WHO GOOD MANUFACTURING PRACTICES FOR BIOLOGICAL PRODUCTS & CELL BANKING

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Advanced therapy medicinal products

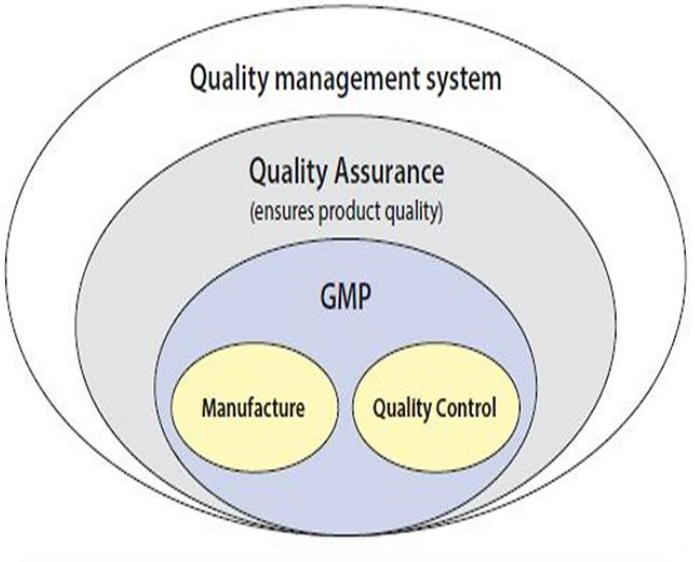
- Stem cell knowledge will be the **basis for new treatments** for diseases for which there is currently no satisfactory treatment.

- **Advanced therapy medicinal products (ATMP) :**
  - **Medicines for human use** that are based on genes, tissues or cells.

What is GMP ?

- GMP (Good Manufacturing Practices) is that part of **Quality assurance** which ensures that the products are **consistently** manufactured and controlled to the Quality standards appropriate to their intended use

- A set of principles and procedures which, when followed by manufacturers for therapeutic goods, helps **ensure** that the products manufacture will have the **required quality**.



Good Manufacturing Practices

- A basic tenet of GMP is that quality **cannot be tested into a batch** of product but must be built into each batch of product during all stages of the manufacturing process.
- It is designed **to minimize the risks** involved in any pharmaceutical production that cannot be eliminated through testing the final product.
- GMPs examine and cover **every aspect** of the manufacturing process to guard against **any risks** that can be catastrophic for products, such as cross-contamination, adulteration, and mislabeling.

Some of the main risks are

- Unexpected **contamination** of products, causing damage to health or even death.
- Incorrect **labels** on containers, which could mean that patients receive the wrong medicine.
- Insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects.

Why GMP is important

- A poor quality medicine may contain toxic substances or not have the intended therapeutic effect.

- **The 5 P's of GMP**
- It is paramount for industry to regulate GMP in the workplace to ensure consistent quality and safety of products.
- Focusing on the following 5 P's of GMP helps comply with strict standards throughout the entire production process.

The 5 P's of GMP

People

- All employees are expected to strictly adhere to manufacturing processes and regulations. A current GMP training must be undertaken by all employees to fully understand their roles and responsibilities.

Products

- All products must undergo constant testing, comparison, and quality assurance before distributing to consumers.

- Manufacturers should ensure that primary materials including raw products and other components have clear specifications at every phase of production.

- The standard method must be observed for packing, testing, and allocating sample products.

The 5 P's of GMP

- **Processes**
  - Processes should be properly documented, clear, consistent, and distributed to all employees.
  - Regular evaluation should be conducted to ensure all employees are complying with the current processes and are meeting the required standards of the organization.

- **Procedures**
  - A procedure is a set of guidelines for undertaking a critical process or part of a process to achieve a consistent result.
  - It must be laid out to all employees and followed consistently.
  - Any deviation from the standard procedure should be reported immediately and investigated.

