



EMA Guidance & Current Experience with New Drug Submissions

PQRI/USP Elemental Impurities November 2017

Sven-Erik Hillver

Medical Products Agency

Sweden

Acknowledgement and Disclaimer

- This presentation is based on discussions within the ICH Q3D EWG and IWG, within the QWP as well as the experience from actual submissions assessed by the Swedish MPA
- Some slides of this presentation contain material from the training modules made by the ICH Q3D Implementation Working Group (IWG) which is published protected by copyright as on the ICH website, that may be reproduced, incorporated into other works, adapted, modified, translated or distributed under a public license
- The views expressed in this presentation represents the view of the author. They are not necessarily in all parts reflecting the opinion of the ICH, the QWP or the MPA

Content

- Implementation Issues and EMA Guidance on them
- ICH Q3D on Elemental Impurities – Current Experience
 - What is the picture so far
 - Summary of Risk Assessment
 - A real example
 - Regulators expectations

Q3D Implementation Timeframes

- New MA for new product (new active substance)
 - June 2016
- New MA for product with existing active substance
 - June 2016
- Marketed products including new MR applications of already approved products
 - December 2017

Existing Marketed Products – Should Comply from December 2017

- Risk Assessment should be performed, documented and be kept available.
- No variation is necessary if the Risk Assessment show that for compliance:
 - **No further controls** on elemental impurities to materials such as the designated active substance starting material, synthesis intermediates, active substance, excipients or the finished product are needed.
 - **No replacement or change of quality of materials** such as the designated active substance starting material, synthesis intermediates, active substance, excipients or of the manufacturing equipment is needed.
 - **No change of the manufacturing process** is needed.
- In other cases a variation is needed.
 - Categorised according the Variation Guidelines (Official Journal 2013/C 223/01)
 - Accompanied with the documentation required in the Variation Guideline.
 - In addition contain a summary of the Risk Assessment and the conclusions drawn.

Q3D Implementation Issues

- After the adoption of the Q3D Guideline, discussions among Regulatory Assessors as well as with Industry Representatives have
 - revealed some areas that would benefit from some further clarification/interpretation
 - raised some questions in relation to the previous EMA Guideline on Catalysts and Reagents
 - indicated a need to clarify the role of the European ASMF and CEP systems in relation to Q3D

Implementation of Q3D in the EU

- I will highlight some aspects
 - Use of the Control Threshold
 - Number of batches needed
 - Intentionally added elements in last step
 - Drug product approach
- Some of these are also discussed in a document
 - Implementation strategy of ICH Q3D guideline (EMA/CHMP/QWP/115498/2017)

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500222768.pdf

Testing for Elemental Impurities

- In ICH Q3D compliance should be ascertained by *testing when necessary*
- Companies want to know when it is **not** necessary
 - no further controls or measures are necessary, where the Risk Assessment/Management predict a low risk
- The basis for this prediction (the Risk Assessment) must be more than just an analytical snapshot
 - as it will provide an assurance for the future that the likelihood of exceeding the PDE is negligible

The Use of the Control Threshold

- The concept of Control Threshold is introduced to facilitate the decision on when it is necessary to test
 - *If the total elemental impurity level from all sources in the drug product is expected to be **consistently less than 30%** of the PDE, then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities. (ICH Q3D)*

What is Meant by *Consistently* Below the Control Threshold?

