NEXT GENERATION SUPPLY CHAINS FOR CELL & GENE THERAPIES AND ATMPS

OPEN
X-CELLerator
COMMUNITY

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Transport and stability of ATMPs from a regulatory point of view

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Approved ATMP Examples

T-cell Products

Store in vapor phase of liquid nitrogen

Tissue Engineered product examples

SmPC

6.3 Shelf life

72 hours

6.4 Special precautions for storage

Store at temperatures between 1 °C and 10 °C.
Do not freeze.
Do not irradiate.
Do not open the outer packaging before use to prevent microbial contamination.

SmPC

6.3 Shelf life

36 hours.
Holoclar must be applied no later than 15 minutes after opening the primary container.

HOLOCLAR®
Ex vivo expanded autologous human corneal epithelial cells containing stem cells

6.4 Special precautions for storage

Store between 15°C – 25°C
Do not refrigerate or freeze
Do not irradiate (e.g. X-rays)
Do not sterilise
Keep the steel primary container tightly closed to protect from bacterial, fungal and viral contamination.

Somatic Cell Therapy: MSC

SmPC

6.3 Shelf life

72 hours.

6.4 Special precautions for storage

Store between 15ºC and 25ºC.
Keep the product within the outer carton and inside the shipping container at all times until its administration, to maintain the required temperature.
Preserve the container away from heat and direct light sources and do not refrigerate or freeze.
Do not irradiate or otherwise sterilise.

Guide for pharmacists:

PRODUCT RECEIPT AND STORAGE

1. The product must be kept at 15ºC-25ºC at all times until it is administered. Keep the shipment container away from heat and direct light sources, and do not refrigerate or freeze.
2. On arrival of the courier, visually inspect the shipping container for any signs of damage. Note any observation from your inspection of the shipping container on the transport documents.
3. Open the shipping container lid, extract the paperwork and the two temperature monitoring devices within, and set them aside. Close the container lid immediately after, to prevent changes in temperature ranges.
4. One temperature monitoring device will be inactive (not yet started) and will have a blank screen. The other monitoring device will be active (started) and a tick and flashing dot will be displayed on the screen.

Label

8. EXPIRY DATE

EXP {XX-XXX-XXXX at XX:XX CET}

9. SPECIAL STORAGE CONDITIONS

Store between 15 ºC and 25 ºC.
Do not refrigerate or freeze.
Keep the product within the outer carton.
Do not irradiate or otherwise sterilise.

Dendritic cells

SmPC

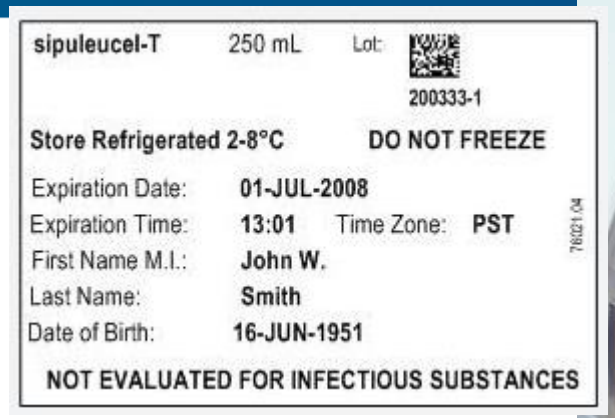
6.3 Shelf life

In the insulated container
18 hours.

After removal from the insulated container
The medicinal product should be used immediately. If not used immediately, in-use storage times conditions should not exceed 3 hours at room temperature (25°C).

6.4 Special precautions for storage

Store the bag in the insulated container to maintain the correct storage temperature (2°C–8°C) until infusion.
Do not refrigerate or freeze the container.



Label

8. EXPIRY DATE

Exp. Date {DD month YYYY}, Exp. Time {hh:mm}, Time Zone

9. SPECIAL STORAGE CONDITIONS

Store the bag in the insulated container to maintain the correct storage temperature (2°C–8°C) until infusion.
Do not refrigerate or freeze the container.

