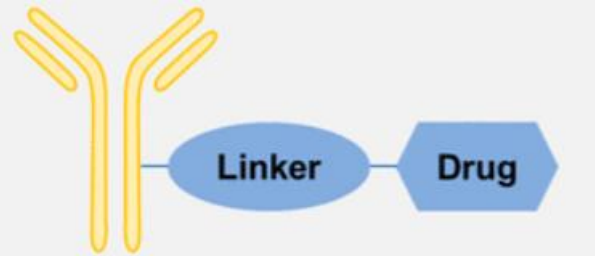
Impurity Qualification Requirements for Drug-Linkers Related Impurities Used to Generate Antibody-Drug Conjugates



QWP/ Interested Parties Meeting

Industry (EFPIA) Presentation

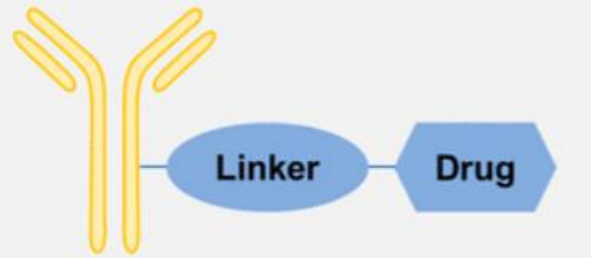
Oct 25

Presenter: Dr Osama Chahrour

Impurity Qualification Requirements for Drug-Linkers Related Impurities Used to Generate Antibody-Drug Conjugates

Comparison Table

Molecule Type	Qualification Threshold	Primary Reference
Small Molecules	**0.15%** (or 1 mg/day)	ICH Q3A
Synthetic Peptides	**1.0%**	Ph. Eur. 2034 / EMA Draft Guideline
Oligonucleotides	**1.5%**	Industry Standards (e.g., OSRT Whitepaper)

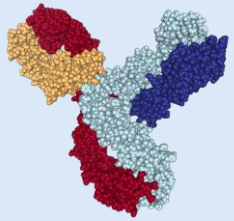


efpia

IQ INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

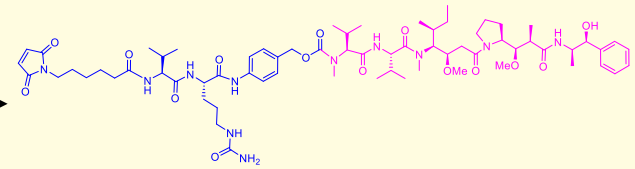
Scope and goals of the IQ ADC Working Group