- The Control Threshold is **not** an extra limit needed to comply with
 - but between the Control Threshold and the PDE compliance must be ascertained by controls
- Therefore it is necessary to judge if being below the Control Threshold is likely **also in the future**
 - variability and uncertainty must be considered
- To justify not testing, it should be unlikely that the Control Threshold will be exceeded in the future
 - the decision will be easy when the levels are far below
 - the closer the levels are, the more difficult to judge

Control Threshold – Number of Batches

- The guideline states
 - *At the time of submission, in the absence of other justification, the level and variability of an elemental impurity can be established by providing the data from three (3) representative production scale lots or six (6) representative pilot scale lots of the component or components or drug product.*
- To justify **no further controls**, this number of batches is a minimum that could be sufficient
- Levels approaching the Control Threshold means that more batches may be necessary for concluding "consistently below"
 - the number of batches should be commensurate with the risk of exceeding the Control Threshold

Intentionally Added Elements – ICH Q3D

- To comply with Q3D
 - Intentionally added elements must **always be included** in the Risk Assessment
 - The need for a specification will **depend on the outcome** of the Risk Assessment

Intentionally Added Elements – ICH Q3D

- Intentionally added elements in active substance should be known to applicant and authorities since
 - Details of the synthetic route including the use of catalysts or reagents is mandatory either
 - in the dossier itself in case of an in-house synthesised substance
 - in an ASMF or
 - in a CEP dossier in case of an outsourced substance

Intentionally Added Elements – Catalyst used in the Last Step of the Synthesis

- This constitutes an elevated risk
 - *Impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations (e.g., washing, crystallisation of isolated intermediates) than impurities generated late in the manufacturing process, and are therefore less likely to be carried into the drug substance (ICH Q11).*
- Special considerations are warranted

Intentionally Added Elements – Catalyst used in the Last Step of the Synthesis

- Less reassurance from purging compared to a synthesis with multiple subsequent steps
- Therefore possibly greater impact in case of any unexpected events
- Due to this
 - the need to have a specification is more likely
 - the absence of a specification must be justified by evidence of purging
 - where evidence is scares but promising, skip testing may be possible

Drug Product Approach

- The Drug Product Approach is an option in Q3D
- It is possible to comply with Q3D by testing the product
- To justify the omission of testing for an element,
 - there must be some level of understanding of possible sources (Risk Assessment)
 - representative batches tested e.g. covering all suppliers
- With a Risk Assessment – depending on its outcome – the number of batches tested should be commensurate with the risk of the elemental impurities present

ICH Q3D on Elemental Impurities – Current Experiences after June 2016

- We have seen some nice examples where we have had nothing to complain about, but
 - a high number of applications
 - are completely missing any Summary of Risk Assessment
 - have included far too short (high level) Summary of Risk Assessment
- In between we have good examples that have been ambitious but may have missed some link in presenting a compelling "story"

Selection of Approach

- Analysis of Drug Product
 - usually with different levels of Component Risk Assessments to justify some omission of testing
 - but also some cases without Risk Assessment, routinely analysing all elements
- Component Approach
 - quite common
 - ending up with no or only limited routine testing
 - a large interest from API manufacturers to include an active substance Risk Assessment in the CEP (more than 150 so far)

Approaches for Other Routes of Administration

- Development of an Acceptable Limit (AL)
 - recalculation of oral PDE considering bioavailability (topical)
- Applying existing PDE:s that can be argued to be sufficiently protective
 - complying with oral PDE (rectal)
 - complying with parenteral or inhalation PDE (nasal, ocular)
- Applying an extra safety margin
 - complying with oral PDE divided by 100 (vaginal)

Any Observed Risks?

- The lack of, or deficient, Summary of Risk Assessments are usually updated and approved after one/two rounds.
- If not – applications are typically rejected/withdrawn on other grounds as well.
- We have not rejected an application based unacceptable presence of elemental impurities
 - summations based on LoQ:s has occasionally been insufficient to conclude levels being below the Control Threshold

A Real Example – Summary of Risk Assessment

New application for an Oral Solution

- *The assessment examined all relevant sources of elemental impurities. During the evaluation of the drug substance, the excipient, the manufacturing process and the packaging material it was identified that the following elemental impurities should be further investigated: Cd, Pb, As, Hg and Ni.*
- *Using Option 2b in the guideline the permitted concentration limits of elemental impurities across drug product component material for a maximal daily dose was calculated and compared to the observed levels of the identified elemental impurities in the excipients and drug substance as declared by the vendor.*

A Real Example – Continued...

