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Challenges in Validating Radiation Sterilization with Low Energy Electron Irradiation

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Low Energy Electron accelerators

80 – 300 keV

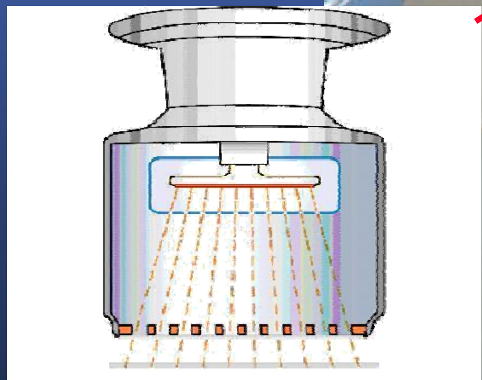
Scanned beam or extended cathodes

Self-shielded

Risø HDRL accelerator

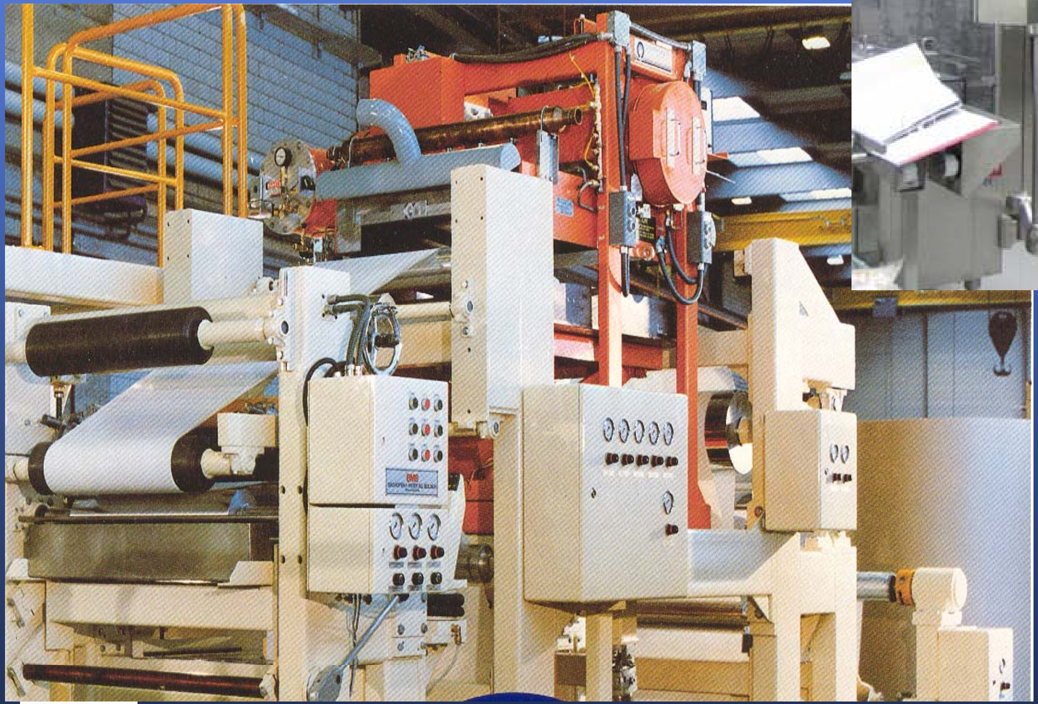
Energy: 80-125 keV

Beam current: 1-10 mA



Low-energy electron beam applications

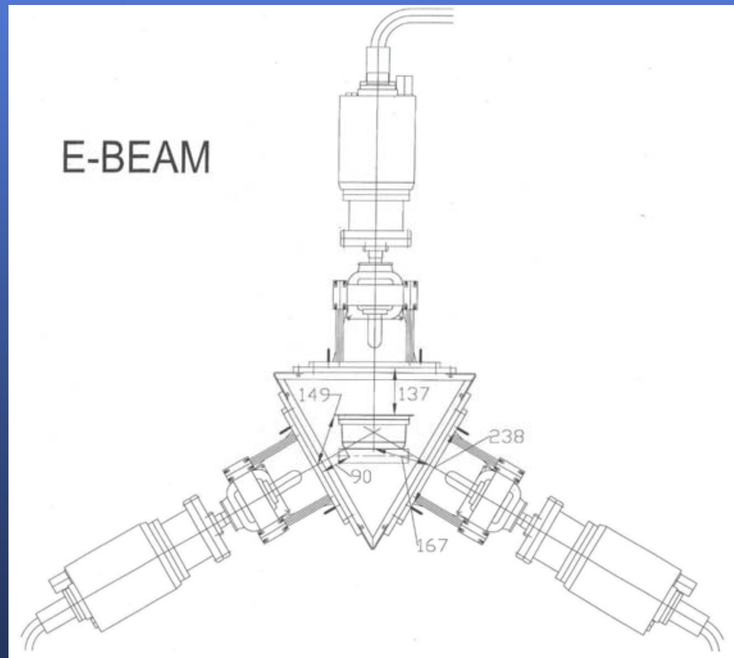
Polymers
– Curing and crosslinking



Pharmaceutical
- Sterilization of
packaging material

Electron beam tunnel

Application: Surface sterilization of tubs with syringes for vaccines



Problem:

- Surface sterilization of tubs is not regulated.
- It concerns sterilization – or decontaminatation – of container for container of pharmaceutical product.
- It is not a medical device.
- It is not a pharmaceutical product.

Suggested solution:

- Use the international standard for Radiation Sterilization as basis for documentation

Documentation requirements for sterilization:

EN ISO 11137 part 1:

Sterilization of health care products – Radiation – Requirements for development, validation and routine process control of a sterilization process for medical devices.

The principles of 11137 can be applied to any irradiation process

- even curing and crosslinking with low-energy electrons
- and also surface sterilization with low-energy electrons

Definition of validation (EN ISO 11137-1, 3.47):

- documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications.

Note 1: For the purpose of this part of ISO 11137, validation has at least the three main elements, IQ, OQ and PQ.

Outline of EN ISO 11137-1:2006

- Calibration and measurement traceability (4)
- Equipment characterization (6)
- Product definition (7)
- Process definition (8)
- Validation (9)
    - Installation Qualification (9.1)
    - Operational Qualification (9.2)
    - Performance Qualification (9.3)
    - Routine Process Control (10)

ISO ASTM standards for characterization of irradiation facilities follow the 11137 outline.

e.g.:

ISO ASTM 51649	High energy electron accelerators (0.3 – 25 MeV)
ISO ASTM 51818	Low energy electron accelerators (80 – 300 keV)

Calibration and measurement traceability

Recommended methods for calibration of dosimeters:

1) Irradiation of dosimeters at the facility of use (in-plant calibration).

   Dose measured with reference dosimeters.

2) Irradiation of dosimeters at calibration laboratory followed by in-plant verification.

Measurement traceability is not established without in-plant irradiation for calibration or verification.

Measurement traceability chain

National Standard

Reference Field → Routine Dosimeter

Reference Dosimeter → Irradiation at Facility

2nd Lab. Ref. Field → Routine Dosimeter

Reference Dosimeter

Irradiation at Facility

Routine dosimeter

Calibration and measurement traceability

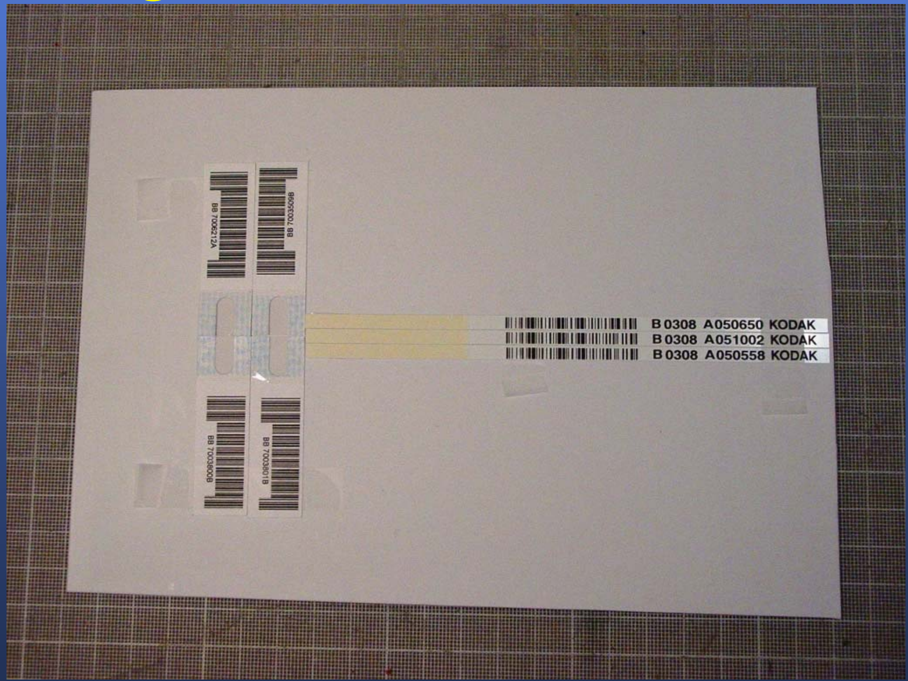
For Irradiation at the facility of use (in-plant calibration) dose is measured with reference dosimeters.