Large molecule (biologic) process



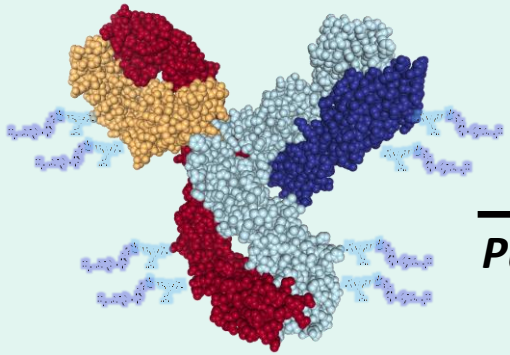
mAb

Small molecule (chemical) process



Drug-Linker

Conjugation

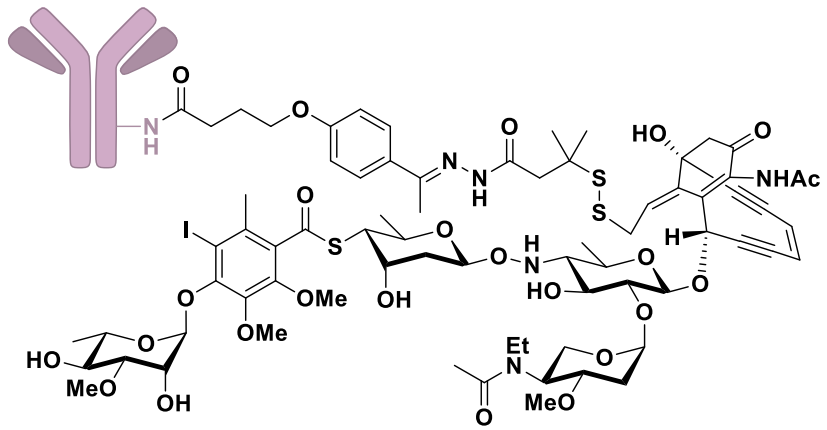


Crude ADC

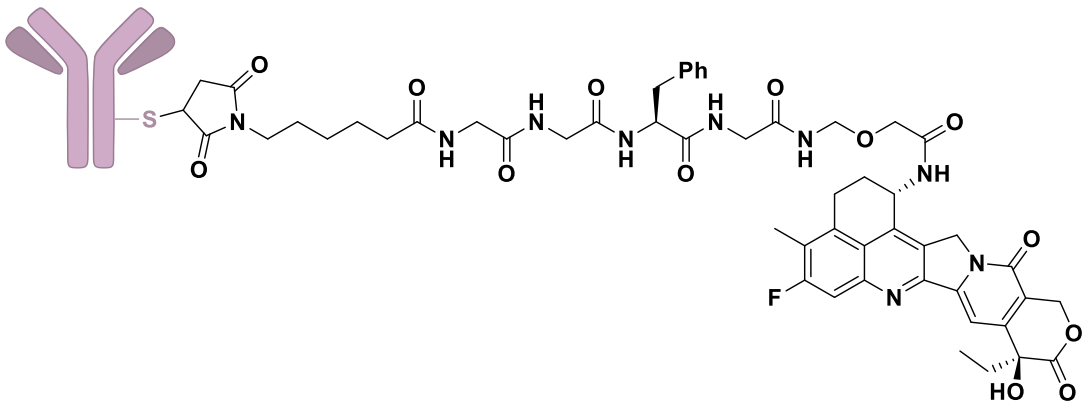
Purification

Drug Substance

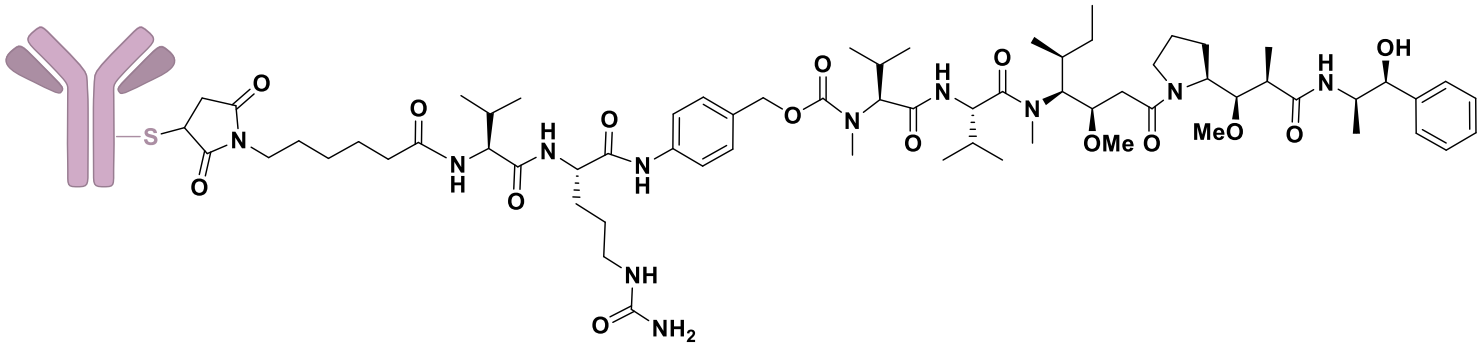
Drug-linkers are structurally complex and diverse



Calicheamicin derivative (Besponsa®)



Exatecan derivative (Enhertu®)



Auristatin derivative (Adcetris®, Polivy®, Padcev®, Aidixi®)

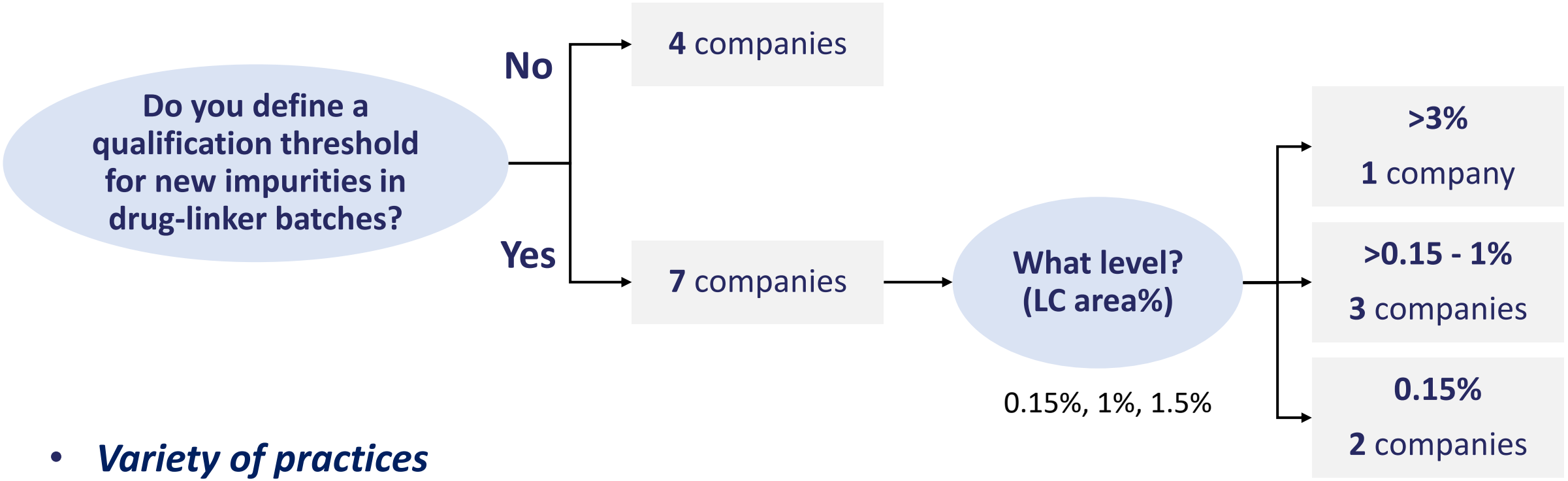
slido

Join at

slido.com

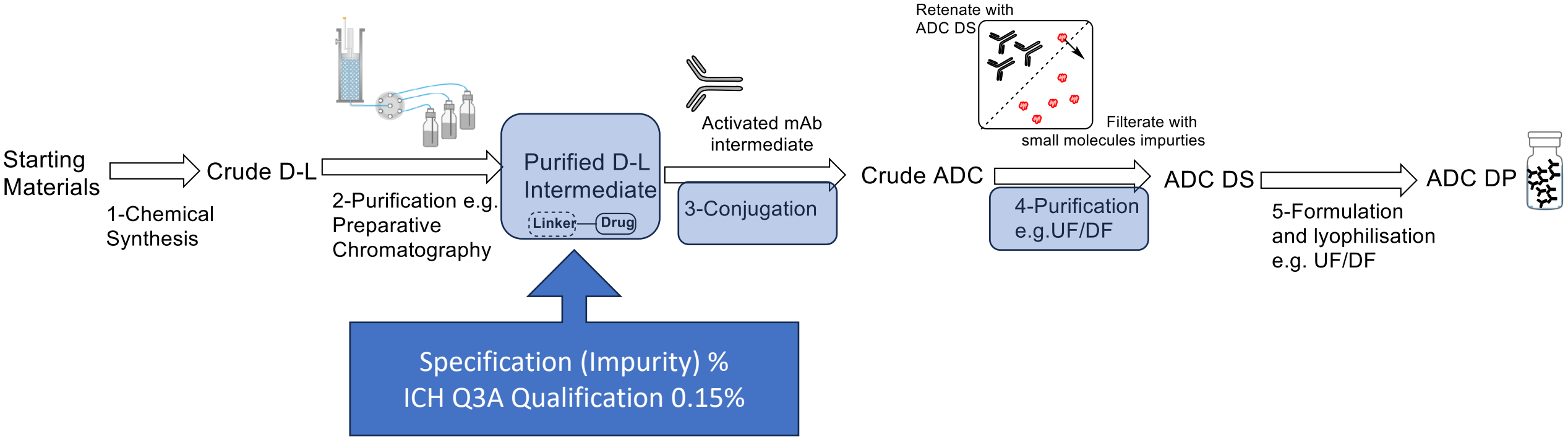
#2570 429

Qualification threshold in drug-linkers



- ***Variety of practices***
- ***Qualification threshold – if defined – generally above ICH Q3A 0.15%***
- ***Could qualification level be used to justify impurity specification limit in D-L?***
- ***Can specification limits be justified through S9 for oncology indications?***

ADC manufacturing and the control of D-L related impurities



Challenge:

- In the absence of regulatory guidance, suggestion to control according to the ICH Q3A.
- ICHQ3A approach does not acknowledge that unlike small molecule APIs, D-L are intermediates.
- It also does not acknowledge the low dose of the drug (or D-L) in ADCs which will reduce associated risks however always drive the use of the 0.15% w/w over the 1 mg/day limits.