The 5 P's of GMP

- **Premises**
- Premises should promote cleanliness at all times to avoid cross-contamination, accidents, or even fatalities.
- All equipment should be placed or stored properly and calibrated regularly
- to ensure they are fit for the purpose of producing consistent results to prevent the risk of equipment failure

Ten Principles of GMP

1. Design and construct the facilities and equipments properly
2. Follow written procedures and Instructions
3. Document work
4. Validate work
5. Monitor facilities and equipment

Ten Principles of GMP

6. Write step by step operating procedures and work on instructions
7. Design ,develop and demonstrate job competence
8. Protect against contamination
9. Control components and product related processes
10. Conduct planned and periodic audits

Designing and constructing facilities and equipment

- Depending on the nature of product being manufactured, there are hygienic design-protocols that need to be followed.
- For pharmaceutical production floors, there could be zoning: low-risk, medium-risk and high-risk areas.
- Each zone has its own set of standards, all in a bid to avoid contamination risks.

Aseptic preparation

- GMP requires a cleanroom or clean area for pharmaceutical manufacturing.
- All materials must be able to withstand frequent cleaning and disinfection.
- Materials must be free of cracks, smooth and level, and able to interlock seamlessly.
- Particulate materials may not be used due to the risk of contamination.

- **Grade A**
- Aseptic preparation and filling of sterile ointments, creams, suspensions and emulsions

- **Grade B**
- Background environment for grade A zone operations, when needed for transfers and other less-critical tasks.

- **Grade C**
- Preparation of solutions that need to be sterile filtered.

- **Grade D**
- Handling of components after washing

CLEANROOM CLASSIFICATIONS

Cleanroom Standard	Cleanroom Classification Guidelines					
ISO 14644-1	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8
Federal Standard 209E	1	10	100	1,000	10,000	100,000
EU GMP	-	-	A/B	-	C	D
Air changes / hour	360-540	300-540	240-480	150-240	60-90	5-48

In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as **HEPA** for grades A, B and C.

(b) The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal Standard 209E and the ISO classifications as follows: **grades A and B correspond with class 10**0, M 3.5, ISO 5; **grade C with class 10000**, M 5.5, ISO 7 and **grade D with class 100000**, M 6.5, ISO 8.

Following written procedures and instructions

- Good documentation and record keeping is an essential part of the quality assurance system and is required in compliance with GMP requirements.
- Accurate record keeping can help managers and supervisors keep track of the historical record of manufacturing procedures and corrective measures implemented.

1. Documents must be **designed, prepared, reviewed, and distributed** with care.
2. Documents should be **clear and legible**.
3. Documents must be **approved, signed, and dated by appropriate** and authorized personnel.
4. Documents must have unambiguous contents such as **title, nature, and purpose.**

Sanitation and hygiene

- **Sanitation** and **hygiene** are vital in every aspect of the manufacturing process.
- It covers anything that can cause contamination such as
  - personnel
  - the premises
  - equipment
  - containers
  - and production materials.

- All potential sources of contamination should be **monitored**, **identified and eliminated** with a comprehensive sanitation and hygiene program.

Validation and qualification

- **Critical steps** in the manufacturing process should be verified to ensure that product quality is consistent and maintained at a high level.

- According to the WHO, qualification and validation should establish and provide documentation stating that:

  - the premises, supporting utilities, equipment, and processes have been designed in accordance with the requirements for GMP (design qualification or **DQ**)