Problem:

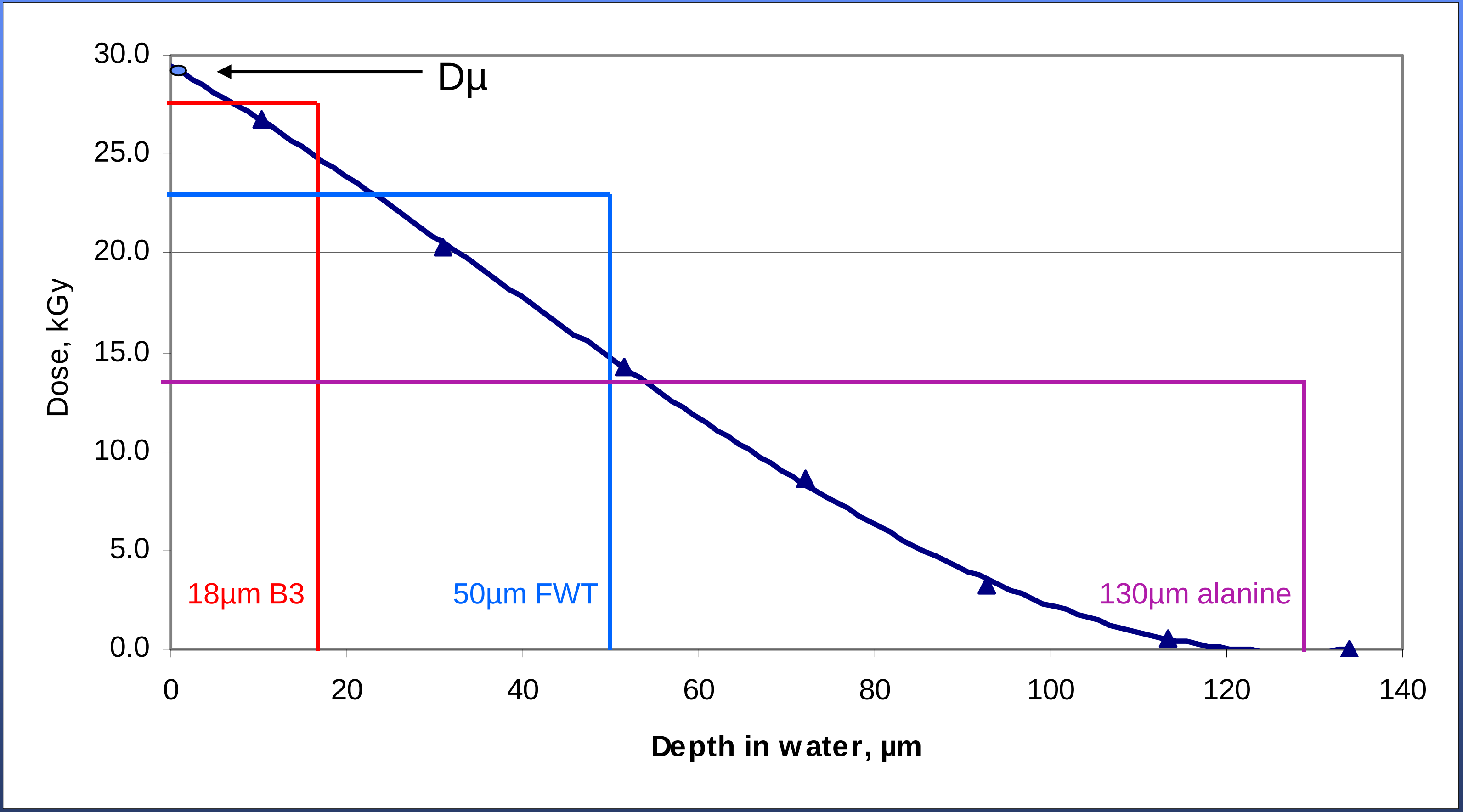
Dose gradients within dosimeters lead to different thickness dosimeters measuring different doses in the same radiation field.

Solution :

Evaluate surface dose – Dµ – for all dosimeters.



Concept of surface dose – Dµ



Process definition

1) - Specifying a maximum acceptable dose.

2) - Specifying a minimum dose for obtaining a required level of sterilization.

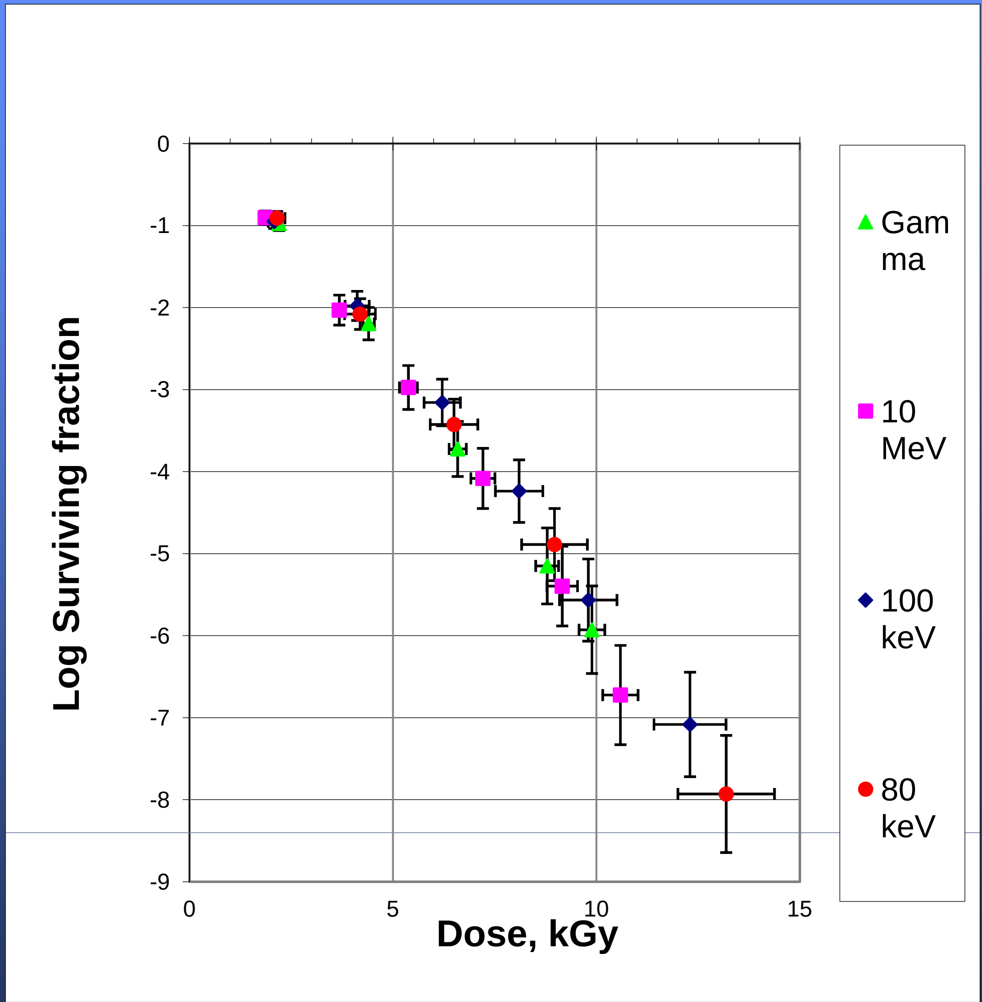
1) Maximum dose concerns Tyvek cover only.

