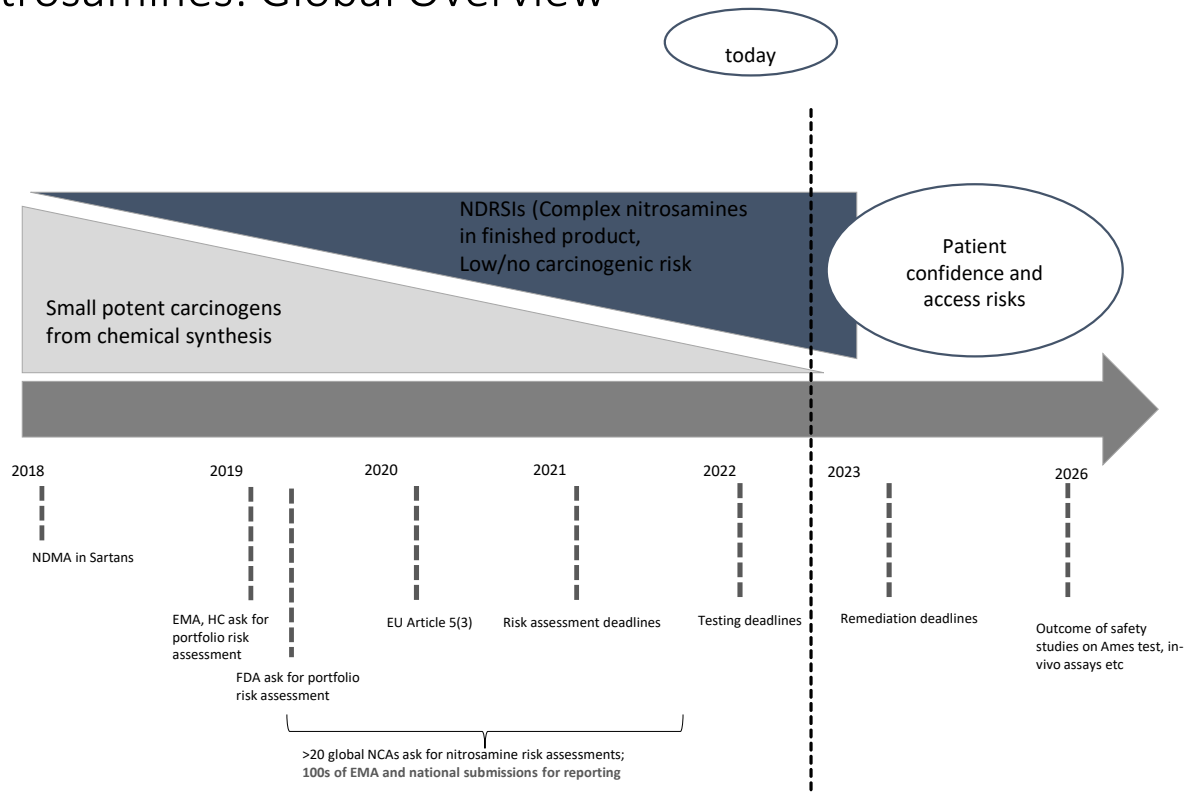
Joint meeting of EMA Nitrosamine Implementation Oversight Group (NIOG) with industry

30 November 2022

Nitrosamines: Global Overview



Outstanding Issues and Priorities

- **Avoidance of unnecessary patient impact**
  - **Supply of medicines**
  - **Confidence in medicines**

- Maintenance of supply of products with levels of complex nitrosamines (short- and mid-term)
  - The Q&As 178ng/day interim, for one year only, does not fully address – see example (Section 6)

- Setting appropriate (science-based) limits for complex nitrosamines (NCWP)
    - **For control and to target remediation**
  - Read-across science-based limits
  - Bacterial mutagenicity test and impact of (robust) negative bacterial mutagenicity test
  - Correlation of negative bacterial mutagenicity test with negative in vivo test
  - Understanding context provided by in vivo / endogenous formation of nitrosamines

Outstanding Issues and Priorities

- Focussing and prioritising control and remediation resources (QWP discussion)
  - General remediation of NDSRIs to 18ng/day likely not technically feasible
    - And even lower levels in API may need to be delivered if can form in API and DP
    - Implementation of CAPAs / remediation, when possible, will likely take several years
  - Analytical capacity for NDSRI testing will quickly be consumed if many products need low level routine testing
  - Agreeing practicable ongoing control strategies, including importation testing (complex analytics)

- Determining inspectional and supplier oversight LL expectations (IWG) – DISCUSSION