- The results showed that none of the identified potential elemental impurities was above the permitted daily concentration. Of all the potential elemental impurities only lead was above the 30% PDE. However since the potential major contributor [Excipient] is controlled by Ph.Eur. no further control strategy was introduced.*

Potential risks	Action/mitigation
Elemental impurities from drug substance	No action required; process control strategy sufficient
Elemental impurities from equipment	No action required; Quality system control strategy sufficient
Elemental impurities from nitrogen	No action required; negligible risk
Elemental impurities from container closure systems	No action required; negligible risk
Elemental impurities from excipients	No action required; major component controlled by Ph.Eur.

22

A Real Example – Continued...

- *The risk assessment for elemental impurities in [Product] was completed. The assessment show that the design and implementation of the inherent controls in the manufacturing and quality system processes ensure that the levels of identified elemental impurities are maintained at or below their respective PDEs.*

A Real Example – The Assessors Concern

- This Summary is not telling a compelling “story”
 - which maximum daily intake of the product is used and how is that calculated?
 - how were the potential sources of EI examined?
 - on what grounds were elements selected or not selected for further investigation?
 - how was Option 2b implemented (individual concentration limits for each element in each component)?

A Real Example – Continued...

- what were the observed or predicted levels of identified elemental impurities that were compared to the established limits?
- how far below the control threshold were these elemental impurities levels?
- how did the Ph.Eur. limit for lead fit into the Company's Option 2b model?
- there was no critical appraisal on the basis for vendor declaration and there validity (specifications, monitoring, other grounds etc.)

A Real Example – Continued...

- Only vague statements without discussion where presented
 - Equipment – quality system control strategy sufficient
 - Nitrogen – negligible risk
 - CCS – negligible risk
- In conclusion it is stated "The assessment show ..."
 - But nothing is shown in the Company's "Summary of Risk Assessment" that enables the Quality Assessor to do a proper assessment

So what are Regulators Expectations?

- The Summary of Risk Assessment should
 - follow the principles lined out in ICH Q3D
 - contain what is **needed to evaluate** the **appropriateness and completeness** of the Risk Assessment process.
 - tell a story to the assessor on what has been **considered, done and concluded**
 - a narrative that clearly explain the assessment made, including all assumptions, calculations etc. made

Regulators Expectations – Continued...

- The Summary of Risk Assessment should
 - **be quantitative**, also when not based on own measurements
 - raw data not necessary, but summary of findings is expected where applicable
 - make it possible to follow the calculations leading to the numbers that are compared with the PDE's
 - tables may be a good way to be transparent and give an overview
 - contain a justification for the **Control Strategy** (what to control and not to control)

Are there Good Examples of Summaries of Risk Assessment?

- The length of good examples submitted preclude introduction in this presentation
- Please,
 - learn from the calculation examples in Annex 4 of Guideline
 - be inspired by the Case studies of the Training Material on www.ich.org
 - Case study 1b is an illustrative example of what a submission could look like
- Important aspects are well illustrated in this Case study as extracted on the next slides

Oversight of Scope of Risk Assessment

(Note: Case Study is an Example – not a Template)

Element	Class	Intentionally added?	Consider in risk assessment	Justification
Cd	1	no	Yes	Included in risk assessment for all components
Pb	1	no	Yes	Included in risk assessment for all components; vendor provided information on observed levels in talc and calcium dihydrogen dihydrate
As	1	no	Yes	Included in risk assessment for all components
Hg	1	no	Yes	Included in risk assessment for all components
Co	2A	no	Yes	Included in risk assessment for all components
V	2A	no	Yes	Included in risk assessment for all components
Ni	2A	no	Yes	Included in risk assessment for all components
Tl	2B	no	No	Not intentionally added in any component.
Au	2B	no	No	Not intentionally added in any component.
Pd	2B	Yes	Yes	Pd is used in the penultimate step of the drug substance process
Ir	2B	no	No	Not intentionally added in any component.
Os	2B	no	No	Not intentionally added in any component.
Rh	2B	yes	Yes	Rh is used to prepare one of the starting materials.
Ru	2B	no	No	Not intentionally added in any component.
Se	2B	no	No	Not intentionally added in any component.
Ag	2B	no	No	Not intentionally added in any component.
Pt	2B	no	No	Not intentionally added in any component.

