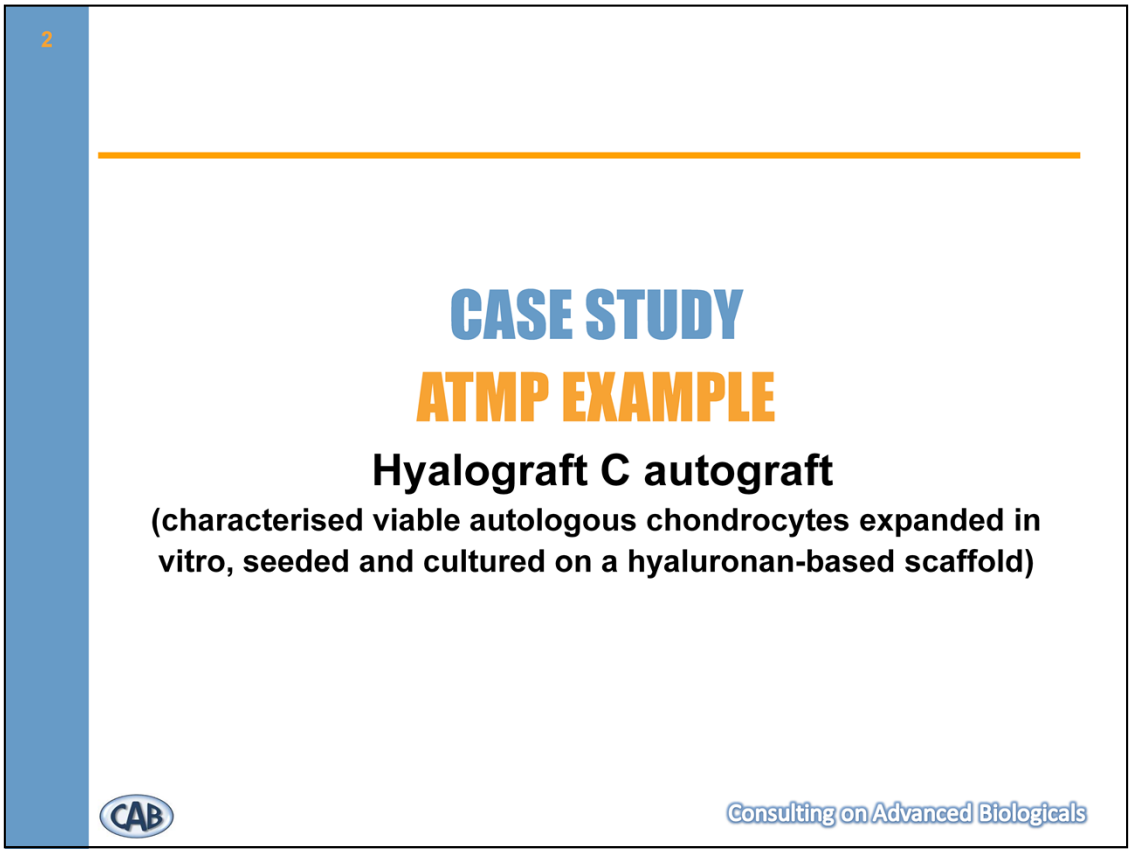
CHAIR INTRODUCTION

Christopher Bravery
cbravery@advbiols.com

Consulting on Advanced Biologicals


2
CASE STUDY
ATMP EXAMPLE
Hyalograft C autograft
(characterised viable autologous chondrocytes expanded in vitro, seeded and cultured on a hyaluronan-based scaffold)
CAB
Consulting on Advanced Biologicals

Withdrawn.

3

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- Validation of the washing steps have been conducted through **validation of the removal of process-related impurities**.
- The description of the manufacturing process for both the drug substance and drug product is considered limited and the available control measures suggest an uncontrolled process. There is insufficient detail of the operating conditions for each step (volumes used etc, with working ranges) which **suggests poor process control**.
- Raw materials are not qualified for human use and the applicant should either provide information on the manufacturing and quality of those materials or change them into materials that are approvable for human use. In the latter case, **additional comparability studies would be needed**.

CAB Consulting on Advanced Biologicals

Possibly comment that impurities may not need to be in release spec if validate their removal – in process testing needed

Hard to do comparability if the process isn't under control (barrier)

Note: they point out that if the quality of the raw material isn't sufficiently well defined, you will need comparability to change it!