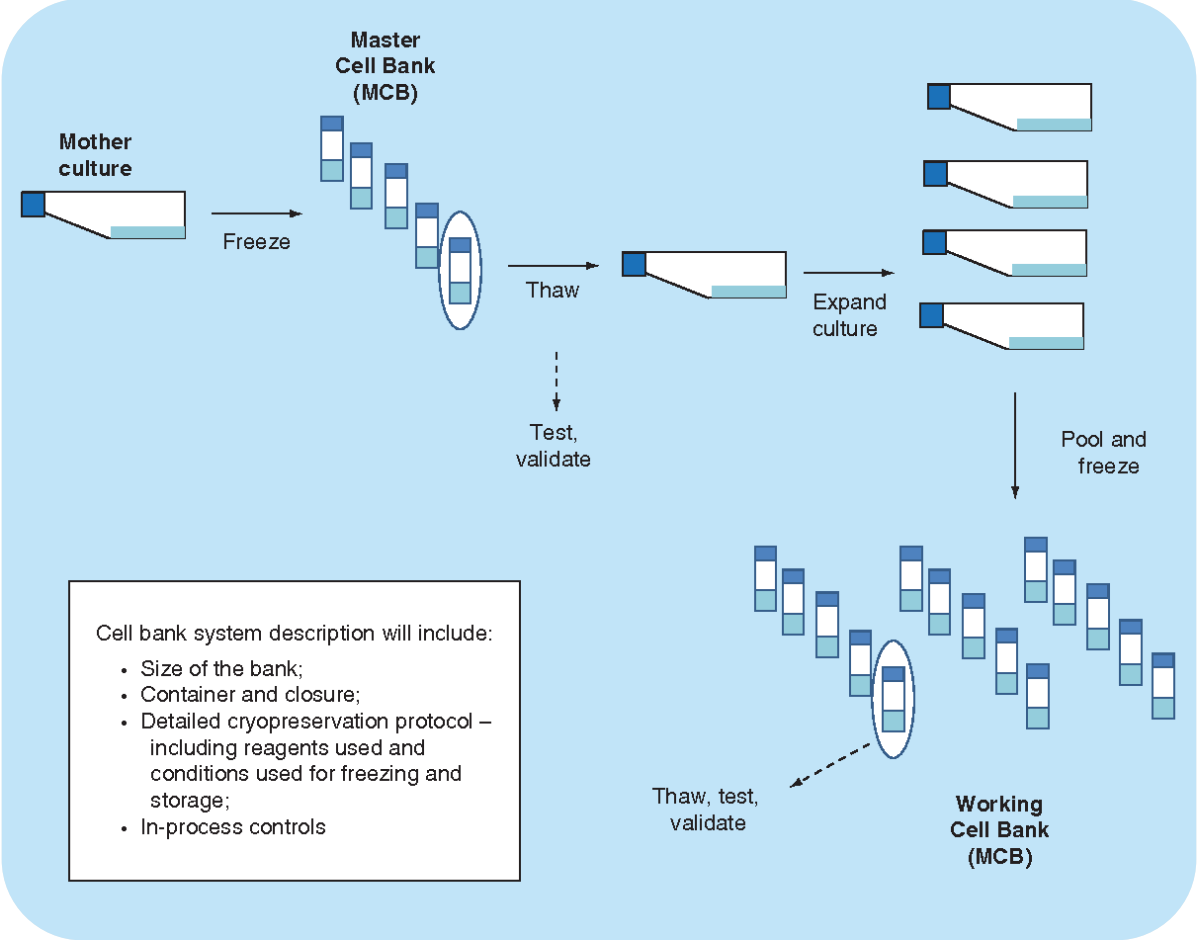
Validation and qualification

- The premises, supporting utilities, and equipment have been built and installed in compliance with their design specifications (installation qualification or **IQ**);
- The premises, supporting utilities, and equipment operate in accordance with their design specifications (operational qualification or **OQ**);
- A specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or **PQ**)

Conducting planned and periodic audits

- An audit is a "**systematic, independent and documented process** for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit are fulfilled.
- Several audit methods may be employed to achieve the audit purpose.
- Audits must be conducted at periodic intervals, such that nothing will be missed.
- Since auditing is an improvement exercise, it must be encouraged across the organization.