Summarize Evaluation

Potential source of elemental impurities	Information evaluated	Further consideration in the risk assessment?
Drug substance	Pd is used in the penultimate step of the synthesis. Batch data and commercial scale data review. Class 1 or 2A elements are not intentionally added and are not found as impurities in the drug substance.	Consider potential impact of Pd levels in the drug substance on the drug product.
Excipients	<p>Information supplied from vendors confirms no elements (Class 1, 2 or 3) are intentionally added.</p> <p>Vendor certificates of analysis indicate negligible levels of the following Class 1 and 2A elements: Cd, As, Hg, Co, Ni and V.</p> <p>Vendor certificates of analysis for talc and calcium hydrogen phosphate dihydrate indicate the presence of Pb.</p>	<p>Consider the potential impact of Pb levels in the 2 identified excipients on the Pb levels in the drug product. The currently observed levels can be found in Table 1.</p> <p>Elemental impurity data are generated using a validated method where the Limits of quantitation are below the control threshold, based on the ICH Q3D: Table A2-2 concentrations.</p>

31

Summarize any Data

Component	No. of lots ¹	Element	Mean $\mu\text{g/g}$	Std. Dev. ² $\mu\text{g/g}$	Min $\mu\text{g/g}$	Max $\mu\text{g/g}$	Upper 95% Confidence Limit $\mu\text{g/g}$
Drug substance	3	Pd	36	3	33	39	41
Talc	3	Pb	4	5	0.3	10	12
Calcium hydrogen phosphate dihydrate	3	Pb	4	4	1	8	10

Quantitative Summary

- Don't forget to be quantitative in the Risk Assessment
 - Summarize any analytical results
 - Show the contribution of upstream controls
 - Explain the magnitude of any purging
 - Quantify worst case scenarios to justify negligible contributions
 - Etc.

Show the Quantitative Relation to PDE

Component	Mass of Component in a 50 mg tablet g	Mass of Component in a daily dose (2 tablets) ¹ g	Pb specification limit µg/g	Total lead contribution to the drug product µg
Greatstuff drug substance	0.05	0.1	-	-
Microcrystalline cellulose (PH102) (MCC)	0.09	0.18	-	-
Calcium hydrogen phosphate dihydrate	0.46	0.92	4	3.68
Magnesium stearate	0.003	0.006	-	-
Croscarmellose sodium	0.3	0.6	-	-
Talc	0.057	0.114	5	0.57
Hydroxypropylmethylcellulose	0.04	0.08	-	-
Total tablet weight, g	1	2		
Maximum lead per daily dose when excipient levels are at the specification limits, µg/daily dose				4.25
Lead (Pb) PDE, µg/day				5

Relation to the PDE

- Don't forget to show the relation to the PDE
- Also very important when you refer to the Control Threshold as justification for no further controls
 - The closer to the 30% of PDE results are – the more evidence is needed (e.g. more batch results)
 - Critically discuss the variability
 - Observed variability
 - Possible future variability – e.g. mined material

Thank you!