Alternative approach to ICHQ3A qualification limit - scope of the presentation

- A comprehensive assessment was completed for the development of appropriate toxicological qualification limits.
- Presenting a conservative recommendation for adoption by industry sponsors and regulatory agencies
  Tox threshold =1.0% w/w or 1 mg/day, whichever is lower).
- D-L related, conjugatable and non-conjugatable.
- ADC therapeutics designed for oncology indications whether treatment is in S9 populations or non-S9 populations
- Small Molecule payloads (not including peptides, Oligonucleotide and other mixed modalities)

Impurity Qualification Requirements for Drug-Linkers Related Impurities Used to Generate Antibody-Drug Conjugates

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Agenda – QWP Interested Parties Meeting

10 October 2025 (9:00 – 13:00) (virtual)

Chair: Blanka Hirschlerova

Vice-Chairs: Nick Lee (H) and Marie Helene Sabinotto (V)

Time	Description
5 min	**Welcome and Introduction to IP meeting**
15 min	**Updates from 2024 IP meeting and update on ongoing guidance work**
20 min	**1. 2025 EMA draft reflection paper on qualification of non-mutagenic impurities: quality considerations** • Presentation from EFPIA • Discussion
30 min	**2. Guideline on the development and manufacture of oligonucleotides** • Presentation from EFPIA • Discussion
20 min	**3. Recycled solvents and risk of nitrosamine contamination** • Presentation from EFPIA • Discussion • Industry response to FDA guidance on nitrosamine leachables (EMA led)
15 min	**4. New active substance (NAS) assessment relating to the chemical structure** • Presentation from EFPIA • Discussion
	Break (15 min 10:45 – 11:00)
20 min	**5. Challenges with API starting material designation** • Presentation from EFPIA • Discussion
20 min	**6. Impurity qualification requirements for drug-linker related impurities used to generate antibody-drug conjugates** • Presentation from EFPIA • Discussion
15 min	**7. API Mixtures (follow up to EMA letter January 2025)** • Update from QWP • Next steps
25 min	**QWP priorities / work plan / general discussion** • Presentation from EMA / QWP • Discussion
5 min	**Concluding remarks**

Invited associations

EFPIA

Medicines for Europe

AESGP

EUCOPE

EIGA

APIC/CEFIC

Animal Health Europe

AccessVetMed

PDA

IPEC

Vaccines Europe

NMEU

EuropaBio

Interaction with EMA QWP – the outcome

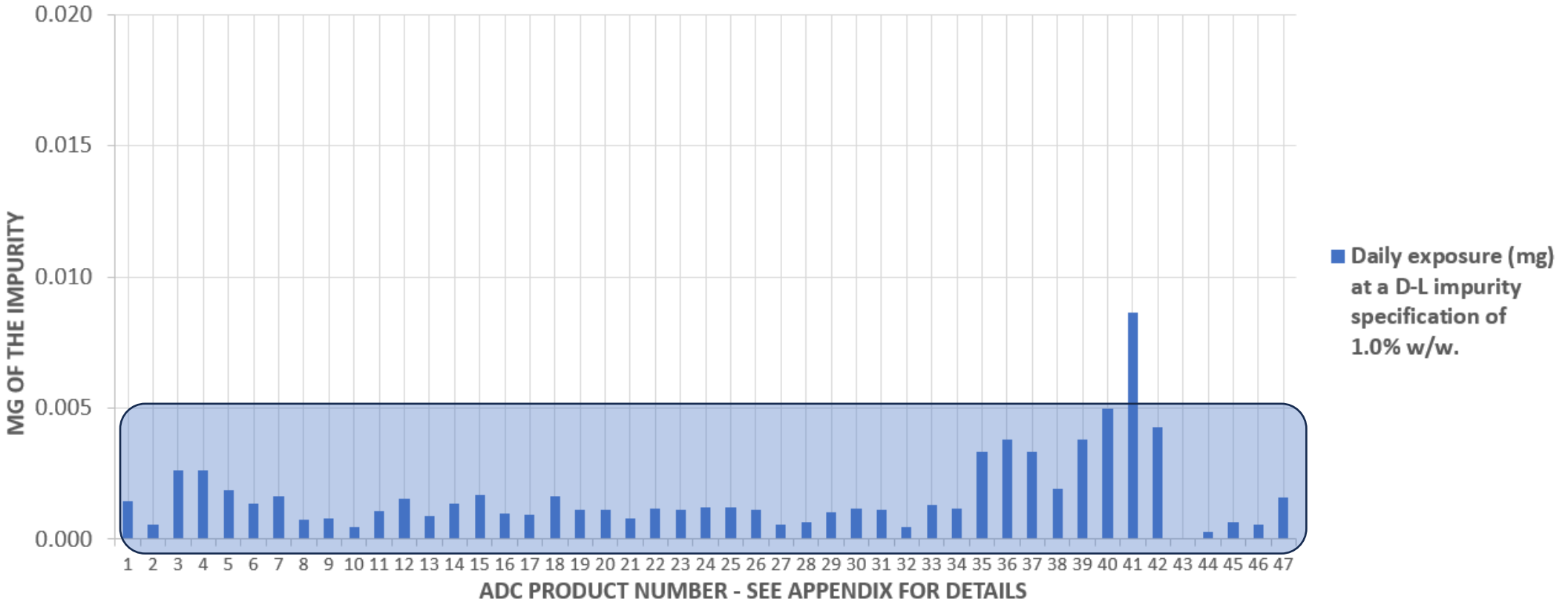
- QWP agreed in principle that EFPIA's proposed general limit of 1.0% w/w is an appropriate qualification threshold for non-purgeable, unqualified impurities in D-L intermediates