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Thawing/ Dilution

6.3 Shelf life SmPC

Unopened vial

5 years. frozen

Preparation and storage prior to administration

After thawing, administer Imlygic as soon as practically feasible.

Thawed Imlygic is stable when stored at temperatures of 2°C up to 25°C protected from light in its original vial, in a syringe, or in the original vial followed by a syringe. Do not exceed the storage times specified in table 7 and table 8.

If storing thawed Imlygic in the original vial followed by a syringe:

- The same temperature range should be maintained throughout the duration of storage until administration.
- The storage time in the syringe at ambient temperature up to 25°C cannot exceed 2 hours for 10^6 (1 million) PFU/mL and 4 hours for 10^8 (100 million) PFU/mL (see table 7).
- The maximum cumulative storage time (storage time in vial plus storage time in syringe) cannot exceed the durations in table 8.

Imlygic must not be refrozen once it has thawed. Discard any thawed Imlygic in the vial or syringe stored longer than the specified times below.

6.4 Special precautions for storage

Store and transport frozen (-90°C to -70°C).
Store in the original carton in order to protect from light.
For storage conditions after thawing of the medicinal product, see section 6.3.

Regulatory requirements

Definitions /Terms

- **Shelf-Life: Expiration date**:
  - The time period during which a drug product is expected to remain within the approved shelf-life specification, when stored under the conditions defined on the container label.
- **Re-Test Date:**
  - The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and suitable for use in the manufacture of a DP
- **Stability**:
  - Provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

- **Final Product:** DP. The dosage form in the final immediate packaging intended for marketing.
- **Active Substance:** DS. The unformulated drug substance.
- **Starting/Raw Material:** Viral vector, Leukapheresis, Lipoaspirate, MCBs
- **Intermediate:** if holding times / extra storage, transport

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Definitions

- **Long-term stability testing**:
  - Stability studies under the recommended storage condition for (the re-test period) or shelf life proposed (or approved) for labeling.

- **Accelerated testing**:
  - Studies designed to increase the rate of degradation or change of (a drug substance or) drug product by using exaggerated storage conditions.
  - Data from these studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. …

- **Stress testing**:
  - DP: Studies undertaken to assess the effect of severe conditions on the **drug product**. Such studies include photostability testing (see ICH Q1B) and specific testing on certain products.
  - DS: Studies undertaken to elucidate the intrinsic stability of the **drug substance**. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

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Regulatory Requirements

- ICH
  - ICH 5QC Stability testing of **biotechnological/biological products** (CPMP/ICH/138/95)
  - ICH Q6B Specifications: Test procedures and acceptance criteria for **biotechnological/biological products** (CPMP/ICH/365/96)

- EMA
  - The **overarching guideline** for human gene therapy medicinal products is the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)
  - The **overarching guideline** for human cell- based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)
  - Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) (EMA/CAT/499821/2019)

CTD Dossier cross-talk with Label

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Cross- talk: EMA approved Dossier and Label

eCTD Dossier

3.2.P.8 (P.3.4/P.2)

Long-term stability

Transport conditions

In-use stability

SmPC

6.3 Shelf-Life

6.4 Precautions

Label:

Expiry date

Special Storage Conditions

Labeling exemption example :

- 72h stability
- Labelling costs 4 h → avoid additional packaging time by using only EN label (All EU languages with the EPAR on the EMA website)

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CTD Dossier relevant to Stability and Transport

Stability: Claim, study protocol and data	• (Starting/Raw Material and Intermediates) • (Active Substance: S.7) • Drug Product: P.8 Stability (P.2 Pharmaceutical development)
Transport Validation	• S.2.4 / P.3.5 Process Validation • P.2 Pharmaceutical development
Container Closure	• Active Substance: S.6 Container Closure • Drug Product: P.7 Container Closure