   Typical maximum acceptable dose 100 kGy

2) Required level of sterilization not specified – and therefore required minimum dose not specified.

   Users have specified required minimum dose at 15 kGy or 25 kGy.

Process definition



Important question:

Is low energy electron radiation effective for killing microorganisms?

Study comparing effectiveness of Cobolt-60 Gamma, 10 MeV electrons and 100 keV electrons using b.Pumilus.

Result: Same effectiveness

Conclusion: Dose setting methods of 11137-2 can be used.

Installation qualification - IQ

- *is carried out to demonstrate that the sterilization equipment and any ancillary items has been supplied and installed in accordance with their specification.*

Whether or not data are “in accordance with their specification” depends on agreement between user and supplier.

Dosimetry measurements are often the same as used for Operational Qualification.

Operational qualification - OQ

OQ shall demonstrate that the irradiator, as installed, is capable of operating and delivering appropriate doses within defined acceptance criteria.

- provides baseline data to show consistent operation of the facility

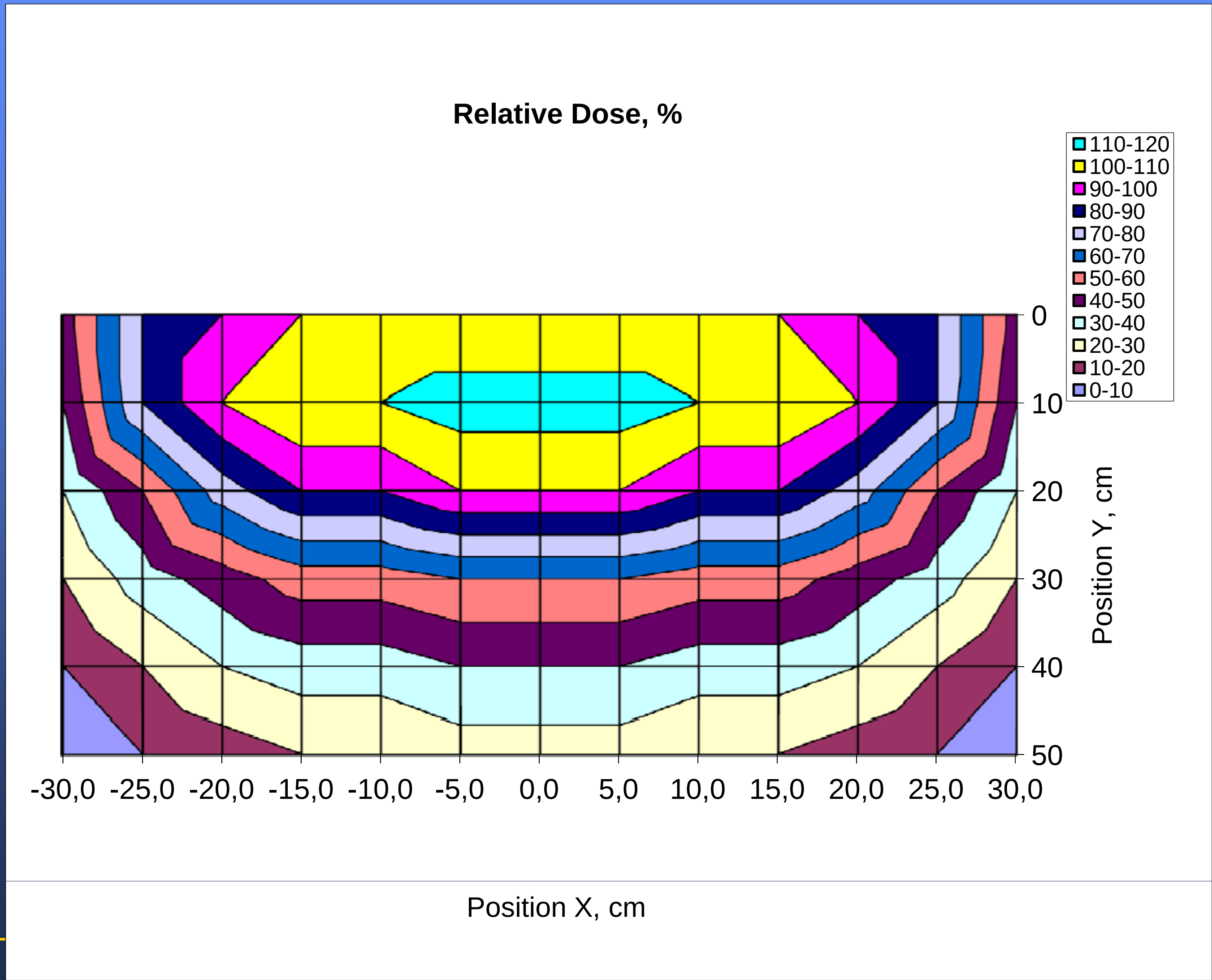
Operational qualification - Electron beam

Characteristics to be measured	
Dose distribution in reference product	Not relevant for low energy
Beam width and homogeniety	Important
Energy and beam penetration	Energy: Not important Beam penetration: Important
Dose as function of speed, current and beam width	Important
Beam spot size	Not relevant for low energy – in most cases
Effect of process interruption	Not relevant for low energy – in most cases