MAINTENANCE OF cGMP CELL BANKS



CELL BANKING SYSTEM (ICH Q5D / EMEA)

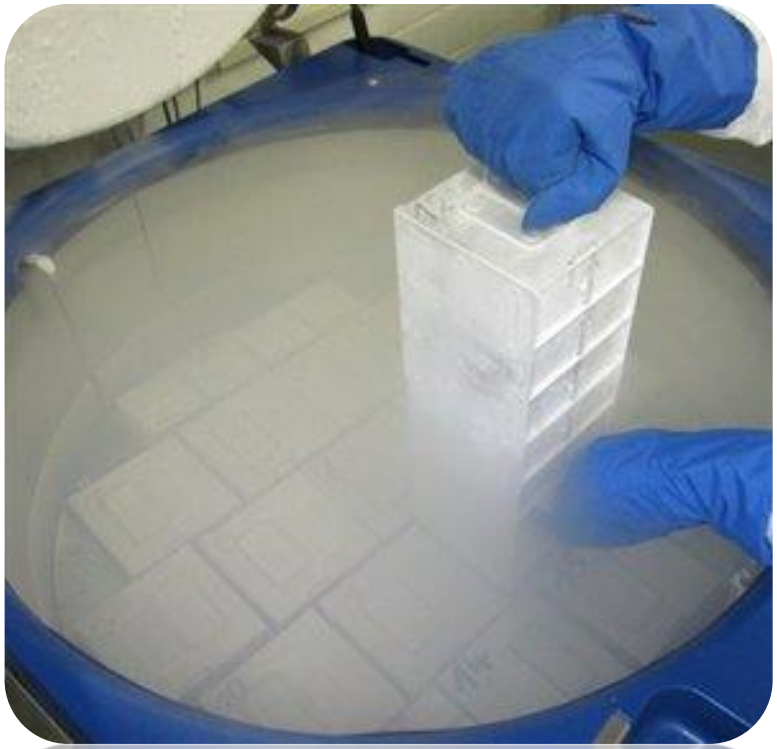
- **Cell bank** – A cell bank is a collection of appropriate **containers**, whose contents are of **uniform composition**, stored under **defined conditions**. Each containers represents an aliquot of **a single pool** of cells.

- The **type** of banking (**Private** vs. **Public**)
- **Size** of cell bank, **container** and closure system, cryopreservation and storage methods.
- The procedures used to avoid **microbial contamination** and cross contamination
- **Labelling system** which can withstand the process of preservation, storage, and recovery from storage without loss of labelling information on the container.

CELL BANKING (ICH Q5D / EMEA)

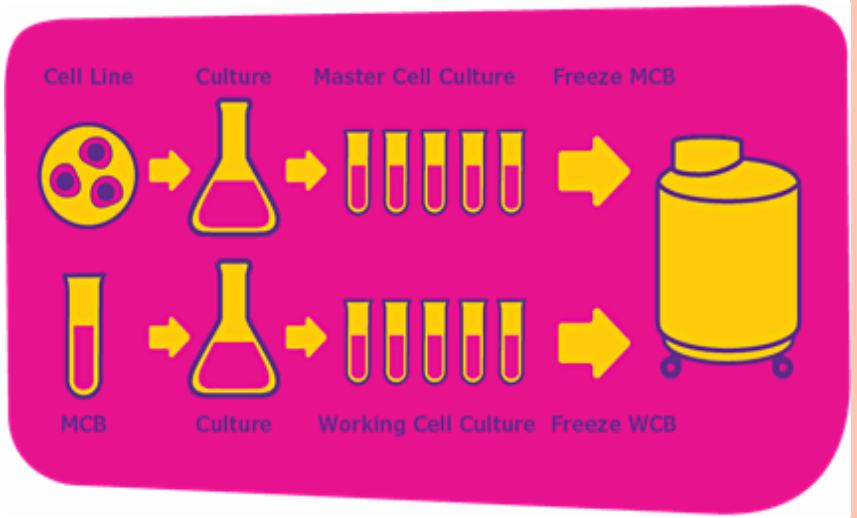
- The cell bank system consists of two tiers:
  1. Master Cell Bank (MCB)
  2. Working Cell Bank (WCB)

- **MCB (Master Cell Bank)** An aliquot of a single pool of cells prepared from the selected clone under defined conditions. The MCB is used to derive working cell banks