Period

ICH Q3D

1

I A

2

II A

3

III B

4

IV B

5

V B

6

VI B

7

VII B

8

VIII B

9

VIII B

10

VIII B

11

I B

12

II B

13

III A

14

IV A

15

V A

16

VI A

17

VII A

18

VIII A

1

H

hydrogen

1.008

3

Li

lithium

6.941

11

Na

sodium

22.99

19

K

potassium

39.10

37

Rb

rubidium

85.47

55

Cs

cesium

132.9

87

Fr

francium

223

2

Be

beryllium

9.012

12

Mg

magnesium

24.31

20

Ca

calcium

40.08

38

Sr

strontium

87.62

56

Ba

barium

137.3

88

Ra

radium

226

21

Sc

scandium

44.96

23

V

vanadium

50.94

25

Mn

manganese

54.94

27

Co

cobalt

58.93

29

Ni

nickel

58.69

31

Zn

zinc

65.41

22

Ti

titanium

47.87

24

Cr

chromium

52.00

26

Fe

iron

55.85

28

Cu

copper

63.55

30

Zn

zinc

65.41

39

Y

yttrium

88.91

41

Nb

niobium

92.91

43

Tc

technetium

98

45

Ru

ruthenium

101.1

47

Rh

rhodium

102.9

49

Pd

palladium

106.4

51

Ag

silver

107.9

53

Cd

cadmium

112.4

71

Lu

lutetium

175.0

73

Ta

tantalum

180.9

75

W

tungsten

183.8

77

Re

rhenium

186.2

79

Os

osmium

190.2

81

Ir

iridium

192.2

83

Pt

platinum

195.1

85

Au

gold

197.0

87

Hg

mercury

200.6

13

Al

aluminum

26.98

15

P

phosphorus

30.97

17

Cl

chlorine

35.45

19

Ar

argon

39.95

31

Ga

gallium

69.72

33

As

arsenic

74.92

35

Br

bromine

79.90

37

Kr

krypton

83.80

49

In

indium

114.8

51

Sb

antimony

121.8

53

Te

tellurium

127.6

55

I

iodine

126.9

57

Xe

xenon

131.3

81

Tl

thallium

204.4

83

Pb

lead

207.2

85

Bi

bismuth

209.0

87

Po

polonium

209

89

At

astatine

210

91

Rn

radon

222

101

Uut

ununtrium

284

103

Fl

flerovium

289

105

Uup

ununpentium

288

107

Lv

livermorium

292

109

Uus

ununseptium

293

111

Uuo

ununoctium

294

57

La

lanthanum

138.9

59

Pr

praseodymium

140.9

61

Nd

neodymium

144.2

63

Pm

promethium

145

65

Sm

samarium

150.4

67

Eu

europium

152.0

69

Gd

gadolinium

157.3

71

Tb

terbium

158.9

73

Dy

dysprosium

162.5

75

Ho

holmium

164.9

77

Er

erbium

167.3

79

Tm

thulium

168.9

81

Yb

ytterbium

173.0

89

Ac

actinium

227

91

Th

thorium

232.0

93

Pa

protactinium

231.0

95

U

uranium

238.0

97

Np

neptunium

237

99

Pu

plutonium

239

101

Am

americium

243

103

Cm

curium

247

105

Bk

berkelium

247

107

Cf

californium

251

109

Es

einsteinium

252

111

Fm

fermium

257

113

Md

mendelevium

258

115

No

nobelium

259

lanthanides
(rare earth metals)