OQ is often carried out using a reference product

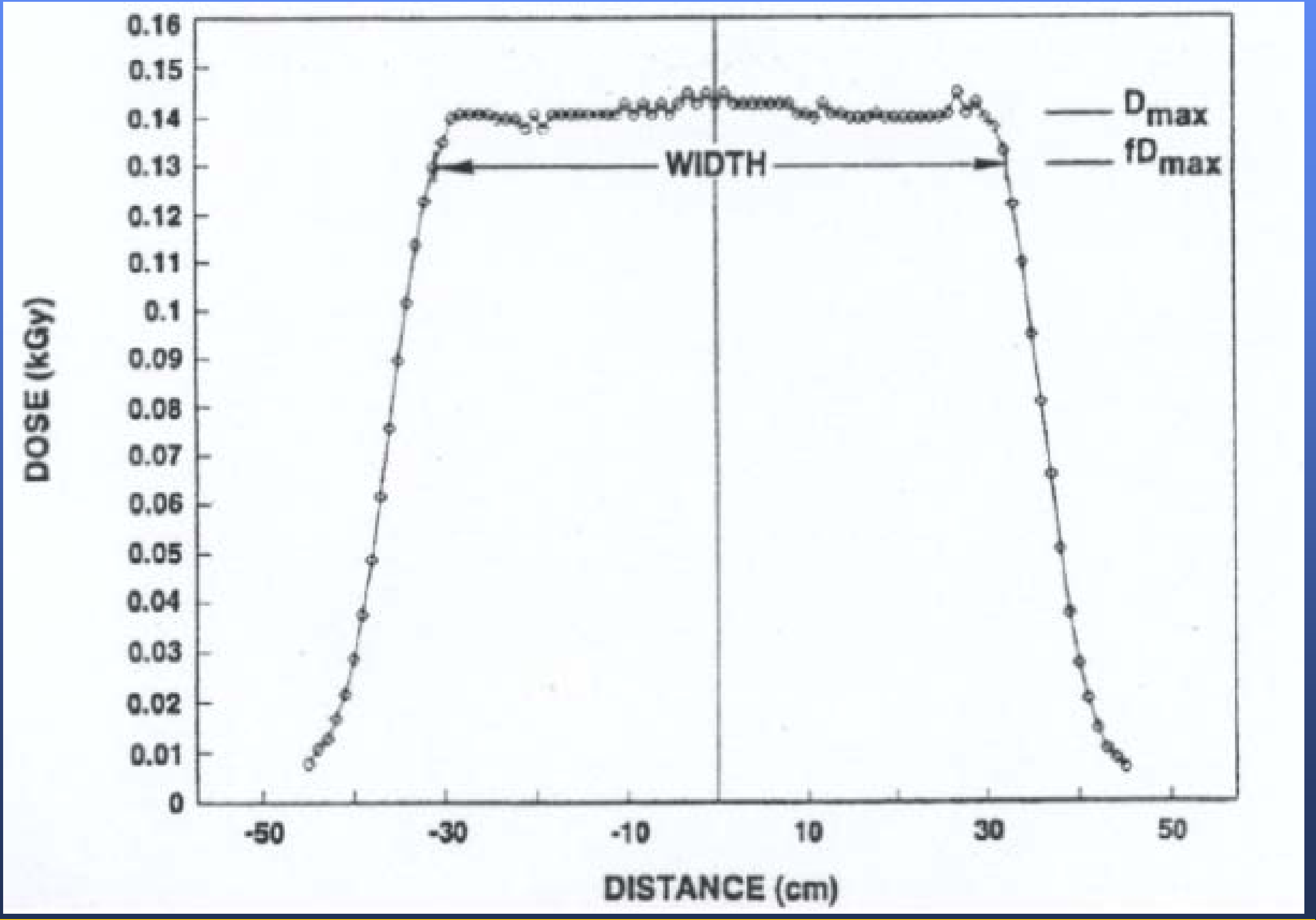
Dose distribution in reference product

High-energy example



Beam width – high energy beam

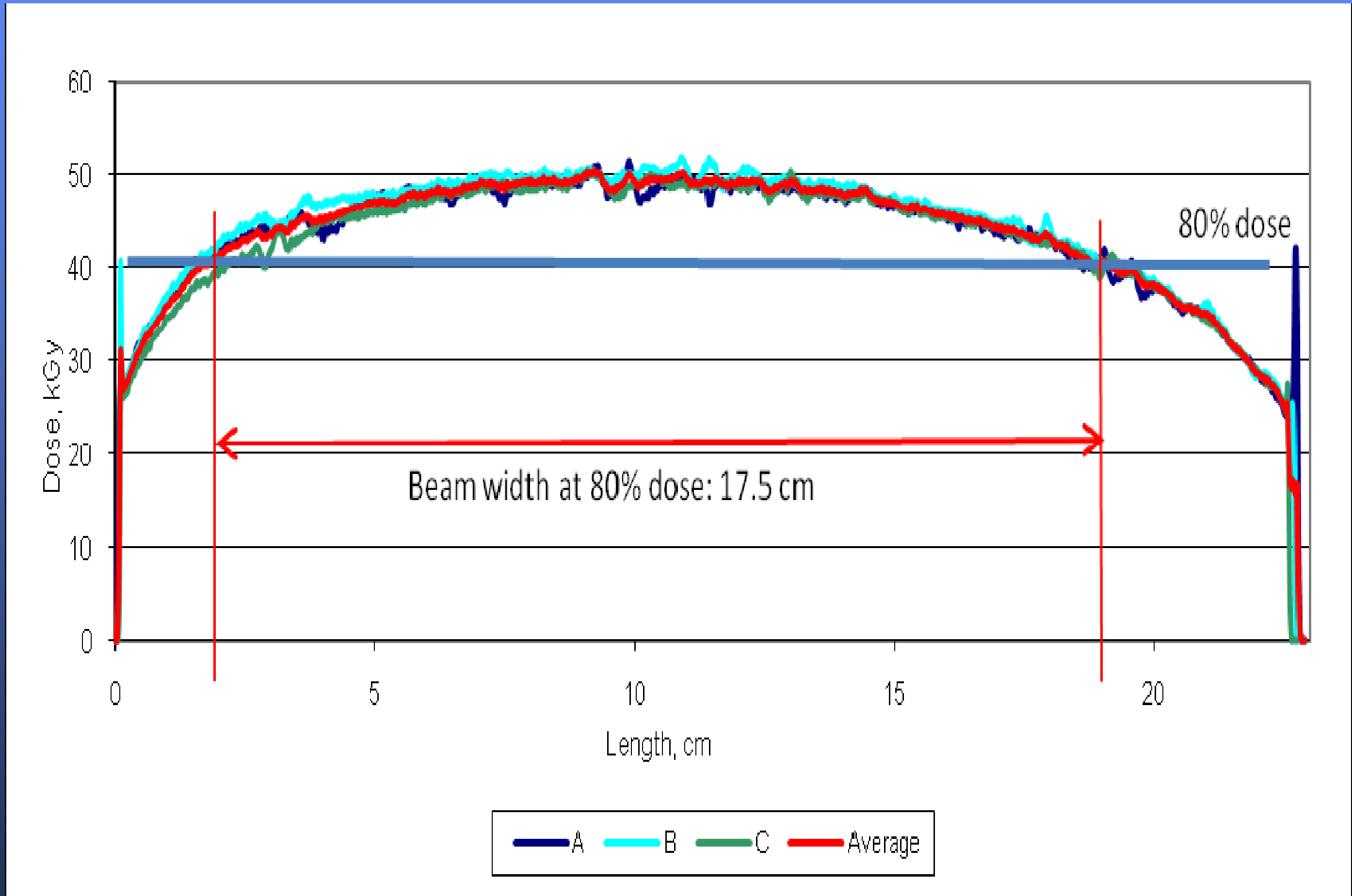
Limits for acceptable variations can be defined.



OQ E-beam cont..

Beam width – low energy beam

Beam width 17.5 cm at 80% dose level

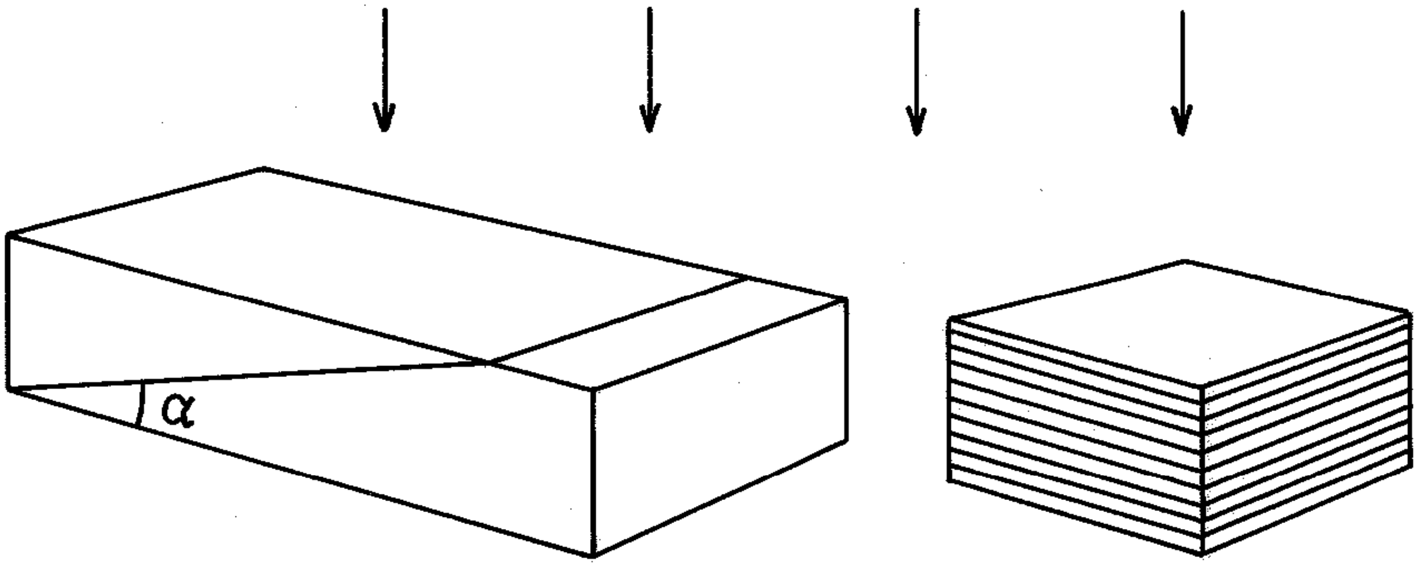


Beam width – low energy beam

Beam wider than measurement

OQ E-beam cont..