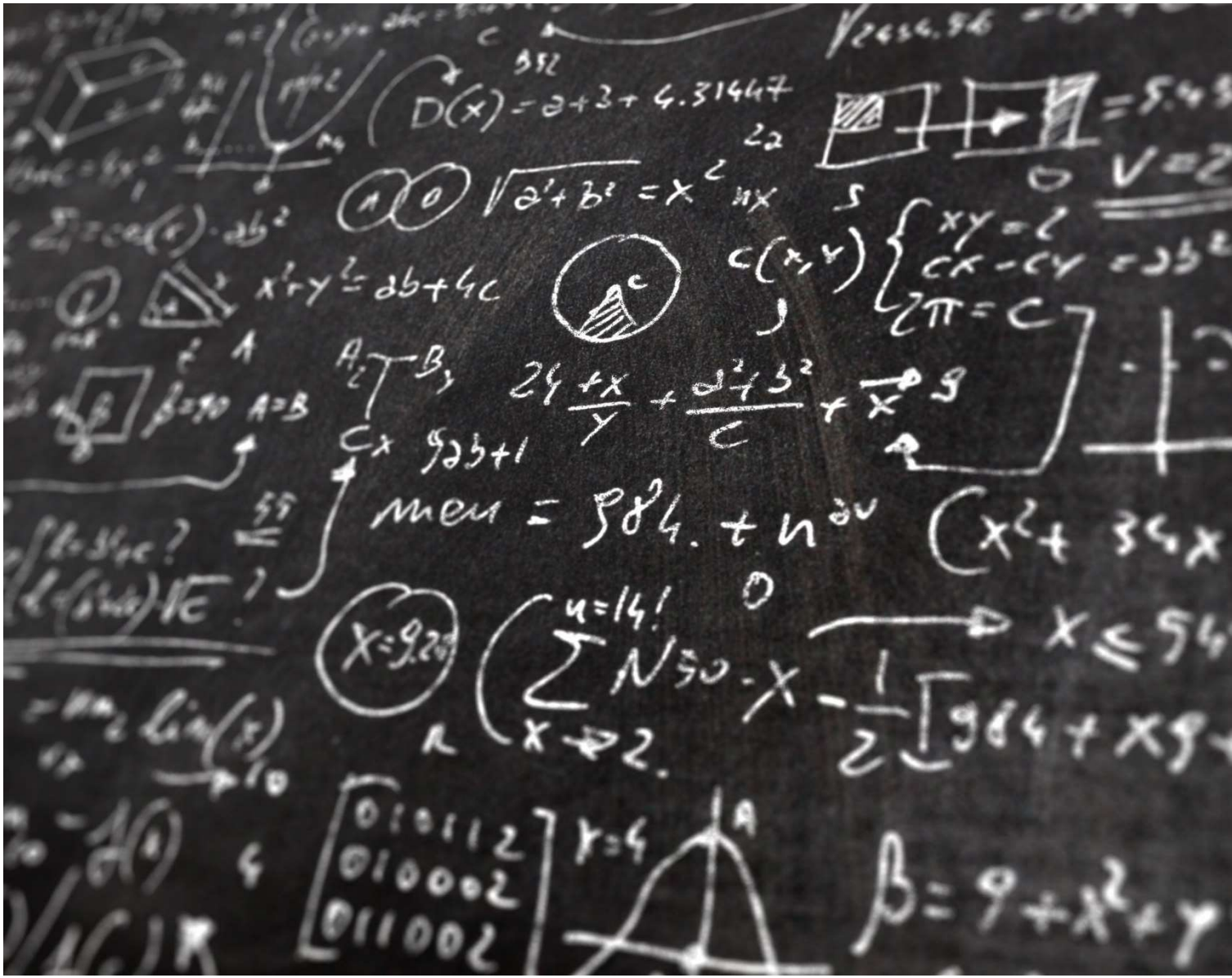
- Embedding Lessons Learned in (1) Active Substance guideline and (2) Development Pharmaceutics guideline (QWP)

- Progression of ongoing procedures / variations stalling –
  - Expectation for nitrosamine risk assessment (complex nitrosamines) when making small supplier changes for existing products / monographed DS … impact on supply of existing medicines (and inhibition of process improvement).
  - **Can discussion be held (NIOG + CMDH) to facilitate ?**

Outstanding Issues and Priorities

- Maintain benefit / risk-based and science-based regulatory oversight
- Maintain secondary amines as viable drug substance substrates
- Managing patient concern re. historic use of medicine with structurally-complex nitrosamine >18ng/day target
- GLOBAL ALIGNMENT
- **There are likely to be ongoing challenges to maintain supply of products potentially containing structurally-complex nitrosamines**

Session 6 – Current challenges – example case study – β blockers



B Blockers – Background

- β-blockers, also known as β-adrenergic blocking agents, are medications that reduce blood pressure by blocking norepinephrine and epinephrine from binding to their receptors.
  - The β-blockers are often called “olols” because their names all end with an -olol.
- β-blockers are used to manage a variety of conditions.
  - They include, but are not limited to cardiac arrhythmias, heart failure, high coronary artery disease risk, diabetes, post heart attack (myocardial infarction), angina pectoris due to coronary atherosclerosis, and hypertension (high blood pressure).
  - Often used in the management of hypertension, it may be used alone or concomitantly with other antihypertensive agents, particularly thiazide diuretics).
- **No clear / obvious alternative for millions of patients**

B Blockers

- Table 1 shows the structures of the nitrosamines of most marketed β-blockers.