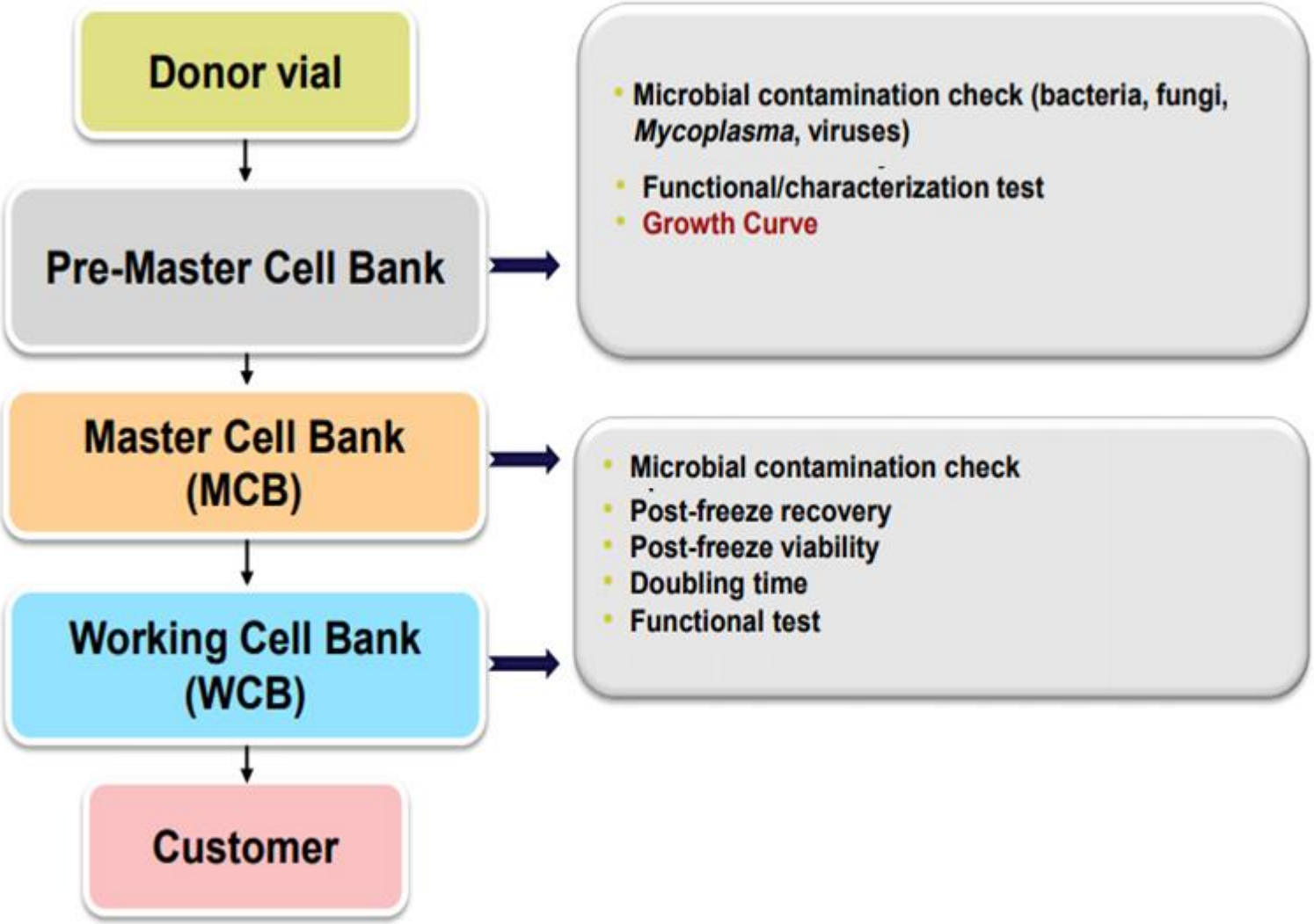
CELL BANKING (ICH Q5D / EMEA)

- **WCB (Working Cell Bank)** – The Working Cell Bank is prepared from aliquots of a homogenous suspension of cells obtained from culturing the MCB under defined culture conditions.



