline development of new molecules as they enter the development pipeline. The platform can highlight trends and correlations not just for one toxin but for all toxins within a given portfolio.
Conclusions: The implementation of a digital data management platform has enhanced many areas of toxin bioprocess development. Information gained during the earlier stages of process development will aid decision making as projects move forward through clinical phases towards commercial manufacturing and lifecycle management.
Funding: Ipsen BioPharm Ltd
Keywords: Bioprocess; Drug substance; Industry 4.0; Manufacture

LONG-TERM EFFECTS OF BOTULINUM NEUROTOXIN TYPE A ON EXPERIMENTAL MUSCLE HYPERTONIA

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Introduction and Objectives: Long-term effects of botulinum neurotoxin type A (BoNT-A) are the basis of its beneficial effects on neurological disorders characterized by muscle hyperactivity, such as spasticity and dystonias. Clinical reports suggest that BoNT-A–mediated normalization of muscle hypertonia does not necessarily correlate with or outlast the duration of muscular flaccid paralysis. The present aim was to reassess these clinical observations in a preclinical model of muscle hypertonia by characterizing the duration of toxin anti-spastic activity in relation to the duration of its muscular effects.
Methods: In male Wistar rats, the muscle hypertonia was evoked by tetanus neurotoxin (TeNT) injection into the gastrocnemius (1.75-2 ng total dose). After the development of spastic hypertonia, BoNT-A was similarly injected into the ipsilateral gastrocnemius muscle 7 days post-TeNT (1, 2 and 5 U/kg//20 μL). The effects of TeNT and BoNT-A were further examined by measurements of resistance to passive ankle dorsiflexion, digit abduction score (DAS), and Basso-Beattie-Bresnahan (BBB) Locomotor Rating Scale. Muscle atrophy was quantified by measurement of the medio-lateral calf diameter. After complete recovery of BoNT-A–mediated peripheral flaccid paralysis, the animals were re-injected with TeNT (day 49 after BoNT-A injection) and assessed behaviorally for another 19 days.
Results: In the immediate period following the first TeNT injection, all BoNT-A doses employed exhibited a similar reduction of the muscle hypertonia. The TeNT-evoked muscle hypertonia ended by day 28 post-TeNT, while the remaining BoNT-A–mediated flaccid paralysis recovered in a dose-dependent manner by day 42 post–BoNT-A. After the second TeNT injection, the anti-spastic activity of BoNT-A was still present up to day 68; however, it was less prominent in rats injected with the lowest BoNT-A (1 U/kg) dose. The level of persisting muscle atrophy, which did not show signs of recovery by the end of the experiment, was similar at all doses employed.
Conclusions: In line with clinical reports, we found that the antispastic effect of BoNT-A in rats persists after the lower limb recovery from flaccid paralysis in a dose-dependent manner. Long-term actions of BoNT-A on muscle hypertonia might be mediated by a mechanism distinct from its local muscular paralytic action.
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Keywords: Botulinum neurotoxin type A; Flaccid paralysis; Muscle atrophy; Muscle hypertonia; Tetanus neurotoxin

REAL-LIFE CRITERIA FOR USE OF MAXIMAL AND SUPRAMAXIMAL DOSES OF ABOBOTULINUMTOXINA IN POSTSTROKE SPASTICITY: IS IT WORTH IT?

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Introduction: Spasticity is a major disabling complication of stroke that may also lead to increased pain, joint contractures, skin problems, sleep impairment, and hence, reduced quality of life. Botulinum toxin type A (BoNT-A) intramuscular injection is the gold standard treatment for focal/multifocal spasticity. This study compares the use of maximal and supramaximal versus submaximal doses of abobotulinumtoxinA (AboBT) in the upper limb.
Methods: One hundred fifty-three adult patients with poststroke spasticity, who were treated with AboBT injections in the upper limb, with a total of 1261 injections were included in this study. They were divided by administered dose: $\geq$ 1000 U in group A (n = 320) and <1000 U in group B (n = 941). The sample was characterized by age, gender, number of treatment sessions, number of injected muscles, and AboBT doses used. The primary outcome was goal achievement measured with Goal Attainment Scaling (GAS). Treatment was successful when scores $\geq$ 0 per goal were achieved.
Results: Group A had a greater number of injected muscles per treatment session (7.60 ± 1.41, P<0.001) than Group B (4.99 ± 1.76, P<0.001). There was a small positive correlation between the increase in dose and the number of injected muscles (rho 0.264, P<0.001). There was no significant difference between the groups in treatment success measured by GAS $\geq$ 0 (primary goal: Group A vs Group B: X^2 (4) = 4.518, P=0.34; all goals: Group A vs Group B: X^2 (4) = 3.029, P=0.55). We did not record significant adverse events in any of the groups.
Conclusion: BoNT-A is a safe and effective treatment for focal poststroke spasticity. The use of maximal/supramaximal doses of AboBT may be an option in cases where more than 5 muscles need to be targeted, by allowing the achievement of the same success rates as within-SMPC (Summary of Product Characteristics) doses do, in the cases where fewer muscles need treatment.
Keywords: AbobotulinumtoxinA; Botulinum toxin; Spasticity; Stroke; Upper Limb