- QWP also confirmed that there are no current plans to issue ADC-specific guidance

				to appropriately justify their selection within the dossier.
	7. Impurity qualification requirements for drug-linker related impurities used to generate antibody-drug conjugates • Presentation from EFPIA • Discussion	**20**	osama.chahrour@astrazeneca.com **hayley.jackman1@astrazeneca.com**	**Discussion** QWP noted in principle that the EFPIA proposal of a general limit of 1.0 % w/w is a suitable qualification limit for non-purgeable unqualifies impurities in D-L intermediates. The approach proposed for technical assessments to demonstrate the suitability of the proposed limit were deemed acceptable for use applicants to assess D-Ls used in their ADC programs, with review on a case-by-case basis. QWP confirmed that there is no plan for specific ADC guidance (at least until after ICHQ6 finalisation). There may be opportunities for ADC related examples in Q6.

Low daily exposure associated with D-L impurities (mg/day)

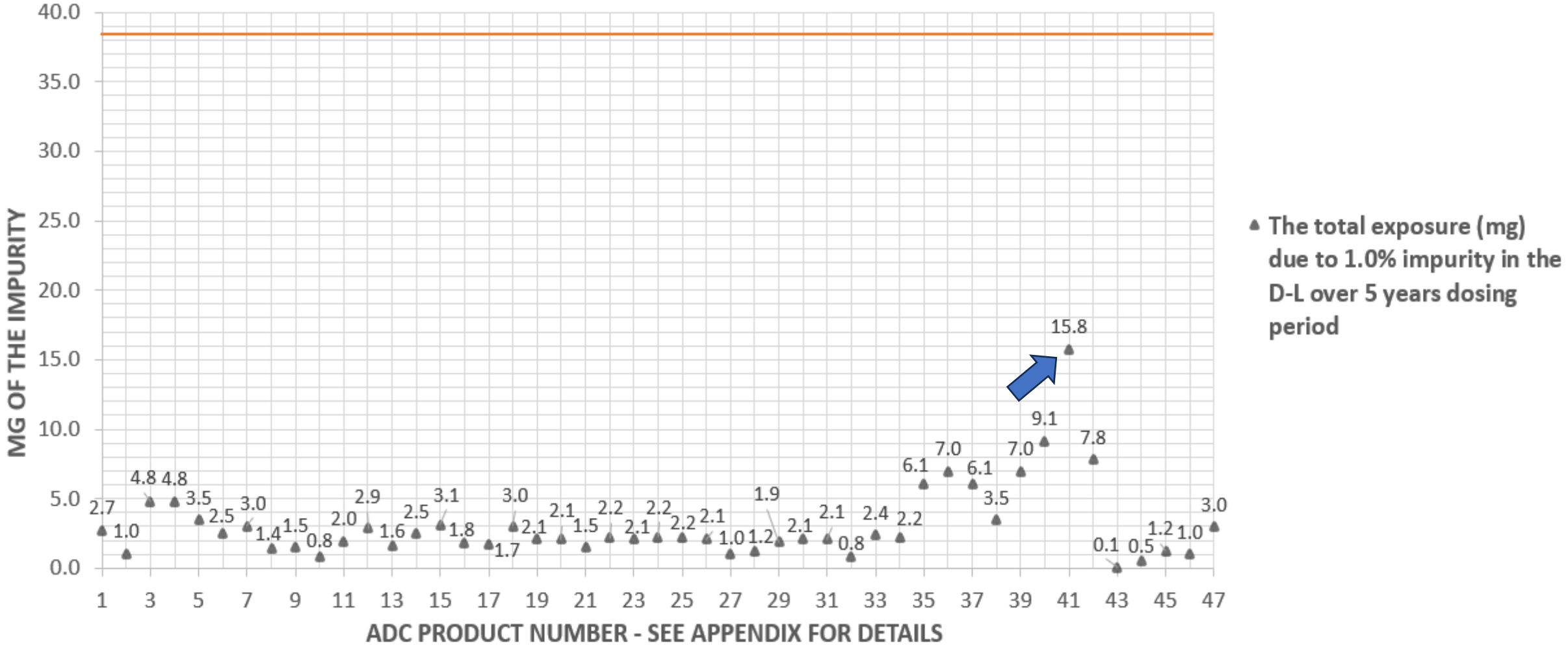
- Compared the exposure that patients will experience against an acceptable limit.



(Colombo and Rich, 2022)