actinides

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

66

67

68

69

70

71

72

73

74

75

76

77

78

79

80

81

82

83

84

85

86

87

88

89

90

91

92

93

94

95

96

97

98

99

100

101

102

103

104

105

106

107

108

109

110

111

112

113

114

115

116

117

118

119

120

121

122

123

124

125

126

127

128

129

130

131

132

133

134

135

136

137

138

139

140

141

142

143

144

145

146

147

148

149

150

151

152

153

154

155

156

157

158

159

160

161

162

163

164

165

166

167

168

169

170

171

172

173

174

175

176

177

178

179

180

181

182

183

184

185

186

187

188

189

190

191

192

193

194

195

196

197

198

199

200

201

202

203

204

205

206

207

208

209

210

211

212

213

214

215

216

217

218

219

220

221

222

223

224

225

226

227

228

229

230

231

232

233

234

235

236

237

238

239

240

241

242

243

244

245

246

247

248

249

250

251

252

253

254

255

256

257

258

259

260

261

262

263

264

265

266

267

268

269

270

271

272

273

274

275

276

277

278

279

280

281

282

283

284

285

286

287

288

289

290

291

292

293

294

295

296

297

298

299

300

301

302

303

304

305

306

307

308

309

310

311

312

313

314

315

316

317

318

319

320

321

322

323

324

325

326

327

328

329

330

331

332

333

334

335

336

337

338

339

340

341

342

343

344

345

346

347

348

349

350

351

352

353

354

355

356

357

358

359

360

361

362

363

364

365

366

367

368

369

370

371

372

373

374

375

376

377

378

379

380

381

382

383

384

385

386

387

388

389

390

391

392

393

394

395

396

397

398

399

400

401

402

403

404

405

406

407

408

409

410

411

412

413

414

415

416

417

418

419

420

421

422

423

424

425

426

427

428

429

430

431

432

433

434

435

436

437

438

439

440

441

442

443

444

445

446

447

448

449

450

451

452

453

454

455

456

457

458

459

460

461

462

463

464

465

466

467

468

469

470

471

472

473

474

475

476

477

478

479

480

481

482

483

484

485

486

487

488

489

490

491

492

493

494

495

496

497

498

499

500

501

502

503

504

505

506

507

508

509

510

511

512

513

514

515

516

517

518

519

520

521

522

523

524

525

526

527

528

529

530

531

532

533

534

535

536

537

538

539

540

541

542

543

544

545

546

547

548

549

550

551

552

553

554

555

556

557

558

559

560

561

562

563

564

565

566

567

568

569

570

571

572

573

574

575

576

577

578

579

580

581

582

583

584

585

586

587

588

589

590

591

592

593

594

595

596

597

598

599

600

601

602

603

604

605

606

607

608

609

610

611

612

613

614

615

616

617

618

619

620

621

622

623

624

625

626

627

628

629

630

631

632

633

634

635

636

637

638

639

640

641

642

643

644

645

646

647

648

649

650

651

652

653

654

655

656

657

658

659

660

661

662

663

664

665

666

667

668

669

670

671

672

673

674

675

676

677

678

679

680

681

682

683

684

685

686

687

688

689

690

691

692

693

694

695

696

697

698

699

700

701

702

703

704

705

706

707

708

709

710

711

712

713

714

715

716

717

718

719

720

721

722

723

724

725

726

727

728

729

730

731

732

733

734

735

736

737

738

739

740

741

742

743

744

745

746

747

748

749

750

751

752

753

754

755

756

757

758

759

760

761

762

763

764

765

766

767

768

769

770

771

772

773

774

775

776

777

778

779

780

781

782

783

784

785

786

787

788

789

790

791

792

793

794

795

796

797

798

799

800

801

802

803

804

805

806

807

808

809

810

811

812

813

814

815

816

817

818

819

820

821

822

823

824

825

826

827

828

829

830

831

832

833

834

835

836

837

838

839

840

841

842

843

844

845

846

847

848

849

850

851

852

853

854

855

856

857

858

859

860

861

862

863

864

865

866

867

868

869

870

871

872

873

874

875

876

877

878

879

880

881

882

883

884

885

886

887

888

889

890

891

892

893

894

895

896

897

898

899

900

901

902

903

904

905

906

907

908

909

910

911

912

913

914

915

916

917

918

919

920

921

922

923

924

925

926

927

928

929

930

931

932

933

934

935

936

937

938

939

940

941

942

943

944

945

946

947

948

949

950

951

952

953

954

955

956

957

958

959

960

961

962

963

964

965

966

967

968

969

970

971

972

973

974

975

976

977

978

979

980

981

982

983

984

985

986

987

988

989

990

991

992

993

994

995

996

997

998

999

1000