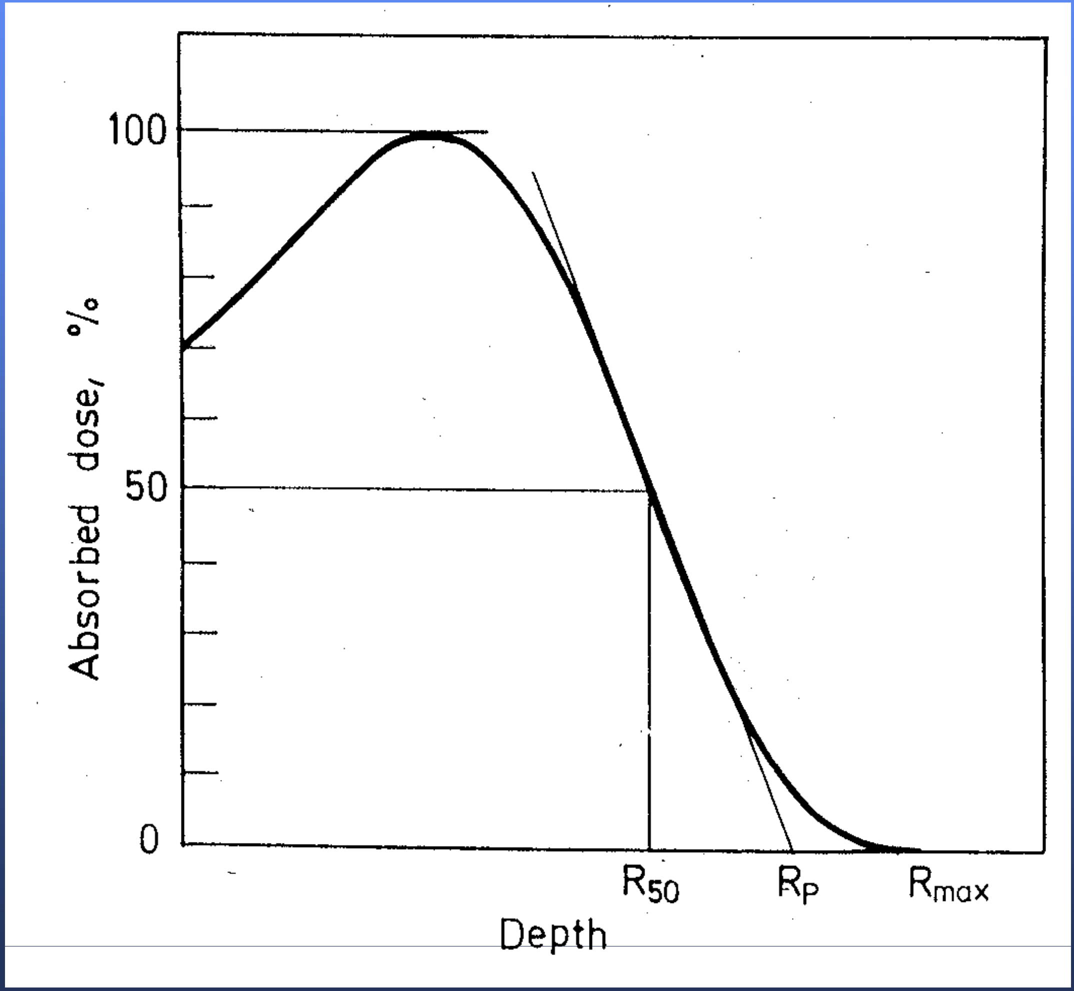
Energy - Wedge and stack for energy measurement



OQ E-beam cont..

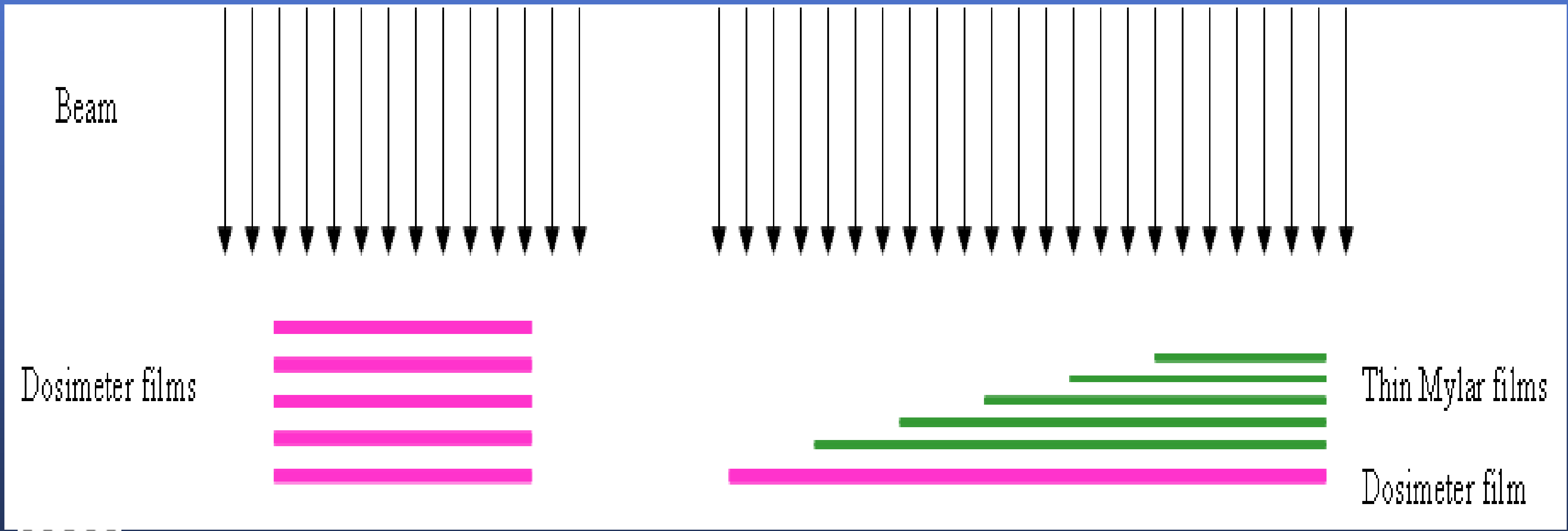
Typical depth-dose curve

Energy – range relationships



OQ E-beam cont..

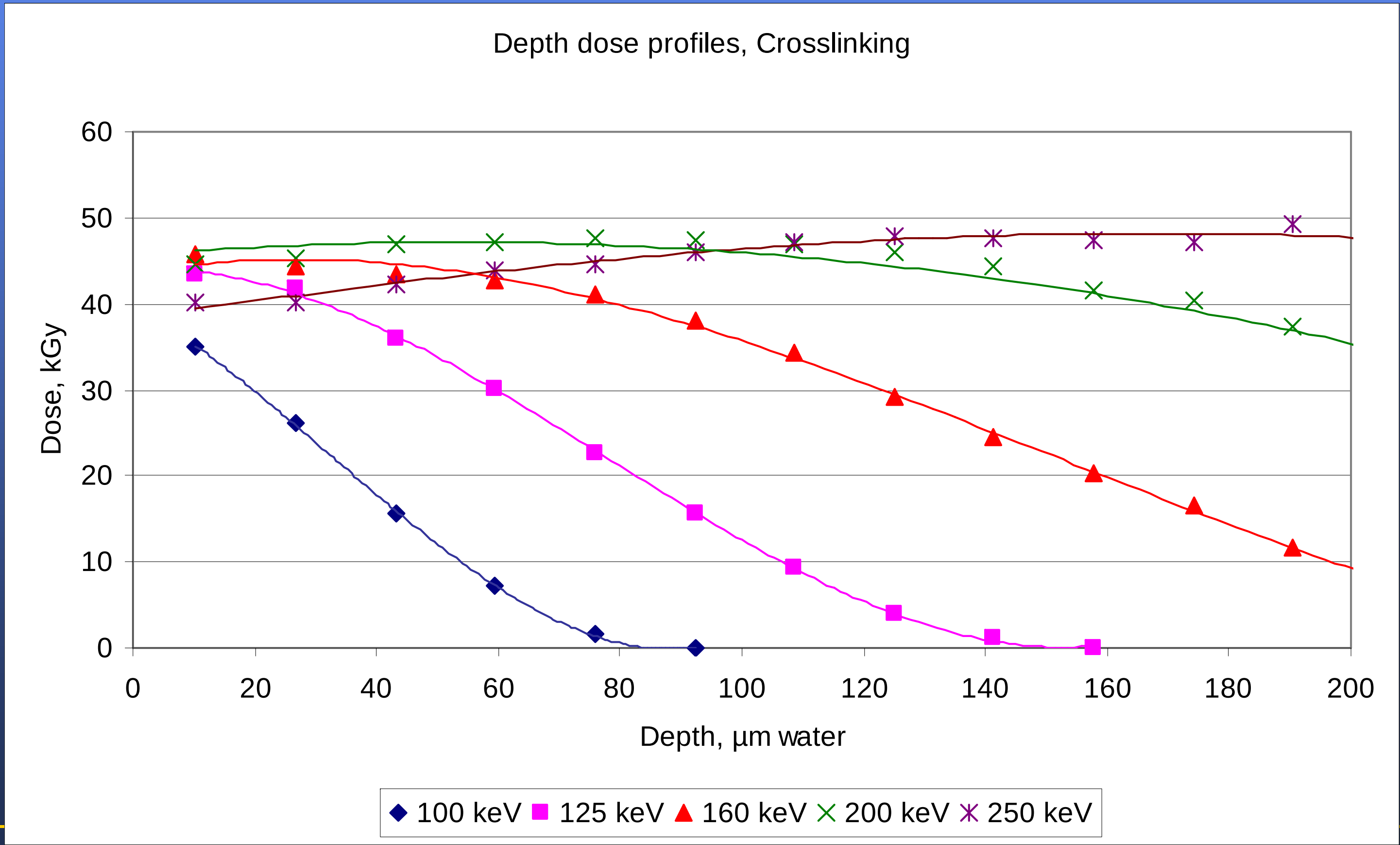
Low energy - arrangements for measurement of depth dose



OQ E-beam cont..