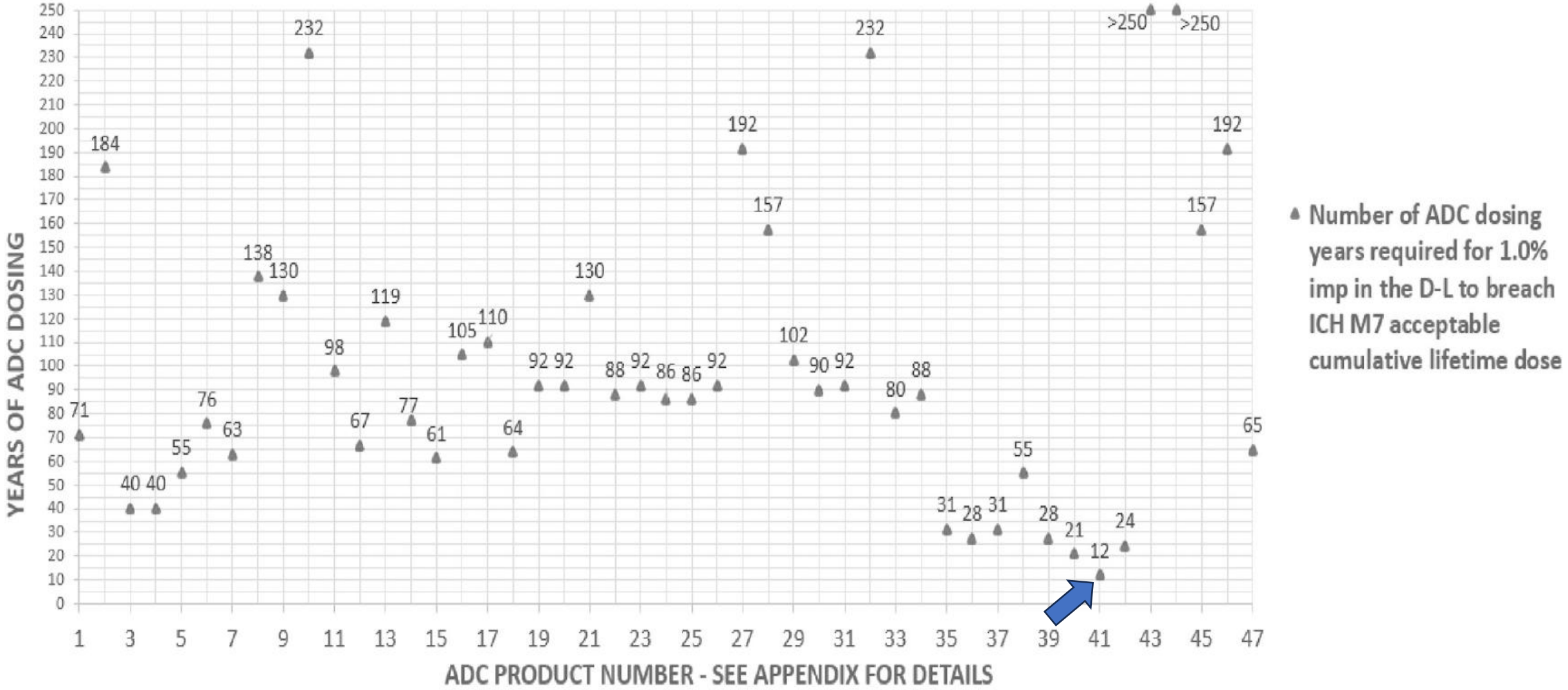
D-L impurities exposure assessment against ICH M7

- Compared the exposure that patients will experience against an acceptable limit.
- One of the strictest impurity control requirements ICH M7 (acceptable cumulative lifetime impurity dose of 38.3 mg).

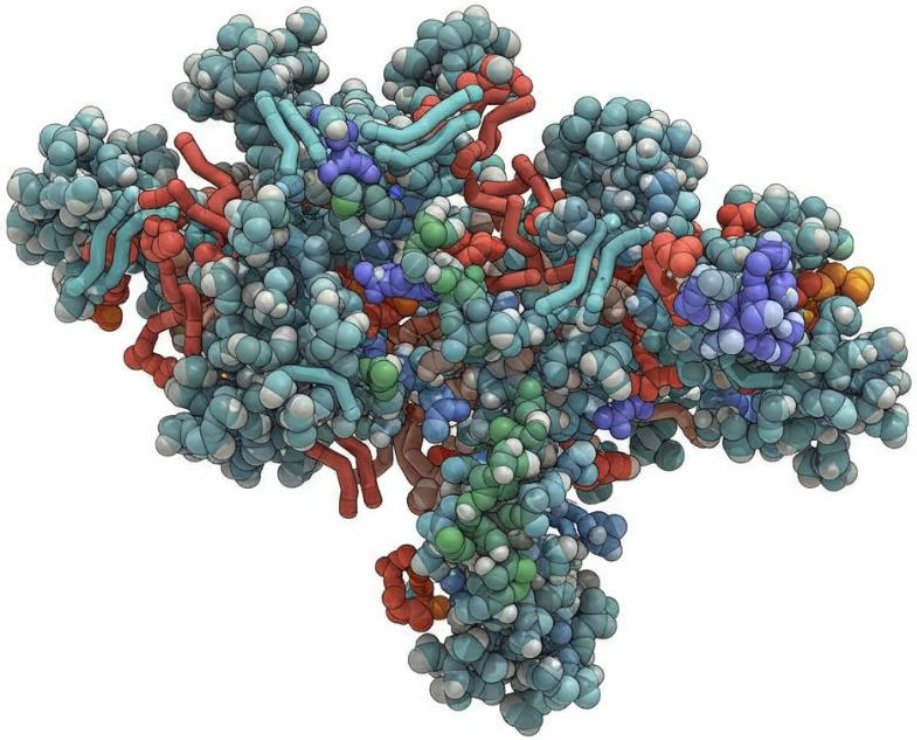


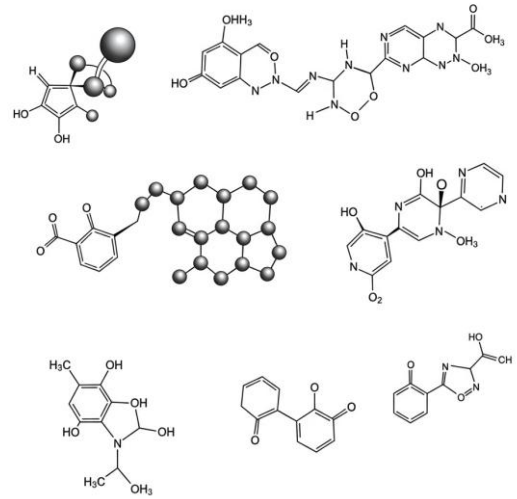
D-L impurities exposure assessment against ICH M7

- More than 12 years of dosing of 1.0 % w/w impurity would be required to exceed the acceptable cumulative lifetime impurity exposure of 38.3 mg.