- A newly prepared WCB should be appropriately qualified by characterization and testing

Cell banking diagram



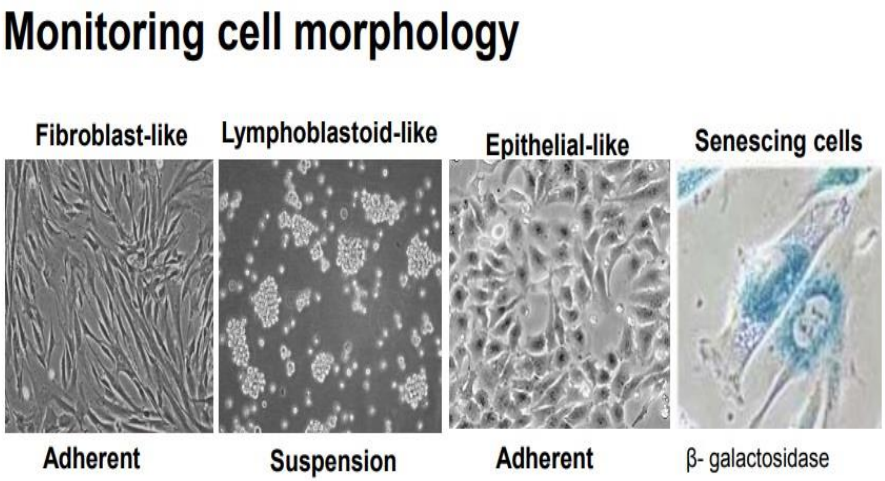
Testing objectives of cells

- Confirm identity
  - Phenotypic (morphology)
  - Flow cytometric immunophenotyping
  - Genotypic (G-banding Karyotyping)

- Confirm purity

1. Tests for presence of Bacteria & fungi
2. Tests for presence of Mycoplasma
3. Sterility testing.
4. Viability testing.

- Confirm Suitability or Stability



Test for microbial contamination

Bacteria and Fungi

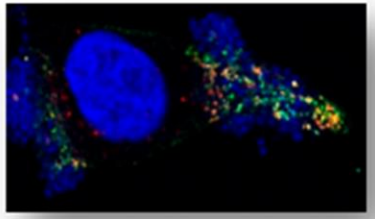
- Microbiological culture (Aerobic, Anaerobic)
- PCR

Mycoplasma

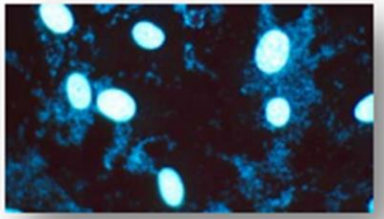
- Direct agar culture
- Indirect Hoechst stain
- PCR

Viruses

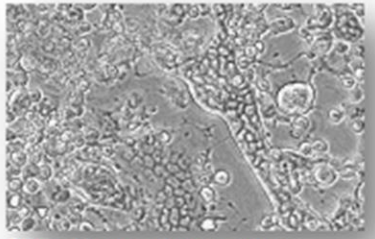
- Cytopathic effect (CPE)
- Indirect immunofluorescent antibody (IFA)
- Enzyme immunoassay (EIA)
- PCR



HeLa contaminated with *E. coli*



M. hyorhinis infection



CPE of human herpes virus

CELL BANK STORAGE

The cell bank storage should be:

- Long term storage
  - liquid nitrogen, ultra-low temperature freezer

  or
  - Vapor phase (as compared to the liquid phase).
- Cell stability under the freezing and storage conditions
  - should be validated using cell recovery or viability data.
- Storage of MCB & WCB should be in two or more locations.
- Access of cell bank should be restricted

REFERENCES

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“GOOD SEEDS GIVES YOU SWEET FRUITS”

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