4

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- A **major objection** is raised concerning the **control strategy** for the key intermediate (cell suspension) the drug substance and the drug product. Of particular concern is the lack of control on the cell expansion phase……..
- This lack of control of the DS manufacturing process is also mirrored by the lack of control at the level of drug substance and drug product. Specifications for release testing should include identity, purity, potency, impurities, sterility, cell viability and cell number, unless suitably justified.

CAB Consulting on Advanced Biologicals

With a major objection over process control, demonstrating comparability may not be possible.

A weak release specification also suggests weak characterisation which together suggest there are no extended characterisation methods to support a weak/deficient release specification. So comparability will not be possible based on quality data (would need clin/nonclin).

5

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- The **deficiencies in process control** are a significant factor in the major objection raised for DS/DP process validation. It is considered the lack of suitable pre-set specifications and controls precludes a proper process validation exercise. More significantly in terms of process validation, the applicant has not performed an appropriate validation exercise, i.e. the manufacture of 3 consecutive full-scale 'commercial' batches (maximum foreseen batch size). Instead the applicant has processed 5 biopsies, divided each in half and processed each half at the maximum or minimum operating condition. This is a development study, not a validation study.

Consulting on Advanced Biologicals

Process validation was also a major objection, goes hand in hand with process control (can't validate without it) and together pretty much preclude being able to underatke a comparability study.

6

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- There are **significant deficiencies in the characterisation** of the drug substance and therefore a **major objection is raised**. In terms of characterisation of cells on the scaffold, the analysis is restricted to analysis of chemical degradation products of the scaffold and homogeneity of cell distribution on the scaffold so the combination product is **poorly characterised in terms of key quality attributes**. The applicant appears to have conducted limited characterisation studies (few reported in the non-clinical part) to identify the critical quality attributes on the actual key intermediate (cell suspension) DS or DP.

CAB Consulting on Advanced Biologicals

Was already hinted at with weak release specifiction, overall weak characterisation – added to all the other deficiencies its easy to see comparability wasn't possible to evaluate.

7

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- A **major objection** is raised regarding the **potency** assay. The company has not studied the level of expression needed to ensure proper cartilage forming capacity of the product. The specification for potency () was not justified in terms of the batch data or for values from batches tested in clinical trials (the applicant provides no information on quality data for batches used in clinical trials) so this potency assay has not been correlated with pre-clinical or clinical efficacy.

CAB Consulting on Advanced Biologicals

Then on top of that the potency assay has issues. Setting a potency specification is very hard though.

8

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- **A major objection is raised concerning comparability**. Comparability of the commercial product and product batches used in clinical studies **cannot be confirmed due to lack of quality detail** (manufacturing process/IPC specifications/release specifications) …

CAB Consulting on Advanced Biologicals

So then we arrive at the **INEVITABLE.**

9

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- In addition, an appropriate comparability exercise has not been conducted. Several changes have been made during manufacture.. A comparability exercise was conducted comparing a "minimum" process versus a "maximum" process, where the incubation/culture times and number of certain steps varied. In these experiments **potency** was considerably **decreased** for all batches produced by the new process () although viability was significantly increased for all batches (). The applicant does not discuss these differences, stating the product is the same and no further clinical testing is required. **This is not supported** and further information/data is required to demonstrate comparability of the clinical materials and the commercial product.

CAB Consulting on Advanced Biologicals

Details of where they went wrong (but emphasise all previous slides contributed to this)

10

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

- The applicant claims a shelf-life however this is not supported by the limited evidence supplied. The quality indicating parameters used to assess stability were viability and potency. The data for viability show considerable variability, however the more significant issue is with the potency assay. These issues are not discussed by the applicant. Even though the potency values are within specification, **the specification is not justified**. **The applicant is advised to test a further range of stability indicating parameters**.

Consulting on Advanced Biologicals

Stability was also going to be an issue given the other deficiencies. Make comment stability reassessment should have been done as part of comparability (probably, depending on the change) – which would have been weak.

11

EMA/CAT WITHDRAWAL ASSESSMENT REPORT
HYALOGRAFT C AUTOGRAFT

Clinical Conclusions

Uncertainty in the knowledge about the beneficial effects

- Unknown quality and manufacturing processes of the products used in the non-clinical and clinical studies remains **one of the key issues** including concerns regarding cell potency and viability **which have varied considerably and thus comparability is an issue which could impact on both efficacy and safety and thus prevents any firm conclusions to be made**.

CAB Consulting on Advanced Biologicals

Good example of how those quality issues can impact clinical conclusions. They added much doubt.