Molar exposure associated with D-L impurities (mol/day)





Typical ADCs:

molecular weight ~ 150 kDa

Dose: 7.5-600 mgs

(Colombo and Rich, 2022, examined ADCs with a published dose in the public domain)

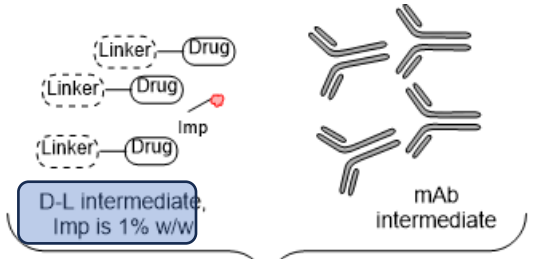
Typical Small molecule:

molecular weight ~ 450 Da

Dose: 0.1-600 mgs

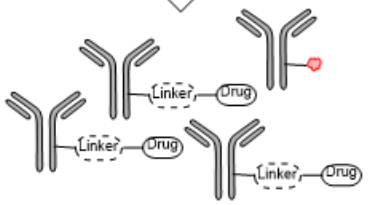
(Stegemann et al, 2023, examined 154 small molecule new chemical entities approved by FDA from 2013 to 2019)

Molar exposure associated with D-L impurities (mol/day)

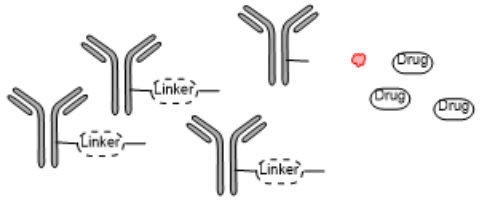


5% of ADC DS is D-L

95% of ADC DS is mAb

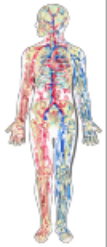


-ADC dose range 7.5 mg - 600 mg
-Mw is approx. 150 000 Da

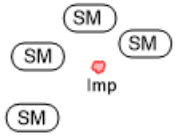


Worst case ADC mole per dose = 0.6/150000 = 0.004 mM
Typical DAR is 4-8
1.0% w/w Imp in D-L results in approx. 0.0003 mM per dose

Small Molecule (SM) Drug, Imp is 1% w/w



-SM drug dose range 0.1 mg - 600 mg
-Mw is approx. 450 g/mole



Worst case API mole per dose = 0.6/450 = 1.3 mM
1.0% w/w Imp in API results in approx. 0.01 mM per dose

Controlling a D-L impurity to 1.0% w/w is approximately equivalent, in terms of molar amounts, to controlling an impurity in a typical small-molecule API drug substance to 0.01% w/w.

ADC intermittent dosing and the associated exposure against the parenteral threshold of toxicological concern (mol/day)

- Intermittent dosing schedule of ADCs is an additional mitigating factor, The approximately 0.0003 mM exposure associated with a 1.0% w/w impurity in the D-L is released gradually over time.

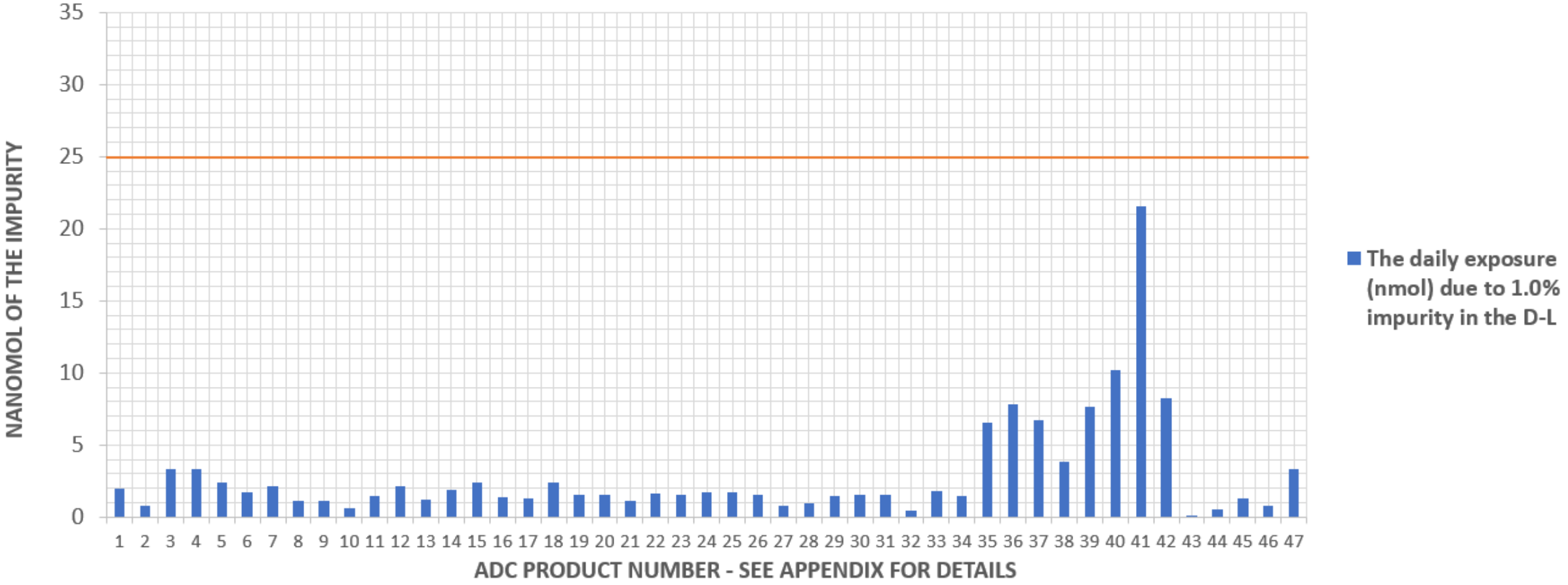
- Intravenous administration is the primary route for parenteral delivery of ADC pharmaceuticals.

- Various reports have detailed methods for determining parenteral Threshold of Toxicological Concern (iTTC), (Arnot et al., 2022) and (Partosch et al., 2015).

- iTTC = 25 nmol per day for Cramer class II/III compounds (moderate to severe tox).

ADC intermittent dosing and the associated exposure against the parenteral threshold of toxicological concern(mol/day)

In all instances, the daily exposure was below the iTTC value of 25 nmol per day derived by Arnot et al.