- All the β-blockers contain an N-alkylethanolamine motif (highlighted below in yellow).

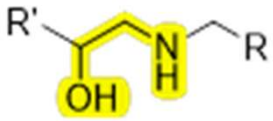


Table 1. Nitrosamines of β-blockers

Nitroso-Acebutolol	Nitroso-Sotalol
Nitroso-Atenolol	Nitroso-Formoterol
Nitroso-Betaxolol	Nitroso-Labetolol
Nitroso-Bisoprolol	Nitroso-Nadolol
Nitroso-Esmolol	Nitroso-Penbutolol
Nitroso-Metoprolol	Nitroso-Timolol
Nitroso-Pindolol	Nitroso-Carvedilol
Nitroso-Propranolol	Nitroso-Nebivolol

B Blocker Structure

- All the β-blockers have a secondary amine that can undergo nitrosylation under suitable conditions to give the *N*-nitrosamine derivative.

- Besides carvedilol and nebivolol, all the other β-blockers have bulky (isopropyl, isopropyl with further substitution, or tert-butyl) groups at the α-position to the secondary amine.

- Carvedilol and nebivolol have CH_2 groups at both α-positions, however the substituents on both sides of the amino group are large/bulky groups that render considerable steric hindrance.

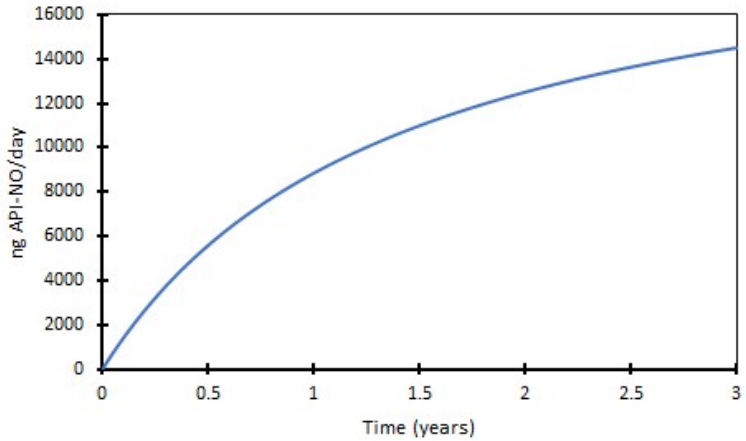
- **It is very likely that these factors reduce the carcinogenic potency of any related N-nitrosamine however it is recognised that further investigation is needed to completely understand this**

Modelling beta-blocker nitrosation in a drug product – indicates a significant concern

Scenario
API is a salt with saturated solution pH of 7
Free-base RMM of 250 daltons
Solubility of API salt is 150 mg/mL
Amine pK_a of 9.5
Tablet contains 20 mg of API (as free-base) and weighs 200 mg
Maximum daily dose (MDD) of 160 mg
0.43 mg of nitrite (9.5×10^{-9} moles)
/tablet
Tablets contain 2% w/w water

/tablet

- Total nitrosation will form 21200 ng of API-NO in the MDD
- Kinetic simulation (saturated solution layer model) predicts 14500 ng/day in MDD after 3 years at 25°C for a product pH of 7



KEY POINT Predicted Levels >> 18ng and >178ng

Proposed interim AI

- A weight of evidence approach, together with the understanding that NDSRIs such as nitrosamines of β-blockers are structurally very different than the small potent nitrosamines that are currently being used as the default surrogates for setting AIs for nitrosamines.
- This leads to the conclusion that nitrosamines of β-blockers are much less potent mutagens and their carcinogenicity potency is probably also much lower than the small nitrosamines.

What is actually seen

- While conservative model is predictive of the extent of formation

- We can present multiple examples across different β blockers / different products – these clearly show even interim limit of 178ng/day is not viable – (examples will be provided in the meeting)

The reality

- Some reduction of nitrite level may be possible but cannot reduce to 18ng
- Scavengers could hypothetically be used but how realistic is this for an entire drug class
- Without revised AIs that take into consideration risk / benefit i.e. criticality of the medicines – withdrawal is inevitable
- This is not isolated to b blockers a review article (in press J Pharm Sci) estimates up to 30% of all medicines are at risk as are the viability of many new drugs in development