Low energy - Depth dose curves

Energy determination difficult – usually not carried out

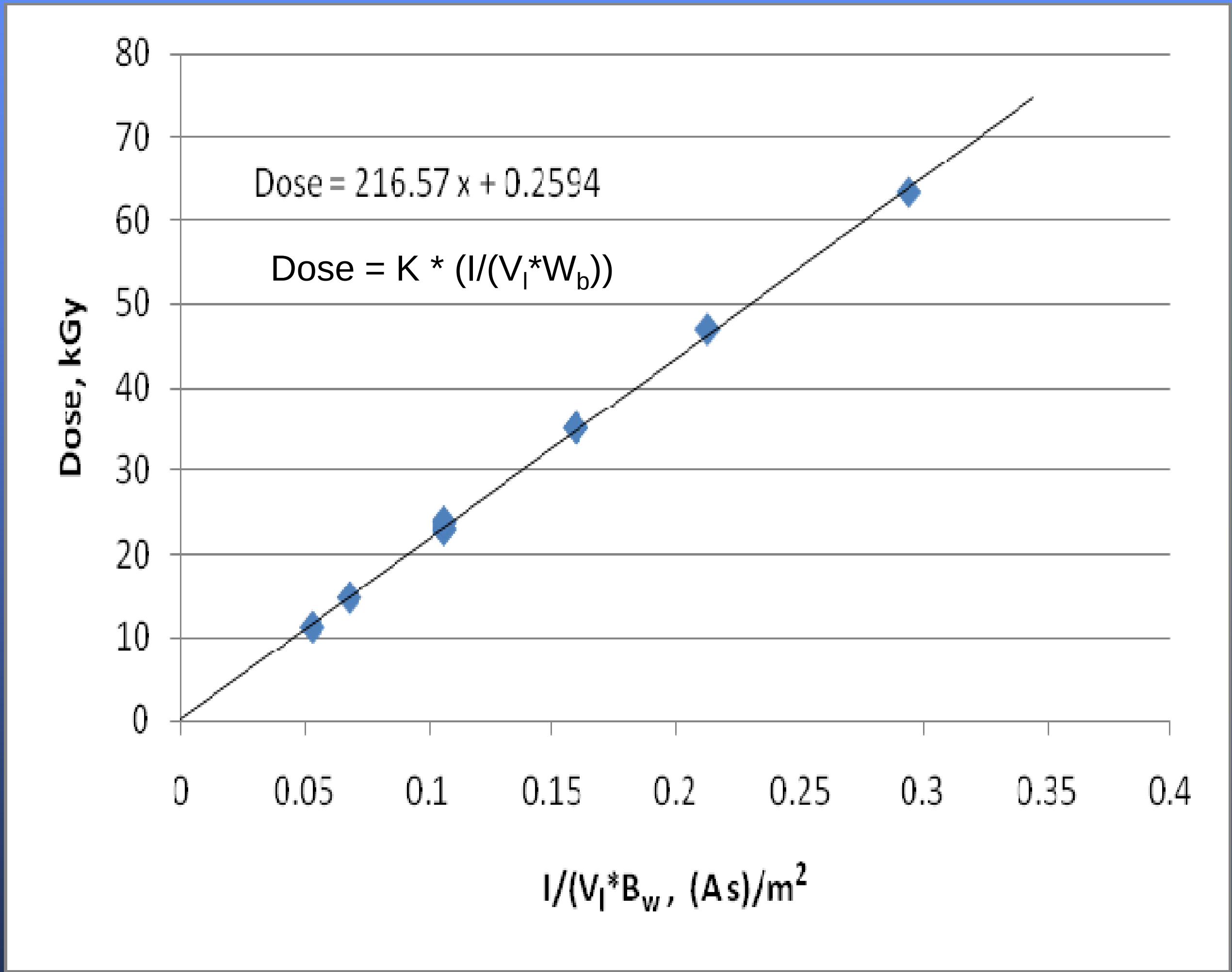


OQ E-beam cont..

Dose as a function of

- beam current
- conveyor speed
- beam width)

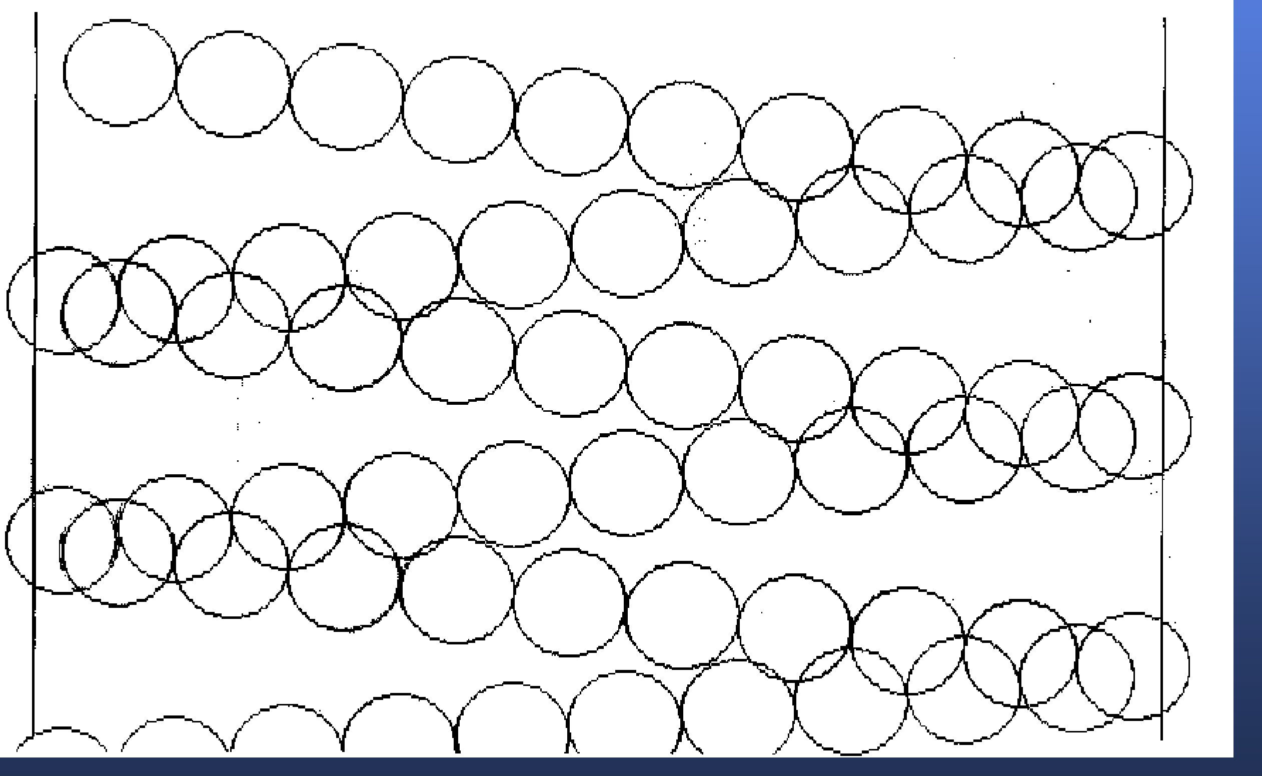
Measured at a low energy accelerator



Beam spot size.