S = Drug/Active Substance, P = Drug Product

Design of stability studies

- What are stability indication parameters? Release = Shelf-Life Specification?
- Test parameters: Viability, ID, Purity, Assay/Activity/Potency, Sterility
  - The manufacturer set a reasonable time frame and temperature condition (e.g. 2-8 °C, < -120°C)
  - Long-term / real-time
  - Accelerated / stress test
  - At least 3 batches
  - Claim depends on results

Tests	0 Months	3 Months	6 Months	12 Months	24 Months	36 Months
Identity & Purity	X	X	X	X	X	X
Potency Assay	X	X	X	X	X	X
Viability & cell count	X	X	X	X	X	X
Sterility	X	-	-	X	X	X
Bacterial-Endotoxin	X	-	-	X	X	X

- Stability after thawing
  - Minutes/hours post-thaw
  - Same parameters, but no sterility, no purity…
  - 1-2 batches depending on testing points and material

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Stability data in Dossier

Example Imlygic from EPAR

- Data for **long-term storage** (and transport: -70 to -90 °C)
- Data for **in-use for product after thawing and in syringe** at two Temperature conditions, resulting in cumulative stability
- (provided in SmPC 6.3 >Shelf-Life)

Table 7. Maximum storage time for thawed Imlygic in syringe

	10^6 (1 million) PFU/mL	10^8 (100 million) PFU/mL
2°C to 8°C	8 hours	8 hours
up to 25°C	2 hours	4 hours

Table 8. Maximum cumulative storage time (storage time in vial plus storage time in syringe) for thawed Imlygic

	10^6 (1 million) PFU/mL	10^8 (100 million) PFU/mL
2°C to 8°C	24 hours	1 week (7 days)
up to 25°C	12 hours	24 hours

- "*Protect from light*" → photostability studies
- (provided in SmPC 6.4 Special precautions for storage)

Stability from Starting/Raw Material to final Product

- **Vector**:
  - Shelf-life for vector substance of 12 months
  - Shelf-life for vector product of 36 months at -60°C to -90°C, supported by real-time stability data
- **Patient leukapheresis**:
  - Packaging and cryopreservation, stability of storage before cryopreservation, real-time storage conditionals after cryopreservation.
- **Drug Substance**: continuous process, see product
- **Drug Product**:
  - Stability data, summaries, and conclusions provided to support
    - Shelf-life of 9 months stored in infusion bags at ≤ -120°C in vapour phase liquid nitrogen,
    - 30 minutes in-use shelf-life after thawing at room temperature 20-25°C.

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Potential risk

- Example EPAR Kymriah
- "Inappropriate handling of the manufactured product including transport, storage in addition to thawing and standing time prior to infusion may result in a decrease of viable cells. This may impact the efficacy and safety profile of tisagenlecleucel. Decrease in cell viability due to inappropriate handling of the product has been categorized as potential risk (see Risk Management Plan)."