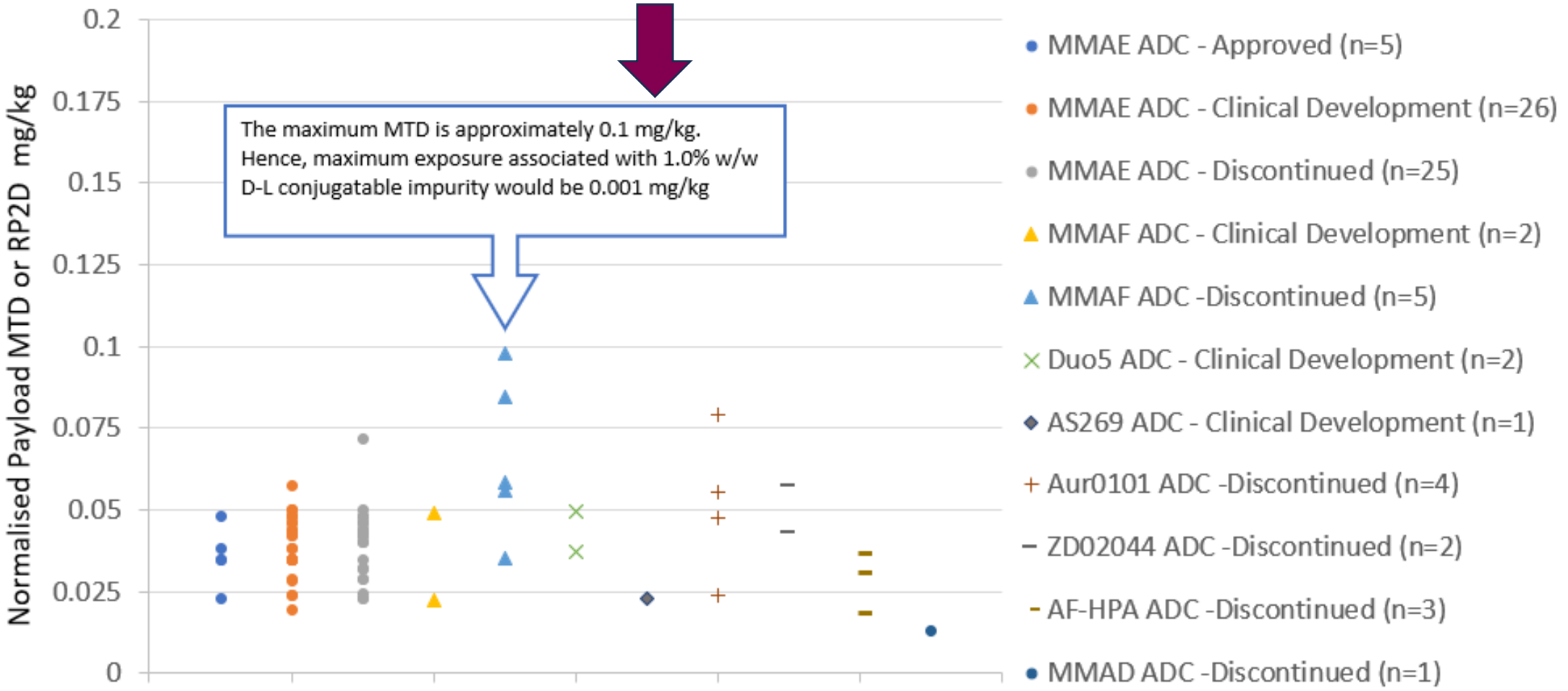
Grouping per payload family and assessment against worst-case surrogate compound

- ADCs display a range of toxicities; however, payload mediated platform toxicities are the determinant of MTD (maximum tolerated dose).

ADC Class	Number of ADCs			Payload Mode of Action
	Discontinued	In clinical development	FDA approved	
Auristatin	>49	>55	4	Synthetic derivative of Dolastatin 10; potent antimitotic agents that inhibit microtubule polymerization to disrupt cell division
Camptothecin	2	>85	2	Inhibit topoisomerase I, an enzyme critical for DNA replication and transcription, causing DNA strand breaks, leading to cell cycle arrest and apoptosis in targeted cancer cells
Maytansinoid	>31	>5	2	Derivatives of the natural product maytansine; antimitotic agents that inhibit tubulin polymerization to disrupt cell division
Calicheamicin	4	None	2	A class of enediyne antibiotics that cause DNA strand breaks
PBD (pyrrolobenzodiazepine)	>25	>5	1	Sequence-selective DNA-interactive agents that form covalent bonds with DNA, leading to cell death

Grouping per payload family and assessment against worst-case surrogate compound (auristatin derivatives)

76 auristatin ADCs that entered clinical trials, the payload exposure associated with each is plotted (from ADC MTD or RP2D)



Grouping per payload family and assessment against worst-case surrogate compound (auristatin derivatives)

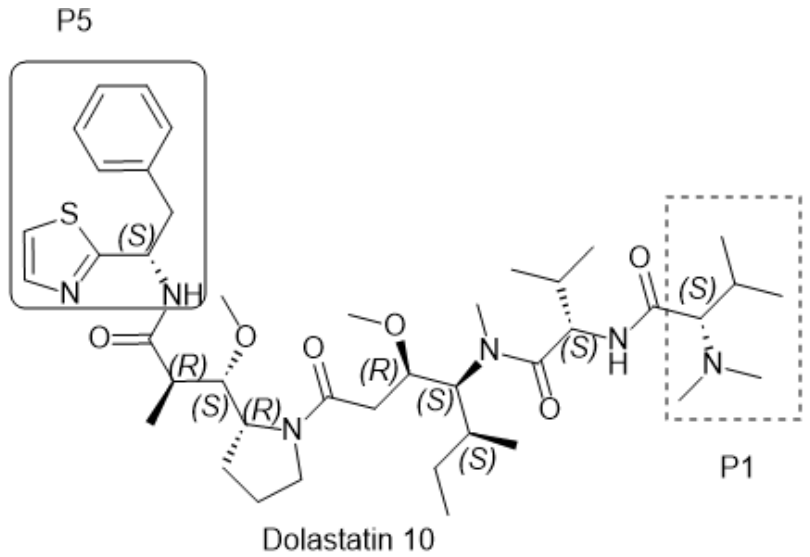
The 0.001mg/kg worst case imp exposure from 1.0% D-L imp is compared to worst case surrogate compound