Might be relevant for scanned beams
at high-speed product movement

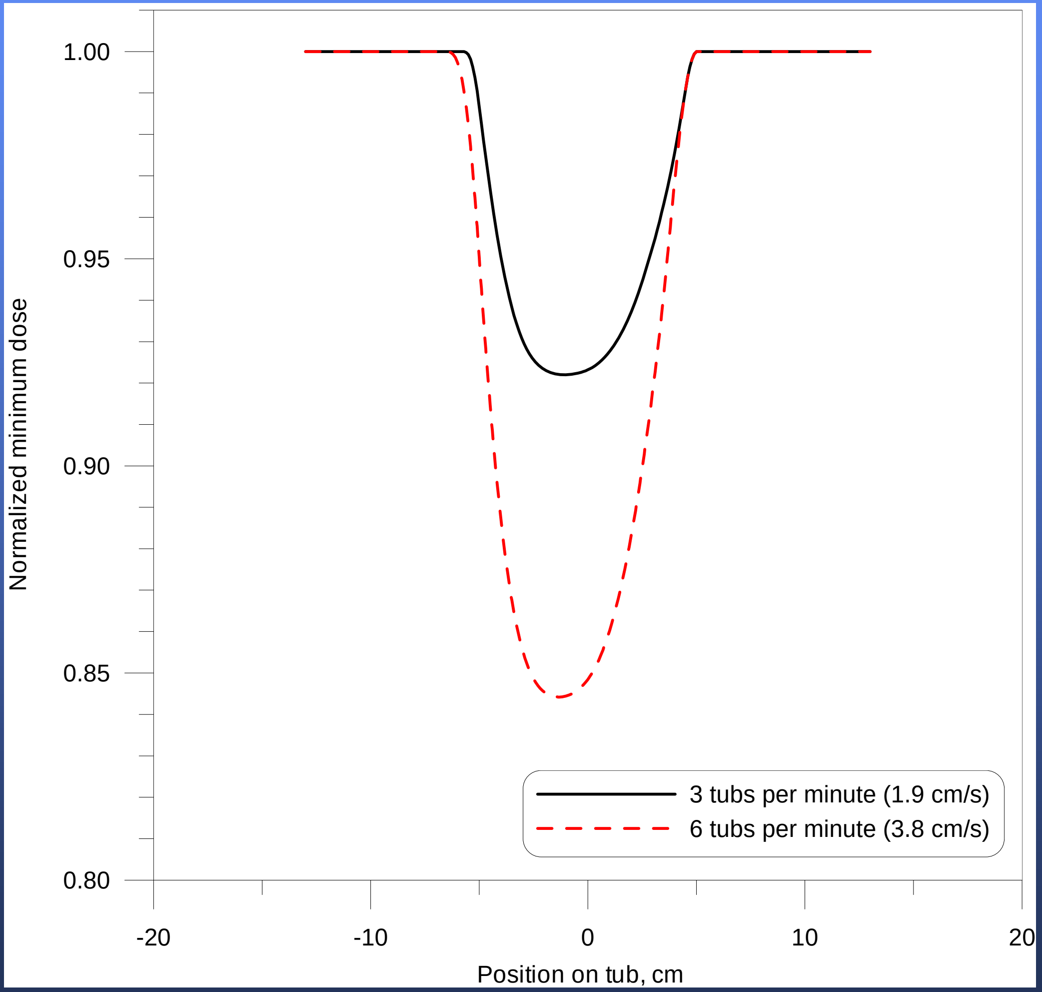
Example of
scanned and
pulsed beam



Process interruption

Normally no problem – product is discarded at process interruptions

Process interruption – effect due to sparks



Repeat of OQ to be specified by operator.

(A.12.4.1) The intervals for requalification of the irradiator should be chosen to provide assurance that the irradiator is consistently operating within specifications.

- Different elements of OQ can be repeated at different time intervals

- If requalification measurements show that the IQ and/or OQ status of the irradiator has changed, then PQ might have to be repeated.

Performance Qualifiaction

- dose mapping of real product

PQ dose mapping is carried out to demonstrate

- that minimum dose to product exceeds the dose required for the intended effect and
- that maximum dose to product does not exceed a maximum acceptable dose.

In many low-energy applications OQ and PQ are combined.

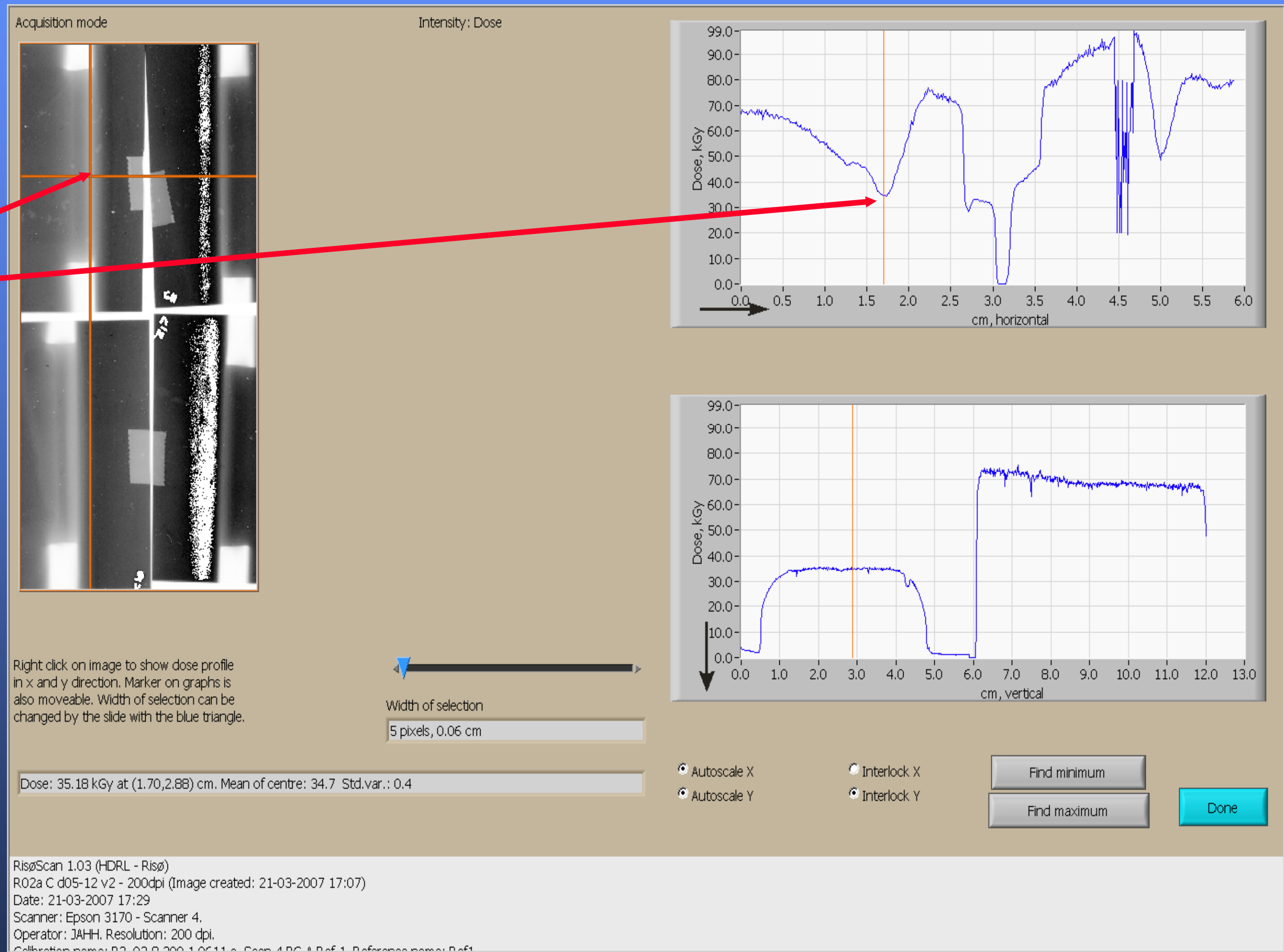
PQ Dose map

Risø B3 dosimeters placed on tub for an isolator in a filling line.