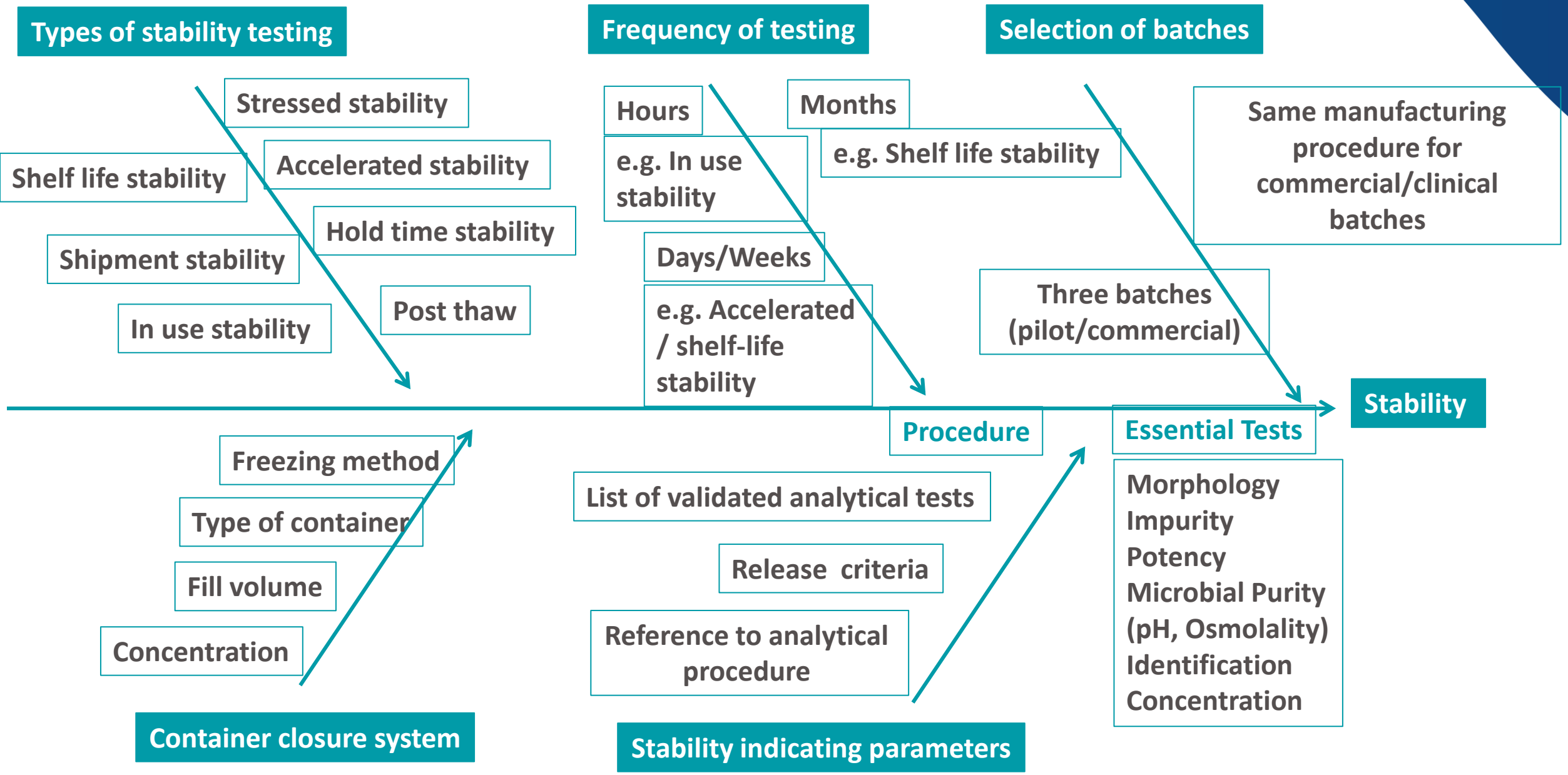
RMP

Decrease in cell viability due to inappropriate handling of the product	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 6.3 Shelf life • SmPC Section 6.4 Special precautions for storage • SmPC Section 6.5 Nature and contents of container and special equipment for use, administration or implantation • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 5 How to store Kymriah • SmPC Section Other sources of information

Additional risk minimization measures

- Controlled distribution program
- Educational program including the Pharmacy/Cell Lab/Infusion Center Training Material

Summary


Types of stability testing
Stressed stability
Accelerated stability
Shelf life stability
Hold time stability
Shipment stability
Post thaw
In use stability
Frequency of testing
Hours
Months
e.g. In use stability
e.g. Shelf life stability
Days/Weeks
e.g. Accelerated / shelf-life stability
Selection of batches
Same manufacturing procedure for commercial/clinical batches
Three batches (pilot/commercial)
Stability
Procedure
Essential Tests
Morphology
Impurity
Potency
Microbial Purity
(pH, Osmolality)
Identification
Concentration
List of validated analytical tests
Release criteria
Reference to analytical procedure
Stability indicating parameters
Freezing method
Type of container
Fill volume
Concentration
Container closure system

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