Ten times higher

Clinical MTD 0.01 mg/kg of the naked Dolastatin 10

SAR of auristatin scaffold

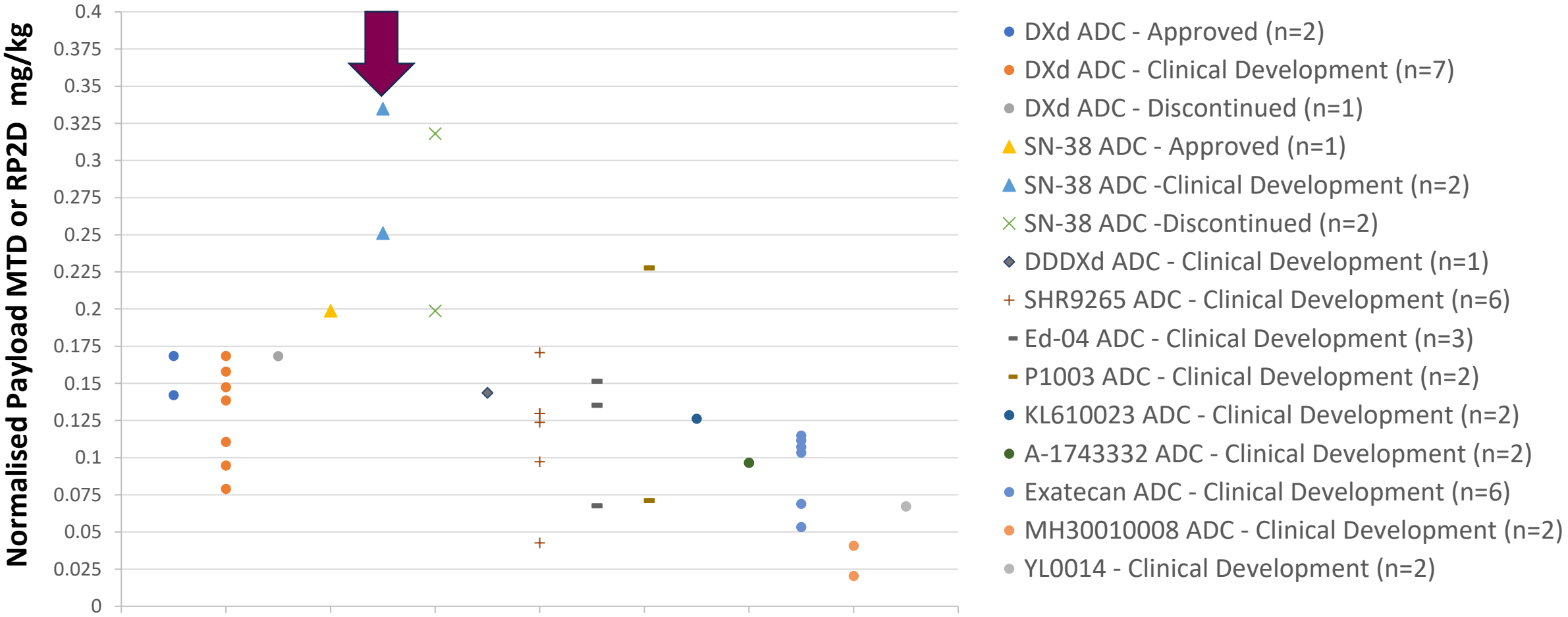
Identified worst case surrogate is Dolastatin 10



Dolastatin 10

Grouping per payload family and assessment against worst-case surrogate compound (camptothecin derivatives)

42 Camptothecin ADCs that entered clinical trials, the payload exposure associated with each is plotted (from ADC MTD or RP2D)



Grouping per payload family and assessment against worst-case surrogate compound (camptothecin derivatives)

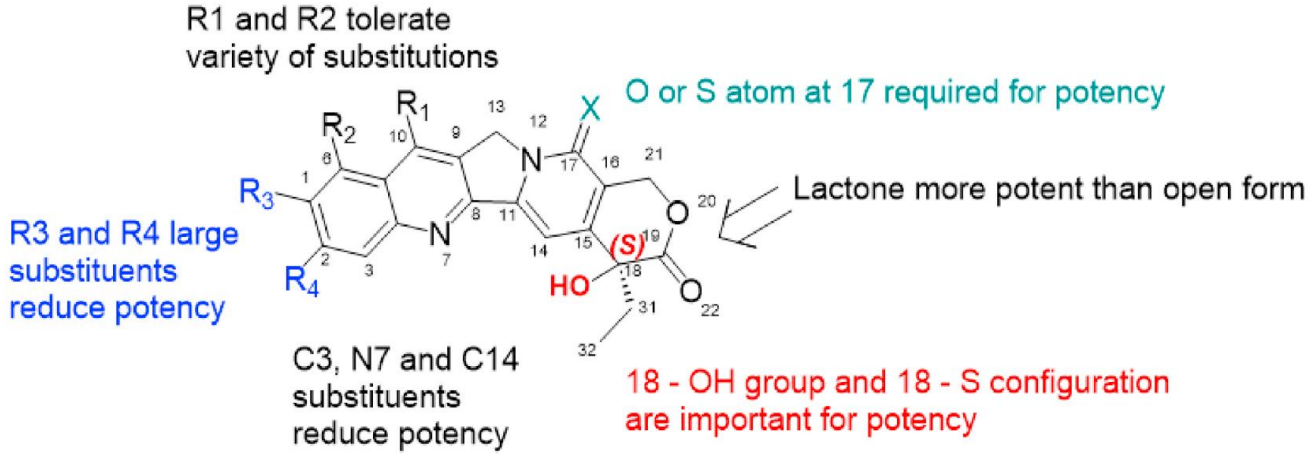
The 0.003mg/kg worst case imp exposure from 1.0% D-L imp is compared to worst case surrogate compound

four times higher

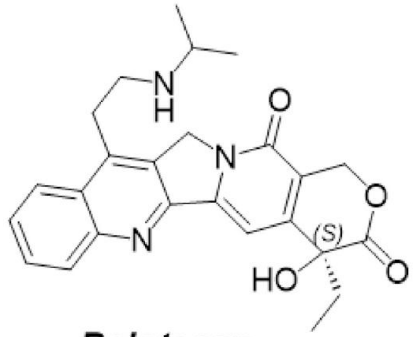
Clinical MTD 0.012 mg/kg of the naked Belotecan

SAR of camptothecin scaffold

Identified worst case surrogate is Belotecan



Camptothecin structure activity relationships



Belotecan

Conclusion

- Evaluated conjugatable impurities in ADC drug-linkers for potential toxicological risks.

- Drug-linker conjugatable impurities present at ≤1.0% w/w are unlikely to pose a risk to patients.

- Data provides science-based justification to increase qualification limit from 0.15% to 1.0% w/w for D-L intermediates.

Thank You