Dose measurement with RisøScan

Minimum dose

34.7 kGy



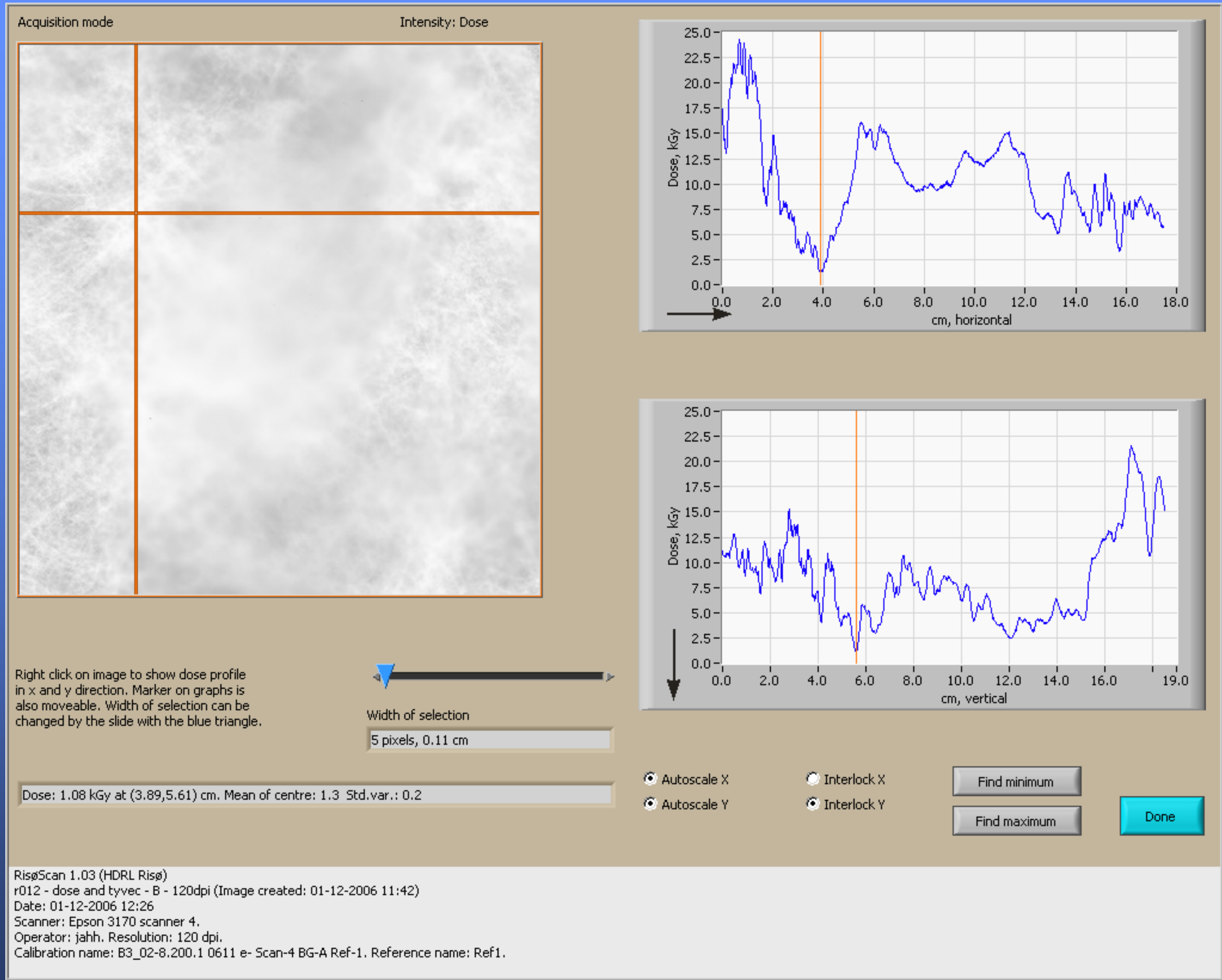
Repeat measurement of minimum dose

Risø B3 dosimeters on 10 trays

Avoid ozone in tub

Dose under Tyvek cover

RisøScan + Risø B3 measurement



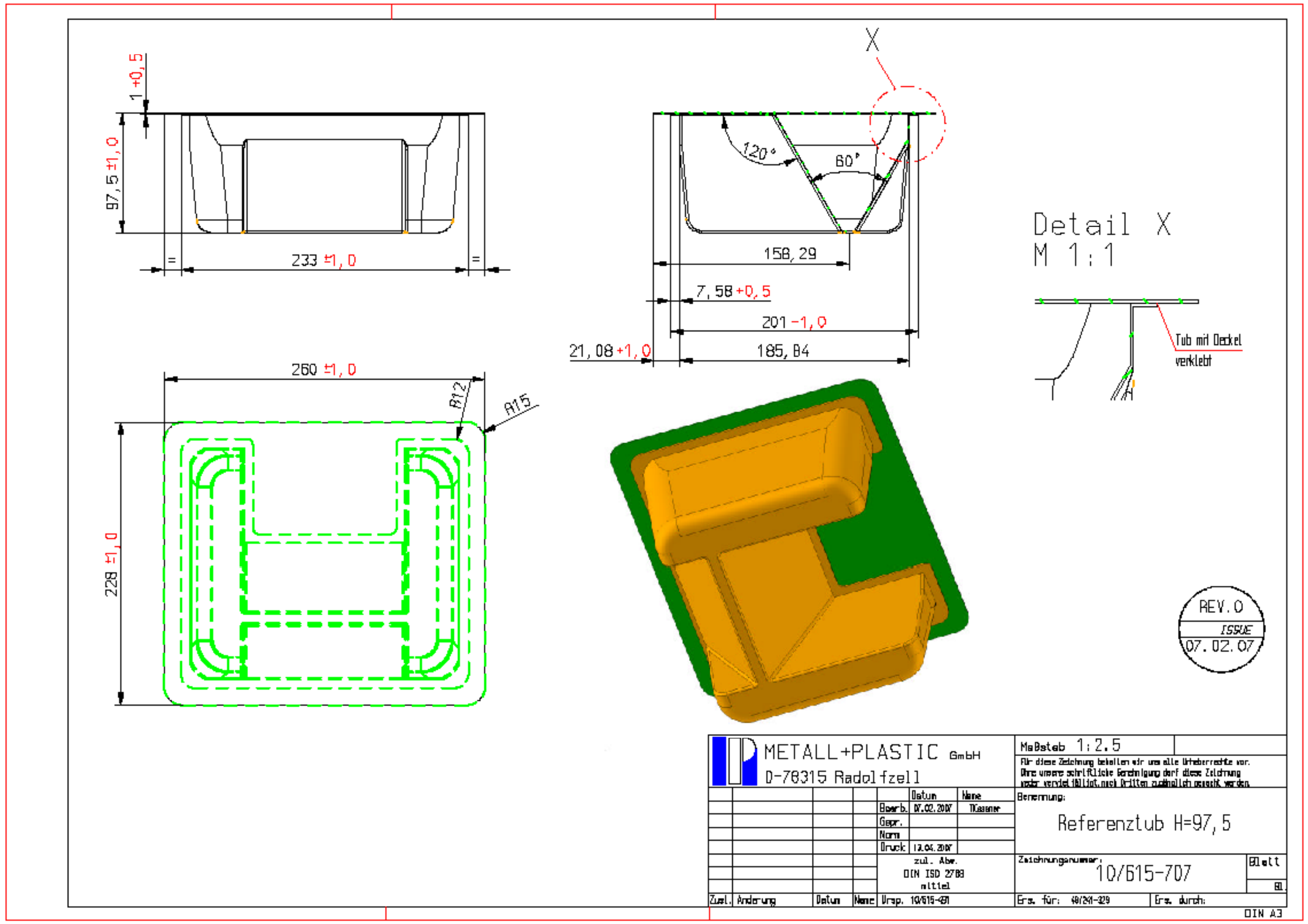
Routine Process control

Measurement of routine dose

The dose at a routine monitoring position shall be measured at intervals specified by the operator of the facility.
The intervals shall be chosen to provide assurance that the irradiator is consistently operating within specified limits.

Low energy E-beam
- characterization and monitoring

Reference product for electron beam tunnels



Low energy electron Dose monitoring

Dosimeters placed on reference tub for routine dose measurement

Or place dosimeters on normal tub

Routine Process control

1) Monitoring of process parameters

The process parameters (beam energy, beam current, beam width and conveying speed) shall be monitored to provide assurance that the irradiator is consistently operating within specifications.

2) Measurement of routine dose

The dose at a routine monitoring position shall be measured at intervals specified by the operator of the facility.
The intervals shall be chosen to provide assurance that the irradiator is consistently operating within specified limits.

3) Apply statistical process control (SPC) on the measured data.